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Original Research Article

Comparative clinical study of the effect of oral clonidine premedication on intraoperative haemodynamics in the patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Background: Pneumoperitoneum created during laparoscopy results in patho-physiologic changes, especially in the cardiovascular system. Clonidine diminishes stress response by reducing circulating catecholamines and hence increases perioperative circulatory stability in patients undergoing laparoscopic surgeries. This comparative clinical study was planned compare with controls the effects of oral clonidine premedication (150 micrograms) on the intraoperative haemodynamics during laparoscopic cholecystectomy.
Methods: Sixty adult patients between 15-50 years, scheduled for laparoscopic cholecystectomy under general anaesthesia were enrolled in the study. The patients were randomly assigned to two study groups of 30 patients each, Group CL: received oral clonidine (150 microgram) 90 minutes before induction of anaesthesia and Group C: received placebo. Anaesthetic technique was same for both the study groups. Hemodynamic variables (Heart rate, systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), and $EtCO_2$ were recorded at specific times - baseline; 90 minutes following study drug administration; induction of anaesthesia; 5 and 10 minutes following intubation; At skin incision; after creation of CO_2 pneumoperitoneum and every 15 minutes thereafter till end of surgery; after desufflation; 5 minutes following extubation.
Results: Patients in clonidine group had lower HR, SBP and DBP values as compared to control group at all points of time after giving the study drug ($P < 0.05$). Percent change from baseline in HR and Blood pressure at different points of time was significantly high in control group than in clonidine group.
Conclusions: Oral clonidine premedication (150 micrograms) is safe and provides perioperative hemodynamic stability in ASA I and II patients undergoing laparoscopic cholecystectomy, and hence can be recommended as a routine premedication for laparoscopic procedures.

Keywords: Intraoperative haemodynamics, Laparoscopic cholecystectomy, Oral clonidine premedication, Pneumoperitoneum

INTRODUCTION

Since the introduction of first laparoscopic cholecystectomy procedure, laparoscopy has expanded impressively in scope and volume. The multiple benefits reported after laparoscopy explains its increasing use.[1] Consequently, laparoscopy has now become the standard technique and is considered gold standard for cholecystectomy.[2] Although they are visually 'minimally invasive' to the patient, the intra-operative requirements

of laparoscopic surgery produce significant physiological changes, which pose many challenges for the anaesthesiologist.[3] Pneumoperitoneum (the act of insufflating the peritoneal cavity with gas, most often carbon dioxide; CO_2) and different patient positions required for laparoscopic surgery results in various patho-physiological changes. Both mechanical and neuro-humoral factors contribute to these alterations in cardiovascular and respiratory physiology.[1,4] The increase in intra-abdominal pressure (IAP) produced by pneumoperitoneum, results in direct mechanical effects on blood flow. This is compounded by the CO_2-stimulated release of various vasoactive substances, including catecholamine's, prostaglandins vasopressin, angiotensin, cortisol, and adrenocorticotropin hormone (ACTH).[5-9] The cardio-respiratory changes occurring during laparoscopy are complex and depend on the interaction of the patients' pre-existing cardiopulmonary status, anaesthetic technique, and several surgical factors including intra-abdominal pressure, CO_2 absorption, patient position and the duration of surgery.[10,11] Although these physiological changes are well tolerated by most of the healthy patients, they can have adverse consequences in elderly patients with multiple co-morbid conditions, the very young, the morbidly obese, pregnant women, the critically ill and the patients with limited cardiac reserve.[12] Thus, there is a need to modify the anaesthetic technique to allow these novel surgical procedures to be performed safely with minimal complications and rapid recovery. Various remedies to minimize these adverse effects have been proposed. These include modifications in surgical techniques like the use of inert gas for abdominal insufflation, gasless laparoscopic surgery and low pressure insufflation.[13,14] Various pharmacological agents such as a beta blocker (esmolol, metoprolol and propranlol), alpha2-agonist (clonidine, dexmetedomidine), vasodilators (magnesium sulphate), opioids (remifentanil), vasodilating anaesthetic agents (isoflurane) or direct vasodilating drugs (nitroglycerin or nicardipine) agents have been used to suppress the haemodynamic changes associated with pneumoperitoneum.[15-17]

Whereas no anaesthetic technique has proved to be clinically superior to any other, the adrenergic alpha 2-agonists have demonstrated beneficial effects in anesthetized patients. The adrenergic alpha2-agonists exert their sympatholytic effect presumably by activating inhibitory alpha 2-adrenergic receptors, both in the central nervous system and on peripheral sympathetic nerve endings (pre-synaptic autoreceptors). Interestingly, alpha 2-adrenergic agonists have been shown to improve haemodynamic stability during gynaecologic laparoscopy.[16,17]

Considering all these observations, the present study was designed to evaluate the type and the extent of haemodynamic changes associated with laparoscopic surgery and also to find out the efficacy of Clonidine as a premedication in the prevention of these haemodynamic changes. This comparative clinical study was designed to study and compare with controls the effects of oral clonidine premedication (150 micrograms) on the intraoperative haemodynamics during laparoscopic cholecystectomy.

METHODS

After obtaining the approval from the Institutional Ethical Committee this randomized prospective study was carried out in 60 adult patients belonging to American society of Anaesthesiologists (ASA) physical status I and II, scheduled for laparoscopic cholecystectomy.

Routine pre-anaesthetic evaluation of all the patients was done. Patients aged less than 15 years and more than 50 years, belonging to ASA physical status III and above, with known hepatic and renal disorder, uncontrolled diabetes, hypertension and ischemic heart disease were not included in the study. Patients with previous known allergy to propofol and patients who were on clonidine, methyldopa, beta blocking drugs, benzodiazepines and MAO inhibitors were also excluded from the study. All the patients, who were enrolled, received tab. ranitidine 150 mg and tab. alprazolam 0.25 mg per oral, on the night prior to surgery. The patients were randomly assigned to one of the two study groups of 30 patients each, GROUP CL: Clonidine Group and GROUP C: Control Group. After confirming the 'Nil per oral' status, the baseline haemodynamic parameters and level of sedation (by Ramsay Sedation score) were recorded. Patients received either clonidine 150 mcg (Group CL) or placebo (Group C) orally with a sip of water on the morning of surgery (approximately 90 minutes before induction of anaesthesia). The observer was blinded about the groups or medications received by the patients. All patients were preloaded with crystalloid 10-15 ml/kg body weight half an hour prior to surgery in the preoperative area.

In the operation room, monitors were attached and baseline parameters such as heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure and peripheral oxygen saturation (SpO_2) were recorded. Level of sedation (sedation score) was assessed by sedation scale: (0 - patient awake and talkative; 1 - patient awake but calm and quiet; 2 - patient drowsy, quiet but easily arousable; 3 - patient asleep). Anaesthetic technique was same for both the study groups. All patients received Inj. Fentanyl 2 micrograms/kg IV as preoperative analgesia just prior to induction. After pre-oxygenation for 3 minutes all the patients were given intravenous Propofol (titrated doses with maximum 3 mg/kg) till the disappearance of eye lash reflex, followed by intravenous Vecuronium 0.1 mg/kg to facilitate tracheal intubation. Patients were ventilated on mask using oxygen in nitrous oxide (50;50) for 3 minutes and with 100% oxygen for 1 minute. Laryngoscopy was carried out with McIntosh curved blade laryngoscope. Oro-tracheal intubation was achieved with cuffed endotracheal tube of appropriate

size. An experienced anaesthetist carried out laryngoscopy and intubation. Study included only those patients in whom intubation was achieved in single attempt within 30 seconds and the surgical stimulation was not allowed until five minute after intubation. Anaesthesia was maintained with 50% oxygen in nitrous oxide + Isoflurane (0.6 - 1.0%) and using closed circuit with circle absorber and controlled Mechanical ventilation AVS 800 ventilator. with Inj vecuronium bromide IV (intermittent regular doses of 0.02 mg/kg). Monitoring of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MAP), oxygen saturation (SPO_2) and end tidal carbon dioxide ($ETCO_2$) was done on a multichannel monitor. Intra-abdominal pressure (IAP) was kept below 14 mm of Hg and monitored throughout.

The tidal volume (VT) and the ventilatory frequency was adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator to maintain end tidal carbon dioxide between 35-45 mmHg. Pneumoperitoneum was created by insufflation of carbon dioxide and operation table was tilted about 15º-20° reverse trendelenburg position. Intra-abdominal pressure (IAP) was not allowed to exceed 15 mmHg throughout the surgical procedure. After pneumoperitoneum, necessary changes in ventilator setting (tidal volume, respiratory rate) were made to maintain normocapnia. Intraoperatively intravenous fluids were administered at the rate of 3 ml/kg/hour. Throughout the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with Inj. propofol infusion as per titration. If duration of surgery lasted for more than 2 hours, then the preoperative analgesia was supplemented with inj. fentanyl 0.5 microgram/kg IV bolus.

At the end of surgery antiemetic Inj. Ondansetron 4mg IV was given. Residual neuromuscular block was reversed by appropriate dose of inj. neostigmine (0.05 mg/kg) and Inj. Glycopyrrolate (8 mcg/kg) intravenously. Trachea was extubated and patients were transferred to recovery room. In the post anaesthesia care unit (PACU) they were monitored for any evidence of complications or adverse events. Diclofenac suppository 100 mg per rectum was given for post-operative analgesia. Inj. tramadol 50 mg IV was used for post-operative analgesia. Duration of surgery was also taken into consideration to have comparable results. Data was collected and parameters were recorded at following points during the study:

Prior to study drug administration; 90 minutes following study drug administration (pre-induction); induction of anaesthesia; at intubation of general anaesthesia; 5 minutes following intubation; 10 minutes following intubation; at skin incision; Just after creation of CO_2 pneumoperitoneum; Immediately after change of position for surgery; every 15 minutes following pneumo-peritoneum till end of surgery; just after desufflation; 5 minutes following desufflation; Just after reversal and extubation; 5 minutes following extubation. The normally distributed data was tabulated as mean and standard deviation. Statistical analysis was done by 'Student t test', and chi-square test. P-value <0.05 was considered statistically significant.

RESULTS

Both the groups were comparable (P >0.005) with respect to age and weight distribution, sex and ASA physical status (Table 1). There was no significant difference in mean duration of surgery between the two groups.

Table 1: Comparison of groups in age (years) and weight (kg).

Parameter	Groups (n = 30)		P value
	Group C	Group CL	
Age (mean±SD)	46.53±10.637	43.33±9.782	0.230
Weight (mean±SD)	58.57±7.846	58.87±5.251	0.862
Sex (n; %)(M:F)	9 (30%); 21 (70%)	15 (50%):15 (50%)	0.114
ASA class (I:II)	10; 20	16;14	0.118
Duration of surgery	115.57±9.100	115.17±8.313	0.860
Dose of propofol	91.17±18.46	78.00±17.93	0.007*

** P<0.005 is highly significant; *P<0.05 is significant.

Table 2: Baseline parameters.

Parameter	Mean±SD		P-value
	Group C	Group D	
HR (beats/min)	75.33±12.366	78.00±8.300	0.331
SBP (mm Hg)	121.20±13.000	121.00±11.847	0.951
DBP (mm Hg)	76.73±9.461	78.93±8.013	0.335
MAP (mm Hg)	91.57±10.663	92.80±8.023	0.615
SpO_2 (%)	99.10±0.403	99.30±0.466	0.081

P<0.005 is highly significant.

Table 3: Heart rate, percentage (%) change from baseline and its comparison between two groups.

Point of time	Mean±SD	% change	P-Value
Group C			
Baseline	75.33±12.366		
Pre-Induction	83.37±11.254	11.53	
Induction	72.70±12.589	-2.88	
Intubation	87.33±12.360	17.62	
5 min after Intubation	83.90±13.399	13.52	
10 min after Intubation	77.00±12.253	4.14	
Skin Incision	76.83±11.905	3.56	
Pneumoperitoneum	80.17±15.494	8.29	
Positioning	84.77±15.415	14.63	
15 min after pneumoperitoneum	83.73±16.471	13.95	
30 min after pneumoperitoneum	83.73±16.619	13.64	
45 min after pneumoperitoneum	84.17±14.837	14.35	
1 hour after pneumoperitoneum	82.17±12.890	10.02	
1 hour 15 min after pneumoperitoneum	82.94±11.371	10.15	
1hour 30 min after pneumoperitoneum	81.08±13.021	11.17	
1hour 45 min after pneumoperitoneum	83.20±8.701	13.37	
Desufflation	81.60±14.345	10.56	
5 min after desufflation	79.20±12.656	7.22	
Reversal and extubation	101.27±18.405	36.20	
5 min after extubation	87.83±14.249	18.41	
Group CL			**w.r.t Group C**
Baseline	78.00±8.300		
Pre-induction	75.10±12.672	-3.84	0.000**
Induction	66.17±13.386	-14.82	0.004**
Intubation	74.77±9.515	-3.44	0.000**
5 Min after intubation	69.90±10.987	-9.87	0.000**
10 Min after intubation	63.03±10.029	-18.87	0.000**
Skin Incision	63.87±10.126	-17.74	0.000**
Pneumoperitoneum	65.57±9.898	-15.48	0.000**
Positioning	69.23±11.808	-10.96	0.000**
15 min after pneumoperitoneum	68.63±9.946	-11.44	0.000**
30 min after pneumoperitoneum	68.10±10.717	-12.02	0.000**
45 min after pneumoperitoneum	68.27±9.762	-11.74	0.000**
1 hour after pneumoperitoneum	69.00±9.692	-11.29	0.000**
1 hour 15min after pneumoperitoneum	68.86±8.896	-11.01	0.001**
1hour 30 min after pneumoperitoneum	69.00±8.965	-11.07	0.007*
1hour 45min after pneumoperitoneum	70.25±4.031	-12.55	0.021*
Desufflation	72.00±10.134	-6.96	0.000**
5 min after desufflation	66.60±8.712	-14.03	0.000**
Reversal and extubation	85.13±9.442	10.10	0.000**
5 min after extubation	72.77±10.461	-6.10	0.000**

** P<0.005 is highly significant; *P<0.05 is significant

The mean baseline values of all the parameters (Table 2) including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) and peripheral arterial oxygen saturation (SpO_2) in both the groups were comparable (P >0.005). Patients in clonidine group (Group CL) had lower HR, SBP and DBP values as compared to control group (Group C) at all points of time after giving the study drug. (P <0.05).

Table 4: Systolic blood pressure, percentage (%) change from baseline and its comparison between two groups.

Point of time	Mean±SD	% change	P-Value
Group C			
Baseline	121.20±13.000		
Pre-induction	134.53±16.228	11.29	
Induction	112.40±12.673	-6.43	
Intubation	152.07±23.400	27.01	
5 min after intubation	128.10±15.253	6.64	
10 min after intubation	119.00±14.360	-0.62	
Skin incision	115.70±15.095	-3.42	
Pneumoperitoneum	132.67±16.612	10.24	
Positioning	135.40±17.563	12.44	
15 min after pneumoperitoneum	147.00±22.348	21.36	
30 min after pneumoperitoneum	141.33±20.709	17.09	
45 min after pneumoperitoneum	140.70±25.296	17.02	
1 hour after pneumoperitoneum	141.54±14.885	17.13	
1 hour 15 min after pneumoperitoneum	138.59±11.286	15.46	
1hour 30 min after pneumoperitoneum	142.92±10.825	17.88	
1hour 45min after pneumoperitoneum	137.40±13.631	21.57	
Desufflation	140.77±21.886	16.89	
5 min after desufflation	140.40±18.582	16.41	
Reversal and extubation	166.10±34.599	37.56	
5 min after extubation	143.30±18.745	18.46	
Group CL			**w.r.t Group C**
Baseline	121.00±11.847		
Pre-Induction	121.30±16.390	0.30	0.000**
Induction	104.70±11.606	-13.11	0.025*
Intubation	120.17±14.638	-0.19	0.000**
5 Min after intubation	106.86±10.885	-11.27	0.000**
10 Min after intubation	102.97±11.199	-14.13	0.001**
Skin Incision	104.17±11.092	-13.16	0.012*
Pneumoperitoneum	112.87±7.789	-5.98	0.000**
Positioning	119.67±13.530	-0.39	0.001**
15 min after pneumoperitoneum	123.43±11.637	2.68	0.000**
30 min after pneumoperitoneum	125.77±12.580	4.54	0.001**
45 min after pneumoperitoneum	124.17±12.573	3.23	0.003**
1 hour after pneumoperitoneum	124.97±10.985	3.33	0.000**
1 hour 15min after pneumoperitoneum	128.71±8.928	5.65	0.010*
1hour 30 min after pneumoperitoneum	130.67±15.257	9.03	0.103
1hour 45min after pneumoperitoneum	131.00±17.378	1.16	0.143
Desufflation	130.23±14.075	8.33	0.000**
5 min after desufflation	122.37±13.730	1.66	0.000**
Reversal and extubation	137.77±15.192	14.46	0.000**
5 min after extubation	118.07±12.423	-1.82	0.000**

** P<0.005 is highly significant; *P<0.05 is significant

Percent change from baseline in HR and blood pressure at different points of time was significantly high in control group than in clonidine group (Table 3 to 6). Seven out of 30 patients (23%) in group C required intravenous propofol infusion (dose in the range of 2 - 6 mg/kg/hr) intra-operatively to attenuate severe hypertension (mean arterial pressure of more than 20% above baseline) following pneumo-peritonium, while no patient from Group CL required intra-operative propofol infusion.

Table 5: Diastolic blood pressure, percentage (%) change from baseline and comparison between the two groups.

Point of time	Mean ± SD	% change	P-Value
Group C			
Baseline	76.73±9.461		
Pre-induction	79.07±10.632	4.02	
Induction	67.10±11.424	-11.32	
Intubation	89.10±20.051	18.47	
5 Min after intubation	74.40±10.718	-1.65	
10 Min after intubation	72.67±11.155	-3.77	
Skin incision	69.60±12.821	-7.84	
Pneumoperitoneum	80.70±11.145	6.91	
Positioning	86.43±11.383	14.22	
15 min after pneumoperitoneum	88.93±13.240	17.09	
30 min after pneumoperitoneum	87.23±12.662	15.33	
45 min after pneumoperitoneum	87.83±9.649	16.09	
1 hour after pneumoperitoneum	87.00±5.437	13.69	
1 hour 15min after pneumoperitoneum	87.65±9.103	15.61	
1hour 30 min after pneumoperitoneum	85.17±9.331	10.28	
1hour 45min after pneumoperitoneum	81.20±8.672	10.30	
Desufflation	84.97±11.385	12.51	
5 min after desufflation	84.07±8.948	10.97	
Reversal and extubation	101.97±13.515	34.75	
5 min after extubation	85.23±10.457	12.59	
Group CL			**w.r.t Group c**
Baseline	78.93±8.013		
Pre-induction	74.17±11.528	-5.78	0.011*
Induction	64.77±10.631	-17.02	0.218
Intubation	72.87±11.602	-6.94	0.000**
5 min after intubation	63.73±8.542	-18.59	0.000**
10 min after intubation	62.37±9.394	-20.19	0.000**
Skin incision	62.80±7.854	-19.79	0.009*
Pneumoperitoneum	70.57±8.365	-9.74	0.000**
Positioning	74.60±12.224	-4.35	0.001**
15 min after pneumoperitoneum	74.67±9.675	-4.63	0.000**
30 min after pneumoperitoneum	75.60±11.096	-3.11	0.001**
45 min after pneumoperitoneum	76.07±10.521	-2.73	0.000**
1 hour after pneumoperitoneum	76.59±10.739	-2.75	0.000**
1 hour 15 min after pneumoperitoneum	79.48±8.465	1.55	0.009*
1 hour 30 min after Pneumoperitoneum	78.75±11.153	1.44	0.227
1 hour 45min after Pneumoperitoneum	73.50±8.505	0.70	0.555
2 hours after pneumoperitoneum	66.00	10.00	0.012*
Desufflation	78.73±9.150	0.61	0.000**
5 min after desufflation	73.83±9.646	-5.63	0.000**
Reversal and extubation	83.23±10.395	6.47	0.000**
5 min after extubation	73.53±9.909	-6.06	0.011*

** P<0.005 is highly significant; *P<0.05 is significant

Table 6: Mean arterial pressure, percentage (%) change from baseline and its comparison between two groups.

Point of time	Mean±SD	% change	P-Value
Group C			
Baseline	91.57±10.663		
Pre-Induction	97.43±11.699	6.92	
Induction	81.83±9.724	-9.71	
Intubation	110.03±18.462	22.24	
5 Min after intubation	88.80±18.092	-2.25	
10 Min after intubation	87.27±11.073	-3.42	

Skin Incision	80.57±18.715	-10.28	
Pneumoperitoneum	97.70±11.665	7.95	
Positioning	101.73±12.348	12.26	
15 min after pneumoperitoneum	107.57±14.853	18.06	
30 min after pneumoperitoneum	104.57±13.828	15.17	
45 min after pneumoperitoneum	106.10±11.748	16.90	
1 hour after pneumoperitoneum	104.25±7.897	14.09	
1 hour 15min after pneumoperitoneum	103.47±8.697	14.14	
1hour 30 min after pneumoperitoneum	102.50±9.596	11.10	
1hour 45min after pneumoperitoneum	99.00±9.798	12.72	
Desufflation	103.33±13.299	14.16	
5 min after desufflation	102.37±10.794	12.78	
Reversal and extubation	125.77±14.635	38.61	
5 min after extubation	101.73 ± 20.445	12.01	
Group CL			**w.r.t Group C**
Baseline	92.80±8.023		
Pre-induction	89.33±12.058	-3.69	0.000**
Induction	76.37±9.974	-17.05	0.040*
Intubation	88.10±11.816	-.4.62	0.000**
5 Min after intubation	77.27±8.952	-16.38	0.002**
10 Min after intubation	75.43±8.993	-18.12	0.000**
Skin Incision	76.10±8.168	-17.49	0.145
Pneumoperitoneum	83.83±7.212	-9.02	0.000**
Positioning	89.00±11.937	-3.38	0.000**
15 min after pneumoperitoneum	90.23±9.284	-2.25	0.000**
30 min after pneumoperitoneum	91.53±10.368	-0.80	0.000**
45 min after pneumoperitoneum	90.93±9.913	-1.42	0.000**
1 hour after pneumoperitoneum	91.69±9.820	-1.20	0.000**
1 hour 15min after pneumoperitoneum	93.52±8.761	0.70	0.003**
1hour 30 min after pneumoperitoneum	94.75±11.940	2.80	0.181
1hour 45min after pneumoperitoneum	92.50±11.328	0.51	0.434
2hours after pneumoperitoneum	82.00	7.89	0.003**
Desufflation	94.17±9.563	2.05	0.000**
5 min after desufflation	88.93±10.211	-3.71	0.000**
Reversal and extubation	100.53±10.686	8.90	0.001**
5 min after extubation	87.93±10.147	-4.87	0.000**

** P<0.005 is highly significant; *P<0.05 is significant

Table 7: End tidal carbon dioxide ($EtCO_2$) (mmHg).

Point of time	Mean±SD		P value
	Group C	Group CL	
5 min after intubation	35.60±2.010	35.33±1.493	0.562
10 min after intubation	35.47±1.795	35.23±1.888	0.626
Skin Incision	35.60±1.476	35.53±1.613	0.868
Pneumoperitoneum	35.83±1.859	36.57±1.906	0.137
Positioning	37.00±2.435	37.60±1.694	0.273
15 min after pneumoperitoneum	37.97±2.385	38.67±1.493	0.178
30 min after pneumoperitoneum	38.30±2.818	39.13±2.713	0.248
45 min after pneumoperitoneum	38.90±2.107	38.63±1.474	0.572
1 hour after pneumoperitoneum	39.75±3.247	38.55±1.572	0.085
1 hour 15 min after pneumoperitoneum	38.82±2.215	39.14±1.769	0.624
1hour 30 min after pneumoperitoneum	39.33±2.188	39.58±0.900	0.718
1 hour 45 min after pneumoperitoneum	40.80±1.304	39.50±1.291	0.179
Desufflation	38.27±2.303	38.03±1.974	0.675
5 min after desufflation	36.70±2.292	36.77±2.063	0.906
Reversal and extubation	36.93±2.434	36.83±2.437	0.874

** P<0.005 is highly significant; *P<0.05 is significant

Table 8: Intra-abdominal pressure (IAP) (mm Hg).

Point of time	Mean±SD		P-value
	Group C	Group CL	
Pneumoperitoneum	11.27±1.760	11.03±1.629	0.596
Positioning	11.23±1.524	10.90±1.373	0.377
15 min after pneumoperitoneum	10.87±1.570	11.27±1.337	0.292
30 min after pneumoperitoneum	10.77±1.716	11.03±1.497	0.524
45 min after pneumoperitoneum	10.93±1.507	11.37±1.564	0.279
1 hour after pneumoperitoneum	10.96±1.488	11.17±1.227	0.568
1 hour 15min after pneumoperitoneum	10.88±1.728	11.75±1.372	0.097
1hour 30 min after pneumoperitoneum	11.17±1.403	11.42±1.165	0.640
1hour 45min after pneumoperitoneum	11.80±1.304	11.25±0.957	0.505

** P<0.005 is highly significant; *P<0.05 is significant.

No significant complications like severe hypotension, brady arrhythmias, ECG changes; nausea, vomiting, dry mouth, etc. were seen in either group.

DISCUSSION

The use of laparoscopy in surgery has increased greatly during the recent years with the technique becoming an important diagnostic and therapeutic modality for general surgeons. Although it is visually 'minimally invasive' to the patient, the intra-operative requirements of laparoscopic surgery produce significant physiological changes, which present the anaesthetist with many challenges. Carbon dioxide remains the most commonly used gas for creating pneumoperitonium during laparoscopy. However, the chief drawback is its significant vascular absorption across the peritoneum, leading to hypercapnia and intravascular embolization. Hypercapnia by itself activates the sympathetic nervous system leading to sudden increase in blood pressure, heart rate, myocardial contractility and arrhythmias'. It also sensitizes the myocardium to catecholamines particularly when volatile anaesthetic agents are used. The extent of cardiovascular changes associated with the creation of pneumoperitoneum is multifacotorial and depends on the intra-abdominal pressure (IAP) attained, volume of carbon dioxide absorbed, patients intravascular volume, ventilatory techniques, surgical conditions and anaesthetic agents used. However, the critical determinants of cardiovascular function during laparoscopy are the IAP and patient position. These physiological changes, can be detrimental especially in elderly and haemodynamically compromised patients.[19,20]

Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum.[21] Clonidine, a centrally acting alpha-2 adrenergic agonist, which was first introduced into clinical practice as an antihypertensive medication, has been recently used for anaesthetic premedication, providing sedative, anxiolytic, and analgesic effects. Clonidine also attenuates hypertension, tachycardia, and nor-epinephrine release in response to stress induced by anaesthetic and surgical procedures.[22] Even in a recent editorial, Longnecker who referred to marked haemodynamic responses in the peri-operative period as 'alpine anaesthesia', had suggested that clonidine may modify the valleys and peaks during this period.

At present, the only clinically available Alpha-2 adrenergic agonist for oral use in our country is Clonidine.[24] Though mainly used as an anti-hypertensive agent, it has many properties of an ideal premedicant and also has beneficial effects on haemodynamics during stressful conditions like laryngoscopy and endotracheal intubation Clonidine, an imidazoline derivative, is well absorbed when given orally and is completely used in the body. The pharmacological effect of Clonidine appears in 1.5- 2 hours, with the peak level in 3 hours.[23,24]

This double blind prospective randomized study was undertaken to evaluate effectiveness of oral Clonidine as a pre-anaesthetic medication and as a drug to attenuate the peri-operative haemodynamic alterations during laparoscopic cholecystectomy.

The dose of oral Clonidine as premedication in our study was approximately in the dose range of 2.5 to 3.0 microgram per kilogram (mcg/kg). Dose of oral clonidine, in various other studies ranged from 2 to 5 mcg/kg. Aho et al had compared 3 mcg/kg and 4.5 mcg/kg oral clonidine for suppression of haemodynamic response to pneumoperitoneum and they observed, rise in blood pressure and heart rate was less in both the groups but 4.5 mcg/kg of clonidine produced greater fall in MAP before induction.[25] So they recommended 3 mcg/kg of clonidine for perioperative haemodynamic stability. Similarly, Sung et al and Yu et al, observed haemodynamic stability during pneumoperitoneum with 150 mcg oral Clonidine.[26,27] Lentschener C et al in their study of 20 ASA I women undergoing laparoscopic surgery used 10 ml/ kg Ringer lactate solution to preload their patients.[28] They concluded that intra-operative haemodynamic and/or humoral changes would not be observed in association with laparoscopic surgery provided that normo-volemia is continuously maintained.

All patients in our study were preloaded with crystalloid 5-10 ml/kg body weight half an hour prior to surgery in the preoperative room so as to prevent the haemodynamic changes during pneumoperitoneum. The anaesthesia technique, induction, maintenance of general anaesthesia, reversal and extubation was same for both the study groups as described in materials and methods.

Isoflurane in 50% nitrous oxide in oxygen was preferred for maintenance of general anaesthesia over other inhalational agents as it ensues least sensitivity to arrhythmias in the presence of increased catecholamines due to hypercapnia with minimal postoperative nausea vomiting and has less myocardial depressant effects. Nitrous oxide was used to provide peri-operative analgesia and to reduce the requirements of inhaled or intravenous anaesthetics.

All patients were mechanically ventilated with 50% oxygen in nitrous oxide + isoflurane (0.6-1.0%) using circle absorber system and AVS 800 anaesthesia ventilator. Following pneumoperitoneum with carbon dioxide, the tidal volume (VT) and the ventilatory frequency were adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator to maintain end tidal carbon dioxide between 35-45 mm Hg (Table 7).

The induction of pneumoperitoneum with the patient in the horizontal position rather than head up or head down position can decrease the severity of these haemodynamic changes. The head up position decreases venous return and cardiac output leading to decrease in mean arterial pressure and cardiac index, as well as an increase in peripheral and pulmonary vascular resistance.

Intra-abdominal pressure (IAP) was limited to below 15 mmHg. To avoid the confounding effect of IAP on haemodynamics, the mean IAP was also monitored and was found to be comparable (P >0.005) in both the groups throughout the procedure (Table 8). Recent studies recommend a moderate to low IAP (<12 mm Hg) as it limits the alteration in splanchnic perfusion. Ishizaki et al, evaluated the safe limit of IAP during laparoscopic surgery and reported significant fall in cardiac output at 16 mm Hg of intra-abdominal pressure.[29] Cunningham et al and Dorsay et al in a similar study observed that there was no significant change in ejection fraction (LVEF) up to 15 mmHg of intra-abdominal pressure.[30,31] Creation of pneumoperitoneum at an IAP of 15 mmHg reduces compliance and increases peak inspiratory and mean airway pressures, which quickly return to the normal values after deflation. Higher IAP reduces the thoracic compliance more and can cause pneumothorax and pneumomediastinum owing to the increase in alveolar pressures. Cardiopulmonary effects are proportional to the magnitude of IAP attained during laparoscopy with significant changes occuring at pressures greater than 12 mmHg. Based on all these observations the current recommendation is to monitor intra-abdominal pressure and to keep it as low as possible. Considering all these facts intra-abdominal pressure was kept below 15 mmHg. to decrease the risk of potentially significant physiological changes.

Nausea and vomiting are particularly troublesome after laparoscopic surgery so prophylactic anti-emetic like IV Ondansetron 4 mg was given. Pain following laparoscopic surgery consists of early transient vagal abdominal and shoulder discomfort due to peritoneal irritation by residual carbon dioxide. Complete removal of insufflating gas is essential on the completion of procedure. Pain from the puncture wounds of the trocars is generally mild because the wounds are small and are produced without the cutting of muscle fibres. We used Diclofenac suppository 100 mg rectally and Inj. tramadol 50 mg IV for post-operative analgesia. Inspite of maintaining normocapnia and keeping intra-abdominal pressure below15 mmHg significant rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed in Group C.

Heart rate (HR)

During intergroup comparison, it was seen that mean HR in Group CL was significantly low (P <0.05) at all points after premedication with Clonidine. Though the HR in group CL increased above baseline after reversal and extubation, this rise in HR was significantly less as compared to that in Group C (P <0.001). The decrease in HR after clonidine could be due to the reduction of the sympathetic outflow, the simultaneous increase of central parasympathetic tone and the influence of Clonidine on neurons which receive baroreceptor afferents. Similar changes were observed by Dipak L et al. Yu HP et al however, reported that pre-medication with 150 mcg clonidine resulted in an unchanged mean RR interval compared with placebo (P < 0.05).[27,32]

Blood pressure

In group CL after a slight fall following premedication (by 3.69% from baseline) and more during induction (by 17.05% from baseline), MAP persistently below baseline even during intubation, surgical incision, creation of pneumoperitoneum and till 1 hour 15 minutes following creation of pneumoperitoneum where the MAP was just above baseline by 0.70%. MAP showed maximum rise at 2 hours following pneumoperitoneum (7.89% above baseline) and during reversal and extubation (8.90% above baseline). During inter group comparison it is clearly noticed that MAP values in both the groups were significantly different (P <0.05), MAP being significantly low in Group CL at all points when compared to the corresponding values in Group C.

The slight fall in SBP, DBP and MAP following the induction of general anaesthesia in the control group (Table 4-6) may be due the effects of propofol and fentanyl. The exaggerated fall in blood pressure in

Clonidine group could be due to potentiation of hypotensive effects of propofol and fentanyl by Clonidine. Also the exaggerated rise in blood pressure recorded during laryngoscopy and intubation was less in group CL than in group C which could be explained by the central and peripheral attenuation of sympathetic outflow by clonidine. The haemodynamics changes observed during and after creation of pneumoperitoneum were due to increase in systemic vascular resistance (SVR) which is considered to mediated by mechanical and neuro-humoral factors and are further aggravated by head up position during laparoscopic cholecystectomy. The return of haemodynamic variables to baseline is gradual and takes several minutes suggesting the involvement of neuro-humoral mediators like catecholamines, vasopressin, cortisol, renin and angiotensin which are all released during pneumoperitoneum.[16] As clonidine is known to reduce neuro-humoral secretion secondary to stress induced sympathoadrenal discharge, the changes in haemodynamic variables were significantly less ($P < 0.05$) in group CL when compared to those in the control group. Our findings regarding changes in SBP, DBP and MAP were corroborating with study of Goel S and Malek et al, Joris et al, Aho et al, Sung et al, and Laisalmi et al.[24-27, 33,34]

In our study it was also observed (Table 1) patients in Group CL required significantly low doses of propofol (78.00±17.93 mg) during induction of general anaesthesia as compared to those in Group C (91.17±18.46 mg) ($P < 0.05$). This suggests that Clonidine premedication (150mcg) reduced the requirement of propofol by 15% in group CL. Imai Y, Mammoto T, et al who investigated the effects of pre-anaesthetic oral clonidine (150 mcg) on Propofol/Fentanyl anaesthesia, reported a reduction of 40% in the propofol requirements. Similar findings were also reported by Hideyuki Higuchi et al, Fehr et al.[35-37]

Patients in group CL were significantly more sedated than the patients in group C, ($P < 0.005$) which could be explained by the action of clonidine on sleep promoting pathways and locus coeruleus. However, with 150 mcg of clonidine the mean sedation scores in clonidine group were never more than 2 before induction i.e the patients were 'awake but uncommunicative'(as per the sedation score). as well as after the patients were extubated.

Imai Y et al reported that pre-anaesthetic oral Clonidine (150 mcg) significantly reduced VAS scores for anxiety, however it did not alter the VAS score for sedation significantly. They concluded that low dose of oral clonidine (approximately 3mcg/kg) is a safe medication for Propofol anaesthesia, and it is important to note that this dose of clonidine exerted these beneficial actions without significant preoperative sedation. U.A. carabine et al, reported that sedation in Clonidine increased with increasing doses.[35,38] Seven patients from Group C required intravenous Propofol infusion (2-6 mcg/kg/hr) for the control of intra operative haemodynamics. However, none of the patients in group CL required intra operative Propofol infusion. Also the cost of Clonidine is low enough compared with that of Propofol, and pre-anaesthetic medication of oral Clonidine reduces the cost of Propofol thereby resolving this problem.

To conclude, premedication with 150 mcg oral Clonidine has been found to be relatively safe as well as effective method that provides stable haemodynamics and attenuates the stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Oral Clonidine (150mcg) can reasonably be recommended as premedicant for all laparoscopic procedures in otherwise healthy patients belonging to ASA physical status I and II. However further study is required to find out its efficacy in patient with compromised cardiovascular system.

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