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Comparison of Haemodynamic Response among Patients Posted for Laparoscopic Cholecystectomy with or without Oral Clonidine as Premedication- A Prospective Comparative Study

Alka Koshire[1], Priyanka Satyanaryan Kandikatla[2] and Hemant Pawar[3*]

[1]Professor and Head, Department of Anaesthesiology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik – 422003, Maharashtra, India
[2]Former PG Resident, Department of Anaesthesiology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik – 422003, Maharashtra, India
[3]Associate Professor, Department of Anaesthesiology, Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik – 422003, Maharashtra, India

Abstract

Background: Laparoscopic cholecystectomy is one of the most commonly performed surgeries and has now being recognized as the gold standard for the treatment of cholelithiasis. It is known fact that laparoscopy has several advantages due to creation of pneumoperitoneum during the surgical procedure which is responsible for several deleterious haemodynamic and cardiorespiratory changes. Thus, our present study was designed tostudy of haemodynamic response to oral clonidine as pre medication in laparoscopic cholecystectomy. **Methods:** In this prospective comparative study, 128 patients between the age group of 18-60 years, belonging to ASA 1 and ASA 2 categories scheduled for elective laparoscopic cholecystectomy under general anaesthesia were categorized into 2 groups as Group C and Group NC with 64 patients in each group. Patients in Group C received premedication with oral clonidine 150µg 90 minutes prior to surgery and Group NC did not receive oral clonidine 150µg. The two groups were compared with respect to heart rate, systolic and diastolic blood pressure and post operative complications. **Results:** There was significant increase in all the haemodynamic variables in group C as compared to group NC where the variables remained close to baseline while the patients in Group C showed less post operative complications as compared to NC group. **Conclusion:** Oral premedication with clonidine helps in blunting the haemodynamic response to pneumoperitoneum and also has less post operative complications.

Keywords: Clonidine, General Anaesthesia, Haemodynamic Response, Laparoscopic Cholecystectomy

1. Introduction

In early 1990; laparoscopy was performed very commonly in gynaecology, mostly for relatively short duration and simple procedures, usually for diagnostic purposes or for tubal ligation. Phillipe Mouret was the one who introduced laparoscopic cholecystectomy in 1897[1], for minor surgeries. In order to combat the additional hemodynamic stress caused by pneumoperitoneum with CO_2 insufflation and also patient's position, it was important to develop proper laparoscopic technique[2,3]. Use of α_2 agonist as a premedicant helps to blunt the adverse haemodynamic response during laparoscopy[4].

Haemodynamic changes during laparoscopy result from the combined effect of pneumoperitoneum, position of the patient, type of anaesthesia and hypercapnia which occurs secondary to absorbed CO_2 along with pathophysiological changes, reflex increase of vagal tone and arrhythmias may develop[5].

2. Aims and Objectives

- To study the haemodynamic response to tablet Clonidineduring laryngoscopic endotracheal intubation and during surgery in patients undergoing laparoscopic cholecystectomy.

**Author for correspondence*

- To study the immediate post-operative complications of Tablet Clonidine in study participants.

3. Material and Methods

This prospective comparative study was conducted in the Department of Anaesthesiology in tertiary health care centre attached to Dr Vasantrao Pawar Medical College, from August 2017 to December 2019 with due permission from ethics committee. A total number of 128 patients (calculated by formula mean of differences) scheduled for laparoscopic cholecystectomy were divided into 2 groups:

Group C (n=64)- Receiving Tablet Clonidine 150 µg orally.

Group NC (n=64)- Not Receiving Tablet Clonidine 150 µg orally included in the study. During study, alternate patient posted for laparoscopic cholecystectomy received Tab clonidine 150µg. Written informed consent was obtained.

After preliminary screening, the patients posted for laparoscopic surgeries were thoroughly examined clinically one day before operation for pre-anaesthetic evaluation. Routine investigations such as blood haemoglobin, serum urea and creatinine levels, blood sugar. Serum electrolytes, liver function tests, HBsAg, urine analysis, X-ray chest (PA view), electrocardiography and cardiological evaluation reports were reviewed and recorded. Resting blood pressure and heart rate were recorded to serve as a baseline value. The purpose and procedure of the study was explained. Patients were selected based on inclusion and exclusion criteria.

3.1 Inclusion Criteria

- All patients undergoing laparoscopic cholecystectomy under General anaesthesia.
- ASA grade 1 and 2. (American Society of anaesthesiologist).
- Age between 18 to 60 years irrespective of gender.
- Informed consent.

3.2 Exclusion Criteria

- During pregnancy and lactation.
- Patients with history of hypertension.
- Patients with recent myocardial infarction, AV heart block, sinus bradycardia.
- Patients having any respiratory disease/chronic kidney disease.
- Patients with psychiatric illness like depression.

3.3 Pre-Operative Preparations

All the patients were kept overnight fasting after 10 p.m.

On the day of surgery patients received Tab. clonidine in the pre-operative room, around 60-90 minutes prior to surgery. The drug was administered with sip of water. On arrival in the operation theatre monitoring started and reading were recorded.

3.4 Pre-medication

All patients were premedicated with Inj., Glycopyrrolate 0.2 mg IV, Inj. Ondansetron 4 mg IV and Inj. fentanyl 1-2 µg/ kg IV. Tab clonidine 150 µg was given with the sip of water about 60-90 min prior to induction of anaesthesia.

3.5 Induction, Intubation and Maintenance

After pre-oxygenating the patients with 100% O_2 for 3 min, anaesthesia was induced with Inj. Propofol 1-2 mg/kg of body weight IV. Laryngoscopy and tracheal intubation with an appropriately sized cuffed endotracheal tube was facilitated under the effect of inj. Succinylcholine 1.5-2mg/kg IV. Anaesthesia was maintained with nitrous oxide 50%, with oxygen 50% and isoflurane. Ventilation was controlled with inj vecuronium bromide (0.08-0.1mg/kg) and maintained the End Tidal Carbon Dioxide ($ETCO_2$) between 30 40 mmHg. Intra-operatively the following vital parameters were monitored and recorded

- Continuous ECG.
- Heart rate.
- Non-invasive blood pressure (NIBP) including systolic, diastolic and mean arterial pressure.
- Continuous intraperitoneal pressure measurement (during pneumoperitoneum) which was maintained at 10-15 cm of H_2O.

Pneumoperitoneum was created by insufflation of carbon dioxide and operation table was tilted about 15°. Trendelenburg positions or reverse trendelenburg position. Intra-abdominal pressure (IAP) was not allowed to exceed 15 cm of H_20 throughout the surgical procedure. After pneumoperitoneum, necessary changes in ventilator settings (tidal volume and respiratory rate) were made to maintain normocapnia. Rise of MAP (greater than 20% of baseline) was treated with Inj. nitroglycerine by an infusion pump. The dose was titrated to maintain the

MAP within 20% of baseline value. Fall of MAP (greater than 20% of baseline) was treated with an Inj. Ephedrine 5 mg IV bolus as and when necessary. Fall in HR less than 55 beats per minute was treated with Inj. atropine 0.6 mg and repeated if necessary. Systemic arterial pressure including the systolic, diastolic, MAP. Pulse rate, were recorded at the following points of time

- Before premedication.
- Before induction.
- During intubation.
- After intubation.
- Before pneumoperitoneum.
- 15 minutes after pneumoperitoneum.
- 30 minutes after pneumoperitoneum.
- 45 minutes after pneumoperitoneum
- 60 minutes after pneumoperitoneum
- Release of CO_2.
- Extubation.
- 15 minutes after extubation.

At the end of the operative procedure, residual effect of the muscle relaxant was reversed by Inj Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 8 µg/kg intravenously. Patient was extubated and transferred to recovery room. Patients were observed for any complications during this

Table 1. Pulse rate changes in clonidine (study) and non-clonidine group (mean±SD)

Pulse rate(beats/min)	Group C	Group NC	p-value
Before premedication	80.78±4.67	82.91±4.65	0.000
Before induction	83.63±4.52	88.44±4.67	0.000
During intubation	87.63±4.81	107.79±5.19	0.051
After intubation	82.94±3.74	98.22±5.92	0.119
Before pneumoperitoneum	80.94±3.62	94.94±5.93	0.011
15 minutes after pneumoperitoneum	85.19±3.26	105.69±4.07	0.000
30 minutes after pneumoperitoneum	82.50±2.83	103.09±4.01	0.000
45 minutes after pneumoperitoneum	80.47±2.78	99.84±4.11	0.000
60 minutes after pneumoperitoneum	78.31±2.92	97.30±4.38	0.000
Release of CO_2	76.19±2.93	84.25±4.71	0.000
Extubation	86.72±3.39	102.50±4.58	0.000
15 minute after extubation	83.69±2.92	100.63±4.69	0.000

*Significant p-value<0.05

Table 2. SBP changes in clonidine (study) and non-clonidine group (mean± SD)

SBP (mmHg)	Group C	Group NC	p-value
Before premedication	127.16±3.80	124.09±5.55	0.000
Before induction	129.91±3.89	126.34±5.49	0.060
During intubation	133.31±3.62	139.53±2.75	0.000
After intubation	130.00±3.49	137.38±2.94	0.000
Before pneumoperitoneum	127.88±3.67	134.63±2.71	0.000
15 minutes after pneumoperitoneum	132.31±3.21	141.94±3.60	0.000
30 minutes after pneumoperitoneum	129.03±3.11	139.97±3.20	0.000
45 minutes after pneumoperitoneum	126.97±4.46	137.97±3.03	0.000
60 minutes after pneumoperitoneum	125.44±5.78	135.94±2.96	0.000
Release of CO_2	124.25±4.24	125.66±4.96	0.087
Extubation	134.47±2.89	140.94±2.74	0.000

*Significant p-value<0.05

period for hypotension, apnea, bradycardia, coughing, nausea, vomiting and shivering.

4. Observation and Results

It can be seen from Table 1 that there was statistically significant difference in pulse rate at all times from before intubation to extubation.

Table 2 shows the systolic blood pressure changes in clonidine (study) and non-clonidine group showed statistical significance in all times except before induction and during release of co_2. In clonidine (study) group, mean SBP before induction was 129.91±3.89mmHg whereas in non-clonidine group it was 126.34±5.49mmHg; the difference was not statistically significant.

While after the release of carbon pneumoperitoneum, the mean SBP was 124.25±4.24 mmHg in clonidine (study) group and 125.66±4.96 mmHg in non-clonidine group; the difference was not statistically significant.

Table 3 shows the diastolic blood pressure changes in clonidine (study) and non-clonidine group at all times the difference highly statistically significant.

Table 4 shows the mean arterial pressure changes in clonidine (study) group and non- clonidine group before

Table 3. DBP changes in clonidine (study) and non- clonidine group (mean± SD)

DBP (mmHg)	Group C	Group NC	p-value
Before premedication	82.56±2.56	80.84±3.47	0.002
Before induction	84.63±3.10	81.91±3.39	0.000
During intubation	86.19±2.95	91.94±2.96	0.000
After intubation	82.91±2.39	90.50±3.02	0.000
Before pneumoperitoneum	81.78±2.02	88.06±3.60	0.000
15 minutes after pneumoperitoneum	85.13±2.19	92.67±2.94	0.000
30 minutes after pneumoperitoneum	82.47±1.84	91.16±2.78	0.000
45 minutes after pneumoperitoneum	81.38±1.88	89.94±2.67	0.000
60 minutes after pneumoperitoneum	80.09±2.70	88.03±3.29	0.000
Release of CO_2	79.34±2.08	80.66±2.96	0.004
Extubation	90.03±3.66	92.19±2.73	0.000
15 minutes after extubation	83.81±2.41	91.28±3.57	0.000

*Significant p-value<0.05

Table 4. Mean arterial blood pressure changes in clonidine (study) and non-clonidine group (mean±SD)

MAP (mmHg)	Group C	Group NC	p-value
Before premedication	97.36±2.19	95.10±3.39	0.000
Before induction	99.69±2.79	96.70±3.46	0.000
During intubation	101.92±2.63	107.80±2.28	0.000
After intubation	98.58±2.21	105.96±2.45	0.000
Before pneumoperitoneum	97.22±2.21	103.58±2.67	0.000
15 minutes after pneumoperitoneum	100.77±2.08	109.03±2.82	0.000
30 minutes after pneumoperitoneum	97.91±1.87	105.85±12.29	0.000
45 Minutes after Pneumoperitoneum	96.66±2.22	106.04±2.42	0.000
60 Minutes after Pneumoperitoneum	95.41±2.45	103.94±2.88	0.000
Release Of Co2	94.21±2.88	95.57±2.79	0.004
Extubation	104.71±2.71	108.30±2.35	0.000
15 Minutes after extubation	99.86±1.86	107.73±2.94	0.000

*Significant p-value<0.05

Table 5. Peri-operative adverse events in clonidine (study) and non-clonidine group

Complications	Group C (%)	Group NC (%)
Hypertension	None	10(15)
Hypotension	3(5)	None
Bradycardia	8(12.5)	None
Vomiting	None	3(5)
Shivering	4(6.25)	9(14)

premedication, before induction, during intubation, after intubation, before pneumoperitoneum,15 mins after pneumoperitoneum, 30 min after pneumoperitoneum, 45 Minutes after Pneumoperitoneum, 60 Minutes after pneumoperitoneum, release of $Co_{2,}$extubation and 15 mins after extubation.

It was found that at all times it showed statistical significance.

Table 5 shows preoperative adverse events in clonidine (study) and non-clonidine group. It can be seen that none of the patients in clonidine (study) group developed hypertension.10% in non-clonidine group developed hypertension. Hypotension developed in 3% of patients in the clonidine (study) group whereas there was no incidence of hypotension in non-clonidine group. Bradycardia developed in 8% of patients in clonidine (study) group, none of the patients in non-clonidine group had bradycardia. None of the patients in clonidine (study) group had vomiting whereas 3% of patients in non-clonidine group had vomiting. Shivering was present in 4% of patients in clonidine (study) group and 9% of patients in non-clonidine group.

5. Discussion

Since the introduction of first laparoscopic cholecystectomy procedure, laparoscopy has expanded impressively in scope and volume. Pneumoperitoneum and different patient positions required for laparoscopic surgery results in various pathophysiological changes. The increase in Intra-Abdominal Pressure (IAP) produced by pneumoperitoneum, results in direct mechanical effects on blood flow. 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. 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. 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.

Kapil Arora and Shivinder Singh[6] used 150µg oral clonidine to study the clinical efficacy of oral clonidine premedication in patients undergoing laparoscopic cholecystectomy. Sung et al.,[7] observed haemodynamic stability during pneumoperitoneum with 150 mcg oral Clonidine.

In our study it was found that mean pulse rate was comparatively lower in clonidine (study) group as compared to non-clonidine group.In clonidine group(study), the mean pulse rate remained close to baseline values. The mean SBP in non-clonidine group ranged from 124.09-141.94mmHg. The minimum SBP in non-clonidine group was 114mmHg whereas maximum SBP was 146mmHg. The mean SBP, DBP and MAP remained almost stable in the clonidine as compared to non-clonidine group. Singhal SK, Kaur K, Arora P et al.,[8] compared the effects of oral clonidine and gabapentin as premedicant in obtunding hemodynamic response to laryngoscopy and intubation in normotensive patients undergoing elective surgery.

It was found that none of the patients in the clonidine group developed hypertension whereas 10% in the non-clonidine group developed hypertension. Developed in 5% of patients in the clonidine group whereas there was no incidence of hypotension in the non-clonidine group. This was mainly due to suppression of the sympathetic drive and decrease in release of catecholamines.

Bradycardia developed in 8% of patients in clonidine (study) group, none of the patients in non-clonidine group had bradycardia.

In the present study none of the patients in the clonidine (study) group had vomiting whereas 3% of patients in the non-clonidine group had vomiting.

Similar findings were reported by Kalra et al.,[9] who found that 25% of the patients in placebo group suffered from nausea and/or vomiting while only 6.89% of patients receiving clonidine has such episodes.

In the present study shivering was present in 4% of patients in clonidine (study) group and 9% of patients in non-clonidine group.

Similar findings were reported by Chandra Shekaraiah et al.,[10] who found that incidence of shivering was seen in 70% of patients in placebo group as compared to none in the clonidine group.

The findings of our study are similar to the findings of Nicolaou et al.,[11] concluded that clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centre. Thus, he opined that tab., clonidine can be used as an effective agent for inhibition of preoperative shivering.

6. Conclusion

To conclude, premedication with 150 mcg oral Clonidine has been found tobe relatively safe as well as effective method that provides stable haemodynamics and attenuates the stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

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