Comparative Study of Oral Clonidine Versus Intravenous Esmolol In Attenuation of Hemodynamic Changes During Laparoscopic Surgeries

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Abstract :

Background and aim : Laparoscopy is the essence of modern surgery but the carbon dioxide pneumoperitoneum used there in significantly impairs patient's cardiopulmonary function.Both Clonidine and Esmolol are known to inhibit catecholamine and vasopressin release and attenuate hemodynamic response to pneumoperitoneum.This randomized, double blinded study was carried out to assess which agent attenuates hemodynamic stress response to pneumoperitoneum better in laparoscopic surgeries. **Materials and methods :** A total of 60 patients scheduled to undergo laparoscopic surgeries were randomly assigned into two groups: Group A: received 150µg of Clonidine orally 60 minute before induction of Group A and Group B received 1.5 mg/kg of Esmolol IV as a loading dose over a period of 5 min just before induction of GA followed by 10 µg/kg/min IV as a maintenance dose throughout the procedure. No hypnotic medication was given on the evening before surgery. Systolic, diastolic, mean arterial blood pressures and heart rate were recorded at (1) baseline, (2) 3 minutes after endotracheal intubation, (3) before pneumoperitoneum,(4) 15 minutes after pneumoperitoneum,(5) 30 minutes after pneumoperitoneum, (6) 5 minutes after release of CO2 and (7) 5 minutes after extubation. **Results :** Both groups were similar with respect to demographic data. Clonidine group showed more stability in hemodynamic responses than Esmolol group in all hemodynamic variables. **Conclusion :** Oral Clonidine provides more stability than intravenous Esmolol in laparoscopic surgeries and also it is relatively safe and easy for oral administration with low cost.

Keywords : Clondine, Esmolol, Laparoscopic surgeries, Pneumoperitonium

Introduction : With the advancements in the field of anaesthesia and surgery minimally invasive procedures using endoscopy have gained importance. Laparoscopy is a minimally invasive procedure with various benefits to the patient in terms of decreased tissue damage, early ambulation, decreased hospital stay and reduced analgesic needs. The hallmark of laparoscopy is the creation of pneumoperitoneum with carbon dioxide (CO2) which leads to stimulation of the sympathetic nervous system, resulting in pathophysiological changes characterized by, increase in arterial pressure and systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) early after the beginning of intra-abdominal insufflation, with little change in heart rate (HR) which can be a risk factor for adverse cardiologic events in patients with pre-existing essential hypertension, ischemic cardiac disease, or increased intra-cranial or intraocular pressure[1,2]. These hemodynamic responses are due to increased release of catecholamines, vasopressin, or both. Moreover, there is a significant change in the homeostasis observed in reverse Trendelenburg position used for laparoscopic surgeries. In addition, the anesthetic agents put together alter the cardiopulmonary function significantly[3].

Different pharmacological agents such as α2 adrenergic agonists, magnesium sulfate[4],beta-blockers[5] and opioids[6] are used to attenuate circulatory response due to pneumoperitoneum. Clonidine is a selective α2 adrenergic agonist which inhibits the release of catecholamine and vasopressin and thus modulates the hemodynamic changes induced by pneumoperitoneum[7]. Esmolol, an ultra short-acting cardio-selective β1-receptor antagonist, has been shown to blunt hemodynamic responses to perioperative noxious stimuli[8]. Also Clonidine as a oral route is a safe method of administration, easy to prescribe and is cost effective.

Hence, the present randomized study is designed to evaluate and compare the efficacy of oral Clonidine versus IV Esmolol on hemodynamic response during laparoscopic surgeries. In other words, the rationale of the study is to reach laparoscopic surgeries with stable hemodynamics.

Materials and Methods : The study was conducted at Department of Anaesthesiology & Critical Care, DVVPF's Medical College & Hospital, Ahmednagar. After getting approval from the institutional ethical committee, an informed consent was taken from every patient enrolled in the study.

A total of 60 patients posted for laparoscopic surgery satisfying the inclusion criteria were selected.

Inclusion Criteria:1) Patients of either sex, aged between 18 and 60 years,

2) American Society of Anaesthesiologists (ASA) physical, Status I or II,

3) Elective laparoscopic surgeries.

Exclusion Criteria:1) Patients not fulfilling eligibility criteria,

2) Lack of patient consent,

3) Anticipated difficult airway,

4) Body mass index (BMI) >25 kg/m2,

5) Diabetic and hypertensive patients,

6) Those taking beta-blocking drugs or sedatives or antihypertensives or

antipsychotics or analgesics,

7) Pregnant or breast-feeding females,

8) Duration of procedure lasting for more than 120 min

Patients were allocated randomly by a computer generated list of random permutations to one of two equal groups (30 patients each):

Group A : Received Tablet Clonidine 150 µg orally 60 minutes before induction.

Group B : Received IV Esmolol 1.5 mg/kg as a loading dose over a period of 5 min just before induction of GA followed by 10 µg /kg/min IV as a maintenance dose throughout the procedure.

Drug administration and data collection was carried out by investigators in a double-blind manner. No hypnotic medication was given on the evening before surgery. On the day of surgery, IV line was secured. Patients were premedicated with Inj.Ranitidine 50mg IV and Inj.Metoclopramide 10mg IV and preloading with Ringer lactate 5ml/kg was started. Patients were shifted to operation theatre one hour prior to the surgery and base line parameters including blood pressure and E.C.G were recorded using multipara monitors.

After pre-oxygenation with 100% O2 for 3 min, anesthesia was induced with a standard anesthetic protocol using Midazolam 0.03 mg/kg, Fentanyl 1 µg/kg,, Thiopentone sodium 5 mg/kg, and tracheal intubation was facilitated by Succinylcholine 1.5 mg/kg intravenously. Lungs were mechanically ventilated with N2O:O2 (60:40) and anesthesia was maintained with Isoflurane 1 % and Vecuronium 0.1 mg/kg as a loading dose then 1/4th of loading dose was given every 30 min. Ventilation was adjusted to maintain normocapnia {end-tidal carbon dioxide (EtCO2)} within normal range. Pneumoperitoneum was created by insufflation of CO2 and operation table was tilted to about 15degree reverse Trendelenberg. Intra-abdominal pressure was kept below 15 mmHg. During surgery, Ringer's lactate solution was administered in maintenance dose as per Holliday-Segar formula. Any hypotension (MAP < 20% preoperative) was managed with a fluid bolus of normal saline 250–300 ml. If hypotension did not respond to fluid administration, then Mephentermine 6 mg i.v. was administered. Any incidence of bradycardia (HR < 50/min) was treated with Atropine 0.6 mg IV. At the end of surgery, residual neuromuscular block was reversed by the injection of Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg IV and patient was extubated when all reflexes regained and patient was following verbal commands.

Esmolol infusion was stopped 5 min after extubation. Patients were transferred to the postanesthesia care unit (PACU) where they were monitored for any evidence of complications or adverse events. Systolic, diastolic, mean arterial blood pressures and heart rate were recorded at the following points of time:

1. Before receiving Clonidine or Esmolol (baseline)
2. 3 minutes after endotracheal intubation
3. Before pneumoperitoneum(PP)
4. 15 minutes after pneumoperitoneum(PP)
5. 30 minutes after pneumoperitoneum(PP)
6. 5 minutes after release of CO2
7. 5 minutes after extubation.

The results obtained in the study are presented in tabulated manner

The primary outcomes of our study were as follows: Systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate. The secondary outcomes were as follows: Postoperative sedation, Any possible side effects of the 2 drugs.

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation, Chi-square, paired t-test and unpaired t-test with windows Microsoft excel software.

Results : There were no significant differences between the two groups with regard to demographic data such as age, sex, weight and ASA grade (Table 1).

There was no significant statistical difference between the two groups of patients regarding HR, SBP, DBP, and MAP before intubation (baseline values of Tables 2–5).

Systolic blood pressure, diastolic blood pressure and mean blood pressure were also comparable in both

groups after intubation, increased slightly and then decreased significantly intraoperatively and after extubation compared to baseline values but it was significantly lower in group A compared with group B (Tables2–4).

One patient suffered from significant hypotension in group A which was managed with a fluid bolus of normal saline 300 ml and Mephentermine 6 mg i.v.

On comparing heart rate after intubation and till 5 min after extubation, mean HR values measured were significantly lower in group A compared to group B and in both groups the values were lower than baseline values. (Table 5).

2 patients in group A required intravenous atropine due to bradycardia (HR < 50).

Incidence of post operative nausea,vomiting and shivering was less in group A as compared to Group B.

None of the patient showed any evidenceof ischaemia or arrhythmia intraoperatively

Table 1 : Demographic data

	Group A (n = 30)	Group B (n = 30)	P-value
Sex Female Male	 15(50%) 15(50%)	 12(40%) 18(60%)	0.87
Age(years) Mean ± SD	 31.13 ± 10.70	 31.8 ± 11	0.43
ASA I II	 22(73.3%) 8(26.7%)	 24(80%) 6(20%)	0.542

Table 2 : Changes in systolic blood pressure.

SBP (mmHg)	Group A (n= 30) Mean±SD	Group B (n= 30) Mean±SD	P-value
Baseline	117.8±3.07	120.84±3.89	0.092
3 minutes after intubation	123.36±2.56	126.60±2.52	0.00018
Before pneumoperitoneum (PP)	114.29 ± 1.46	122.67 ± 2.38	0.0016
15 minutes after pneumoperitoneum(PP)	119.26 ± 2.74	125.82 ± 2.09	0.00028
30 minutes after pneumoperitoneum(PP)	116.36 ± 2.51	123.37 ± 1.98	0.00019
5 minutes after release of CO2	112.12 ± 2.32	122.27 ± 1.89	0.00081
5 minutes after extubation.	108.95 ± 2.58	118.97 ± 2.17	0.0003

Table 3 : Changes in diastolic blood pressure.

DBP (mmHg)	Group A (n= 30) Mean±SD	Group B (n= 30) Mean±SD	P-value
Baseline	89.8±2.17	92.84±2.09	0.018
3 minutes after intubation	93.06±2.86	98.18±2.12	0.00076
Before pneumoperitoneum (PP)	81.29 ± 1.16	91.32 ± 1.83	0.0006
15 minutes after pneumoperitoneum(PP)	84.26 ± 2.62	90.62 ± 2.54	0.0008
30 minutes after pneumoperitoneum(PP)	82.36 ± 1.11	88.39 ± 1.58	0.00092
5 minutes after release of CO2	79.92 ± 2.56	86.97 ± 2.69	0.0001
5 minutes after extubation.	78.95 ± 1.88	84.74 ± 2.97	0.00046

Table 4 Changes in mean arterial pressure.

MAP (mmHg)	Group A (n= 30) Mean±SD	Group B (n= 30) Mean±SD	P-value
Baseline	99.13±2.23	102.17±2.14	0.0884
3 minutes after intubation	103.16±2.01	107.65±2.47	0.00059
Before pneumoperitoneum (PP)	92.29 ± 2.26	101.77 ± 2.12	0.00046
15 minutes after pneumoperitoneum(PP)	95.92 ± 1.18	102.35 ± 2.66	0.0001
30 minutes after pneumoperitoneum(PP)	93.69± 1.21	100.05± 2.31	0.00064
5 minutes after release of CO2	92.28 ± 2.49	98.73 ± 2.01	0.00012
5 minutes after extubation.	88.95 ± 2.26	96.15 ± 2.42	0.00038

Table 5 Changes in Heart rate

MAP (mmHg)	Group A (n= 30) Mean±SD	Group B (n= 30) Mean±SD	P-value
Baseline	85.58±2.15	84.04±2.47	0.0352
3 minutes after intubation	84.58±1.36	90.60±2.38	0.00070
Before pneumoperitoneum (PP)	77.23 ± 2.16	82.67 ± 1.78	0.00021
15 minutes after pneumoperitoneum(PP)	74.26± 2.18	81.52 ± 2.31	0.00049
30 minutes after pneumoperitoneum(PP)	72.13 ± 2.78	79.17 ± 2.37	0.00075
5 minutes after release of CO2	71.35 ± 2.14	81.21 ± 1.74	0.00068
5 minutes after extubation.	68.24 ± 2.89	79.39 ± 2.14	0.00085

Discussion : Laparoscopic surgery became a corner stone in the treatment of many surgical procedures like cholecystectomy, appendicectomy, hernia repair, varicocoele ligation, nephrectomy, hysterectomy and several of gynaecological diagnostic and therapeutic procedures. This opened a sub speciality in anaesthesia for laparoscopy. Laparoscopic anaesthesia aims at optimising conditions for laparoscopy and attenuating several systemic changes that occur in laparoscopic surgery. Utmost importance is given to the hemodynamic changes induced during laparoscopic anaesthesia and surgery. Even though laparoscopy became popular as early as 19th century, studies for minimising adverse effects for laparoscopy began towards the end of 19th century.

Hemodynamic changes with pneumoperitoneum were first recognized in 1947.[9] Pneumoperitoneum using CO2 for laparoscopic surgery causes a rapid and immediate increase in plasma catecholamines and vasopressin[10] possibly due to an increase in intraperitoneal pressure and stimulation of the peritoneum by CO2. At intraabdominal pressure of 15 mmHg, Joris et al.[2] 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. Plasma concentrations of renin also increase during laparoscopy.[11] The increase in catecholamines, renin and

vasopressin induces a cardiovascular response characterized by abrupt elevations of arterial pressure, SVR and HR.[12] The increase in these hemodynamic values significantly increases the incidence of myocardial ischemia, infarction and other complications.To date, many different techniques and pharmacological agents have been used to reduce the detrimental effects of pneumoperitoneum. Pharmacological agents like β-blockers, opioids, increasing concentration of inhalational anesthetic agents, nitroglycerine and α2-adrenergic agonists have been tried.[2,10]

Our study compared between oral Clonidine versus intravenous Esmolol because both of these drugs have been shown to reduce sympathetic nervous system activity and plasma catecholamine concentrations during laparoscopy surgeries which have been a corner stone in producing the cardiovascular complications.

Clonidine, an imidazoline derivative is a selective α2 adrenergic agonist (α2:α1=220:1) with an elimination half-life of 6 to 10 hours. It is a potent antihypertensive drug with an easy oral administration, excellent absorption, prolonged action and good safety profile as a premedicant for laparoscopy. The central sympatholysis induced by Clonidine takes care of the tachycardia and hypertension seen after peritoneal insufflation. Additional properties like analgesia, sedation, anxiolysis, antiemesis and anti-shivering actions make it a near-ideal agent for laparoscopies where PONV is a problem. Thus it not only helps in the intra-operative period but also has effect on preoperative anxiety and postoperative pain, shivering and emesis.

Malek et al.[13]used 150 µg of Clonidine as intravenous infusion while Sung et al.[14]and Yu et al. [15]used 150 µg of oral Clonidine as premedication for maintenance of hemodynamic stability during pneumoperitoneum. Yu et al. even recommended its routine use as premedication in laparoscopic surgeries.

Das et al.[16]also used 150 µg of oral Clonidine 90 min prior to surgery to prevent hemodynamic response to pneumoperitoneum in laparoscopic cholecystectomy. Kalra et al.[17]used Clonidine 1 µg /kg intravenously over a period of 15 min before pneumoperitoneum and Clonidine group patients showed significantly better hemodynamic control than control group.

Esmolol is an ultra-short-acting cardio seiective β1-receptor antagonist. The structure of Esmolol contains an ester linkage; esterases in red blood cells rapidly metabolize Esmolol to a metabolite that has a low affinity for beta receptors. Esmolol has a short half-life of about 10 minutes. During continuous infusions of Esmolol steady-state concentrations are achieved quickly and the therapeutic actions of the drug are terminated rapidly when its infusion is discontinued[8].

As optimal intravenous (IV) Esmolol dose for use during anesthesia induction (laryngoscopy and intubation) and emergence (extubation) has been previously determined in some studies to be 1.5 mg/kg, we used the same bolus dose in our study.[18] Moreover, many studies have demonstrated that beta adrenergic blockers that exert depressive effects on the central nervous system as Esmolol also decreases the need for intraoperative anesthetic agents, leading to rapid recovery from anesthesia.[19]

In this study, we compared between Clonidine and Esmolol in reduction of stress response and hemodynamic changes associated with laparoscopy. Both groups showed attenuation in SBP, DBP, MBP and HR in response to intubation with group A showing little increases compared to group B which was statistically significant. It was found that the SBP, DBP, and MBP

values were lower with Clonidine group compared to baseline values during pneumoperitoneum, release of CO2 and after extubation than Esmolol group and it was statistically significant. Just one patient in Clonidine group suffered from significant hypotension but it was managed rapidly with fluids and Mephentermine. Generally, the fluctuations in blood pressure during such operation were attenuated in both groups; therefore, we can safely conclude that Clonidine and Esmolol stabilize blood pressure during various phases of anesthesia and laparoscopy. After intubation, Esmolol group showed little increase in mean heart rate compared to baseline value while in Clonidine group, mean heart rate was lower than baseline value. However, the heart rate was lower in both groups during the surgery as compared to baseline values and it was statistically significant. Moreover, the mean heart rate was lower in group A compared with group B throughout the procedure and it was statistically significant. In spite of

its more pronounced effect on heart rate, just 2 patients receiving Clonidine suffered from significant bradycardia and required atropine injection. None of Esmolol group suffered from bradycardia. Definitely, the heart rate lowering effect of both study drugs reduces the myocardial oxygen demand of the patient which can be very useful in patients suffering from coronary artery disease. The sedative effect of Clonidine was obvious postoperatively compared with Esmolol group but sedation was not that deep as patients were arousable either verbally or by touch.

Limitations : Invasive blood pressure monitoring was not done in our study due to nonavailability of the required setup. Additionally, we did not record postoperative total analgesic requirement. Also our study was conducted on ASA-I and II class patients. So further studies on elderly and compromised cardiac function patients are required to recommend its use in such high risk patients.

Conclusion : Both Clonidine and Esmolol were able to attenuate the haemodynamic response to pneumoperitoneum but Oral Clonidine will provide more hemodynamic stability as compared to Esmolol. Besides excellent absorption, ease of administration and multiple favourable additional effects on PONV, pain, shivering etc. make oral clonidine a safe and effective premedicant for use in laparoscopy. Based on our study we conclude that 150 µg clonidine (3 µg/kg) orally can be safely used for premedication in ASA-I/II patients for laparoscopy as it has a good safety profile. But further studies are needed for confirming its safety in elderly patients and patients with compromised cardiovascular function.

References:

1. Sharma KC, Brandstetter RD, Brensilver JM, Jung LD. Cardiopulmonary physiology and pathophysiology as a consequence of laparoscopic surgery. Chest 1996;110:810–5.
2. Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy.Anesth Analg 1993;75:1067–71.
3. Jean LJ. Anaesthesia for laparoscopic surgery. In: Miller RD, editor. Anesthesia. New York: Churchill Livingstone; 2010. p.2185–202.
4. Kalra NK, Verma A, Agarwal A, Pandey HD. Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2011;27:344–8.
5. Koivusalo AM, Scheinin M, Tikkanen I, et al. Effects of esmolol on haemodynamic response to CO2 pneumoperitoneum for laparoscopic surgery. Acta Anaesthesiol Scand 1998;42:510–7.
6. Lentschener C, Axler O, Fernandez H, et al. Haemodynamic changes and vasopressin release are not consistently associated with carbon dioxide pneumoperitoneum in humans. Acta Anaesthesiol Scand 2001;45:527–35
7. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin 2000;38:23–9.
8. White PF, Wang B, Tang J, Wender RH, Naruse R, Sloninsky A. The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg 2003;97 (6):1633–8.
9. Booker WM, French DM, Molano PA. Further studies on the acute effects of intra abdominal pressure. Am J Physiol 1947;149:292–8.
10. Mann C, Boccara G, Pouzeratte Y, Eliet J, Serradel-Le Gal C, Vergnes C, et al. The relationship among carbon dioxide pneumoperitoneum, vasopressin release, and hemodynamic changes. Anesth Analg 1999;89(2):278–83.
11. Baratz RA, Karis JH. Blood gas studies during laparoscopy under general anesthesia. Anesthesiology 1969;30:463–4.

12. Larsen JF, Svendsen FM, Pedersen V. Randomized clinical trial of the effect of pneumoperitoneum on cardiac function and haemodynamics during laparoscopic cholecystectomy. Br J Surg 2004;91(7):848–54.
13. Malek J, Knor J, Kurzova A, Lopourova M. Adverse hemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication.Comparison with intravenous and intramuscular premedication. Rozhl Chir 1999;78:286–91.
14. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin 2000;38:23–9.
15. Yu HP, Hseu SS, Yien HW, Teng YH, Chan KH. Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2003;47:185–90.
16. Mrinmoy Das, Manjushree Ray, Gauri Mukherjee. Hemodynamic changes during laparoscopic cholecystectomy: effect of oral clonidine premedication. Indian J Anaesth 2007;51:205–10.
17. Kalra NK, Verma A, Agarwal A, Pandey HD. Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2011;27:344–8.
18. Topcu I, Ozturk T, Tasyuz T, et al. The effects of esmolol on anesthetic and analgesic requirement. Turk J Anaesth Reanim 2007;35:393–8.
19. Collard V, Mistraletti G, Taqi A, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg 2007;105:1255–62.