Original Article

Comparative Study of Clonidine versus Lignocaine for Attenuation of Hemodynamic Responses during Laparoscopic Hysterectomy

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ABSTRACT

Background: Hemodynamic changes due to reflex sympathetic discharge are of great concern in laparoscopic surgeries. **Aim:** To compare hemodynamic changes following premedication with lignocaine or clonidine during laparoscopic hysterectomy. **Subjects and Methods:** This prospective cross-sectional randomized double blinded controlled trial was conducted one year in a tertiary care hospital in West Bengal. After taking institutional ethical clearance and consent of patients, hundred subjects of ASA Grade I and II undergoing elective laparoscopic hysterectomy were included in the study. Patients were allocated into two groups. Group A received clonidine and Group B received lignocaine. Baseline clinical parameters were recorded. Patients received clonidine or lignocaine as a bolus over a period of 15 minutes before induction and as continuous intravenous infusion throughout the surgical procedure. The dose of clonidine was 2.25 µg/kg bolus and 0.9 µg/kg/hr infusion while that of lignocaine was 1.5 mg/kg bolus and 0.6 mg/kg/hr infusion. Patients were given 1 µg/kg of fentanyl citrate intravenously. Following inductionwith intravenous propofol, endotracheal intubation was facilitated by atracurium. Anaesthesia was maintained by nitrous oxideIN and oxygen and along with propofol infusion. Muscle relaxation was achieved by intermittent bolus doses of atracurium. The patients were mechanically ventilated to keep $EtCO_2$ between 35 and 40 mm Hg. Residual neuromuscular block was reversed by an appropriate dose of neostigmine and glycopyrrolate. All patients were shifted to PACU/POCU. Ramsay Sedation Score was assessed. Data was analyzed using SPSS version 16. **Results:** In comparison to group B, attenuation of heart rate, Systolic blood pressure, diastolic blood pressures were significantly more in group A. There was no difference in sedation score between the two groups. **Conclusion:** In an attempt to attenuate both the effects of layngoscopy and insufflations with carbon dioxide in laparoscopic surgery infusions of clonidine and lignocaine were run all through the procedures in the present study and it was found that use of clonidine and lignocaine attenuated the haemodynamic responses. However clonidine being found to be more effective.

KEY WORDS: Clonidine, hemodynamic responses, hysterectomy, lignocaine

INTRODUCTION

Laparoscopic hystrectomy has its own specific risks and anaesthetic techniques must be refined to anticipate these differences from open surgery. Hemodynamic changes due to reflex sympathetic discharge are of great concern in laparoscopic hystrectomy. To minmise these effects drugs may be used.[1-3]

Pneumoperitoneum using insufflated carbon dioxide to enable sufficient visualization and patient positioning causes several haemodynamic and respiratory consequenses. As the volume of the abdomen increases, abdominal wall compliance decreases and intra-abdominal pressure (IAP) rises. When the IAP exceeds physiological thresholds, different systems become compromised, increasing patient morbidity and mortality. Pneumoperitoneum causes an increase in Systemic Vascular Resistance (SVR) while causing a decrease in Cardiac Output (CO). Mean Arterial Pressure (MAP) is increased overall because increases in SVR exceed decreases in CO. Despite a decrease in intracardiac blood volume, intracardiac filling pressures may be elevated due to pressure transmitted across the diaphragm to the heart.[1-5] There are analagous effects in the pulmonary circulation that manifest as an increase in pulmonary vascular resistance (PVR) and decrease in CO to the lungs. If

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the patient is placed in extreme Trendelenburg, a decrease in venous return from the head may result, thus leading to increased intracranial and intraocular pressures. The head up (reverse Trendelendburg) position reduces venous return, which may lead to a fall in cardiac output and arterial pressure. The lithotomy position will induce auto-transfusion by redistributing blood from vessels of the lower extremities into the central body compartment, which thus will increase the preload of the heart. Bradyarrhythmias, dysrhythmias, and asystole can occur during insertion of laparoscopic ports or during insufflation ofabdomen. Sudden stretching of the peritoneum can precipitate areflexive, and sometimes profound increase in vagal tone.[1-5]

Lignocaine is local anesthetic that acts on Na + channels and interacts with dorsal horn neurons, muscarinic/ dopaminergic/k/nicotinic receptors. It reduces neural response to pain by blocking and inhibiting nerve conduction. It is achieved through suppression of neuronal excitability in dorsal horn neurons and depression ofconduction in myelinated A-delta and unmyelinated Cfibers.[6-9]

Alpha-2 adrenoreceptors agonists have been recently used perioperatively for their sedative, analgesic, sympatholytic and cardiovascular stabilizing effects with reduced anaesthetic requirements.[10-14] Clonidine, a central sympatholytic offers beneficial pharmacological properties producing dose dependent sedation, analgesia, anxiolysis without relevant respiratory depression. Clonidine, a centrally acting α_2 agonist, has beneficial effects on hemodynamic changes during laryngoscopy and endotracheal intubation and reduces bleeding.[15,16] It attenuates stress responses to painful stimuli, improves the intraoperative hemodynamic stability, reduces the incidence of perioperative myocardial ischemic episodes in patients and decreases anaesthesia requirements during surgery. Pre-medication with clonidine reduces the requirement for propofol, which may be a pharmacokinetic effect.[12,13,15,16]

The present study was conducted, to compare hemodynamic changes in different phases of laparoscopic hysterectomy following use of lignocaine or clonidine. In an attempt to attenuate both the effects of layngoscopy and insufflations with carbon dioxideinfusions of clonidine and lignocaine were run all through the procedures.

SUBJECTS AND METHODS

This prospective cross-sectional randomised double blind controlled trial was conducted in a time period of one year in a tertiary care hospital in West Bengal after obtaining institutional ethical clearance and informed consent of patients.

Inclusion criteria

Hundred subjects in the age group of 30-60 years and of ASA Grade I and II undergoing elective laparoscopic hysterectomy were included in the study. Patients were allocated into two groups using an online randomizer, Group A and B. Group A (n = 50) received clonidine and Group B (n = 50) received lignocaine.

Exclusion criteria

ASA ≥III, pregnant mothers, BMI ≥35 kg m^2 and <18.5, reported adverse reactions to any of the drugs included in the study, and chronic or acute intake of sedatives, analgesics, or any other drug affecting the metabolism of anaesthetics used, any chronic pain syndrome, history of seizures, medication use that affects cytochrome P450-3A4 or P450-1A2 metabolism (including smokers and tobacco addicts).

Following proper history, physical assessment and review of laboratory investigations, the procedure for/complications of general anaesthesia was explained to the patients. All patients eligible for the studyhad the following information documented: Medication list, age, sex, height, weight, body mass index, serum urea, fasting sugar, creatinine, calculated creatinine clearance (Cockroft-Gault), Liver Function Tests (AST, ALT, Total Bilirubin), serum electrolytes, coagulation profile, ECG, Chest X-Ray, primary diagnosis, and scheduled procedure.

Airway Assessment was done. Patients who were predicted to have difficult intubation were excluded.

Methods

On the day of surgery baseline clinical parameterswere measured (SpO_2). Intravenous line was gained. For Group A patients 600 μg clonidine (4 ml) was diluted with 16 ml distilled water in a 20-ml syringe (1 ml = 30 μg). 20 ml preservative free lignocaine hydrochloride was taken in a 20 ml (1 ml = 20 mg) syringe for Group B patients. An investigator not involved in the case prepared the corresponding drugs. Drugs werediluted to a fixed volume of 20 ml. The anaesthetist in charge of the patient, blinded to which group each patient belonged, started the infusion. Patients received 0.075 ml/kg of solutions as a bolus over a period of 15 minutes before induction. Same solution was administered at a rate of 0.03 ml/kg/hour as continuous intravenous infusion throughout the surgical procedure. The dose of clonidine was 2.25 μg/kg bolus and 0.9 μg/kg/hr infusion while that of lignocaine was 1.5 mg/kg bolus and 0.6 mg/kg/hr infusion.

The depth of anaesthesia was monitored with bispectral index (BIS™). The target BIS range was 40-60 for surgical anaesthesia. After preoxygenation for 3 minutes, patients

were given 1 µg/kg of fentanyl citrate intravenously. Anaesthesia was induced with propofol, administered at a rate of 20 mg per 5 seconds until BIS was below 60. Endotracheal intubation was facilitated by muscle relaxant atracurium. Anaesthesia was maintained by nitrous oxide and oxygen (50% +50%) along with propofol infusion, started at the rate of 10 mg/kg/hour and titrated to maintain BIS in the range of 40-60. Signs of inadequate analgesia, defined as an increase of heart rate and MAP of more than 20% of baseline, were to be managed by a bolus dose of fentanyl 0.5 µg/kg [if BIS was within the recommended range (40-60)].[1] Muscle relaxation was achieved by intermittent bolus doses of atracurium. The patients were mechanically ventilated to keep $EtCO_2$ between 35 and 40 mm Hg. Following parameters were recorded throughout the procedure: Continuous ECG (lead-II) and Heart rate, SpO_2, Non invasive arterial blood pressure (SBP, DBP), measurement of $EtCO_2$. The target BIS range was 40-60 for surgical anaesthesia. All surgical procedures were one to one and half hour long. Readings were taken during laryngoscopy and tracheal Intubation and 1 min, 3 mins, 10 mins, 30 mins, 60 mins, and 90 mins, following laryngoscopy and tracheal intubation.

At the end of the surgical procedure, residual neuromuscular block was reversed by an appropriate dose of neostigmine and glycopyrrolate. All patients were shifted to PACU/POCU.

Moist O_2 for 2 hours was administered to all patients. Ramsay Sedation Score was assessed. Postoperative sedation, Heart rate, SpO_2, Systolic blood pressure (SBP), Diastolic blood pressure (DBP) was monitored for 24 hours following surgery.

Results were expressed as number of occurrences, percentage and mean (SD). Demographic characteristics, preoperative vitals were compared using Student's't' test. Data was analyzed using SPSS version 16. *P* value $< 0.05^{*}$ was considered as significant and $< 0.01^{**}$ as highly significant.

RESULTS

There was no significant difference in age, sex, weight, height and ASA grading, resting heart rate, blood pressure, between the 2 groups.

Group A

During intubation of anaesthesia, there was 6% increase in the mean values of heart rate. At 1 minute from the onset of laryngoscopy, the Mean Heart Rate was 89.7 (7.5) per min and remained 5.3% higher than the Baseline Heart Rate, at 3 minute 88.0 (7.6) per min which was 3.8% higher than the Baseline Heart rate, at 10 minutes was 97.6 (6.8) per min which was 10.5% higher than baseline Heart rate.

In group A it was seen that the Heart rate response during laryngoscopy and intubation was not significantly higher than the pre-operative values [Table 1 and Figure 1].

The mean preoperative Systolic blood pressure was 119.4 (6.9) mm of Hg. During Intubation the mean Systolic blood pressure 3.7% increased compared to baseline Systolic blood pressure, and the mean Systolic blood pressure was 124.9 (5.9) mm of Hg.

At 1 minutes, the mean Systolic blood pressure 1.2% increasedcompared to baseline Systolic blood pressure, andthe mean Systolic blood pressure are 120.8 (6.4) mm of Hg.

At 3 minute following laryngoscopy, a 0.9% decrease in Systolic blood pressure was noted with a mean value of 118.4 (6.7) mm of Hg.

At 10 minutes there was a 7.9% fall in Systolic blood pressure to 109.9 (6.4) mm of Hg [Table 2 and Figure 2].

The mean pre-operative Diastolic Blood Pressure in this group was found to be 77.2 (4.7) mm of Hg. At intubation the mean Diastolic blood pressure was 78.9 (4.1) mm of Hg, which was 1.8% higher than baseline Diastolic blood pressure. The Diastolic blood pressure showed a 0.8% increase at 1 minute after intubation and the mean was 77 (4.6) mm of Hg. The Diastolic Blood Pressure showed a 9.1% decrease 10 minutes after intubation and 1.9%

Table 1: Comparison of the heart rate responses

Heart rate (beats/min)	Mean (SD)		*P* value
	Group A	Group B	
Baseline	85.4 (6.4)	87.2 (8.3)	0.14
At induction	90.3 (7.9)	105.4 (8.9)	<0.001**
1 Min after induction	89.7 (7.5)	110.9 (7.7)	<0.001**
3 Min after induction	88 (7.6)	111.6 (7.9)	<0.001**
10 Min after induction	97.6 (8.4)	112.3 (6.8)	<0.001**
30 Min after induction	83.2 (3.1)	82.4 (2.3)	0.66
60 Min after induction	82.6 (2.7)	83.6 (2.3)	0.50
90 Min after induction	83.4 (1.9)	82.8 (1.9)	0.61

P value, **Highly significant

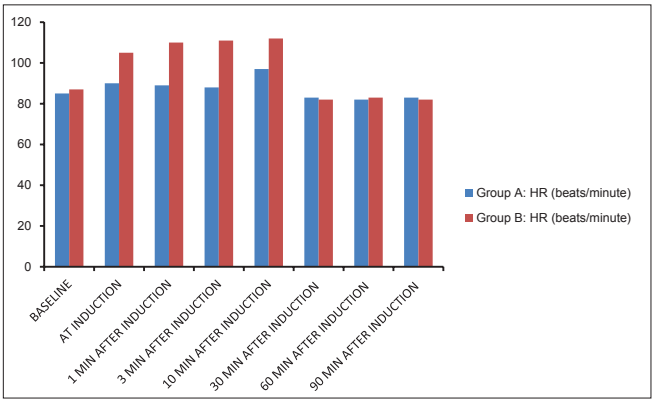

Figure 1: Comparison of heart rate

decrease at 3 minute after intubation It was seen that the mean diastolic blood pressure were 70.2 (5.7) mm of Hg and 74.7 (4.9) mm of Hg respectively [Table 3 and Figure 3].

Group B

During intubation, there was 20.7% rise in Heart rate with a mean rate of 105.4 (8.9)/min. At one minute from the onset of laryngoscopy, the Heart rate was 110.9 (7.7) per min with an increase of 26.9% from the pre-operative values. At 3 minutes Heart rate wasobserved to be 111.6 (7.9) per min which was 27.9% higher than baseline Heart rate. Subsequently an increasing trend in Heart rate at 10 minutes after laryngoscopy was maintained and the mean Heart rate at 10 minutes was 112.3 (6.8) per min which was 28.6% higher than the pre-operative values [Table 1 and Figure 1].

Pre-operative Systolic blood pressure was 119.2 (7.1) mm of Hg. At intubation there was 24.5% increase in Systolic blood pressure with values of 147.9 (22.7) mm of Hg. At 1 minute there was 19.7% increase in Systolic blood pressure with values of 142.7 (8.2) mm of Hg. There was an 18.9% increase in Systolic blood pressure following 3 minute after laryngoscopy with a mean value of 141.8 (8.5) mm of Hg. 10 minutes after intubation Systolic blood pressure was 139.9 (8.6) and this 17.4% higher than baseline Systolic blood pressure [Table 2 and Figure 2].

The mean baseline Diastolic blood pressure in the group B was 74.5 (4.7) mm of Hg. At intubation minute the mean Diastolic blood pressure were 91.9 (3.9) mm of Hg which was 23.3% higher than the baseline diastolic blood pressure respectively. At 1 minute the mean Diastolic blood pressure was 91.1 (3.8) mm of Hg, which was 22.3% higher than the baseline diastolic blood pressure. At 3 minute the diastolic blood pressure showed a 21.1% increase and the mean DBP was 90.2 (3.7) mm of Hg. At 10 minutes DBP was 88.7 (4.1) mm of Hgwhich was 19.2% higher than baseline diastolic blood pressure [Table 3 and Figure 3].

In comparison to group B, attenuation of heart rate, Systolic blood pressure, diastolic blood pressure were significantly more in group A ($P < 0.001$). There was no difference in sedation score between the two groups (Group A 2.3 (0.4) vs Group B 2.1(.04), *P* value: 0.55).

DISCUSSION

The sequence of induction of anaesthesia, laryngoscopy and intubation are associated with marked haemodynamic changes and autonomic reflex activity which may be a cause of concern in many high risk patients. Marked fluctuations in haemodynamic response are often seen in geriatric patients. Autonomic nervous system abnormality in elderly may clinically manifest as a hyperkinetic circulation characterized by elevation in heart rate and blood pressure.[18,19] Loss of cardiovascular reflexes causes tachycardia at rest. Cardiac vagal tone is well known to decrease with increasing age. Sympathetic nervous system

Table 2: Comparison of systolic blood pressure

Systolic blood pressure (mm of Hg)	Mean (SD)		*P* value
	Group A	Group B	
Baseline	119.4 (6.9)	119.2 (7.1)	0.86
At induction	124.9 (5.9)	147.9 (22.7)	<0.001**
1 Min after induction	120.8 (6.4)	142.7 (8.2)	<0.001**
3 Min after induction	118.4 (6.7)	141.8 (8.5)	<0.001**
10 Min after induction	109.9 (7.9)	139.9 (8.9)	<0.001**
30 Min after induction	120.3 (1.4)	121.6 (1.9)	0.19
60 Min after induction	123.3 (2.5)	125.3 (2.7)	0.31
90 Min after induction	124.7 (3.9)	127.7 (2.9)	0.17

P value, **Highly significant

Table 3: Comparison of diastolic blood pressure

Diastolic blood pressure (mm of Hg)	Mean (SD)		*P* value
	Group A	Group B	
Baseline	74.52 (3.26)	77.20 (3.27)	0.25
At induction	78.92 (4.009)	91.88 (3.931)	<0.001**
1 Min after induction	77.00 (4.63)	91.14 (3.79)	<0.001**
3 Min after induction	74.74 (4.99)	90.22 (3.69)	<0.001**
10 Mins after induction	70.18 (5.72	88.70 (4.09)	<0.001**
30 Min after induction	80.5 (2.56)	80.88 (2.03)	0.19
60 Min after induction	80.62 (2.4)	81.5 (1.22)	0.39
90 Min after induction	81.3 (2.4)	82.15 (2.16)	0.53

P value, **Highly significant

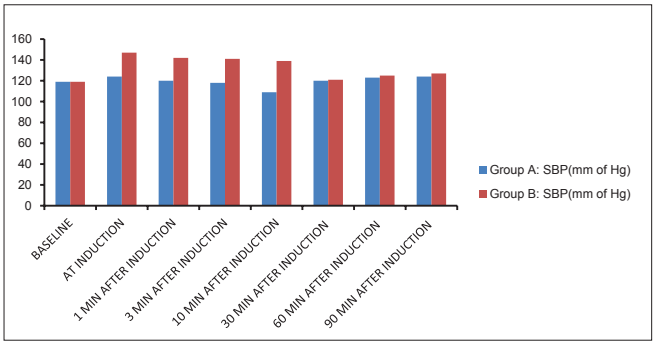

Figure 2: Comparison of systolic blood pressure

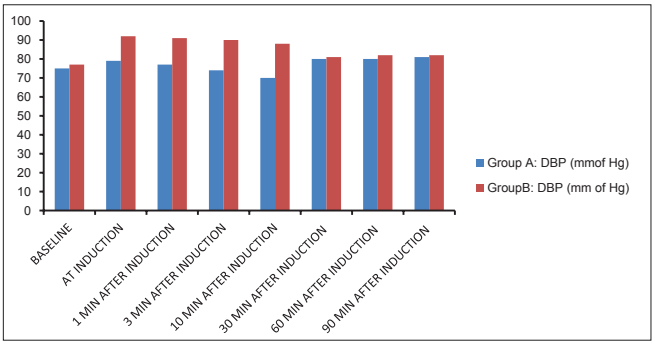

Figure 3: Comparison of diastolic blood pressure

activity increases with age as well as plasma epinephrine and nor epinephrine level. There is decrease in response to β adrenergic receptor stimulation and decreased baroreceptor sensivity.[17-19] So in our study, we selected an optimal age range of 30 to 60 years. Readings were taken during laryngoscopy and tracheal Intubation and 1 min, 3 mins, 10 mins, 30 mins, 60 mins, and 90 mins, following laryngoscopy and tracheal intubation. The rationality was that up to 3 mins, the effect of sympathetic surge due to laryngoscopy and intubation will be present; at 10 mins, effect of pneumoperitoneum and change in position will start taking effect; by 30, and 60 mins, the persistent effect of pneumoperitoneum will be observed and by 90 mins, the effect of extubation will be prominent. In comparison to group B, attenuation of heart rate, Systolic blood pressure, diastolic blood pressure (at 1 min, 3 min and 10 min) were significantly more in group A ($P < 0.001$). Attenution of haemodynamic responses at 30 mins, 60 mins and 90 mins were comparable in both groups. No significant hypotensive or hypertensive episodes were noted any group.

Altan *et al*.[20] used clonidine 3 μg/kg intravenously over a period of 15 minutes before induction and 2 μg/kg/hour by continuous infusion intraoperatively. They observed significant incidences of bradycardia and hypotension. Ray *et al*.[21] administered clonidine 3 μg/kg intravenously 15 minutes before induction and reduced the infusion to 1 μg/kg/hour intraoperatively. In spite of this reduced infusion rate of clonidine, significant incidences of bradycardia and hypotension were seen. We used 2.25 μg/kg intravenously 15 minutes before induction and reduced the infusion to 0.9 μg/kg/hour andintraoperative and fall in blood pressure, pulse rate was noticed in case of patients receiving clonidine, but there was no episode of hypotension and bradycardia observed. Preoperative Alpha-2 adrenoreceptors agonists protects against the pressure response to intubation. In laparoscopic surgical procedures where adverse cardiovascular change like increased arterial pressure is common, haemodynamic effect like hypotension, bradycardia caused by clonidine may actually be beneficial.[6,22]

Kumari *et al*.[16] compared clonidine and midazolam as premedication agents. Administration of clonidine before induction and intraoperatively improves perioperative haemodynamic stability. Clonidine premedication is considered to be safe without episodes of hypotension, bradycardia, low oxygen saturation, nausea, vomiting. Lignocaine has been found to attenuate the haemodynamic response to endotracheal intubation.[6,9,23,24] In our study, both clonidine and lignocaine lowered the haemodynamic response to intubation but clonidine was found to be more effective in attenuating the sympathetic response.

CONCLUSION

In an attempt to attenuate both the effects of layngoscopy and insufflations with carbon dioxide in laparoscopic surgery infusions of clonidine and lignocaine were run all through the procedures in the present study and it was found that use of clonidine and lignocaine attenuated the haemodynamic responses. However clonidine being found to be more effective.

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