Original Article

Comparative Study between Oral Clonidine and Placebo in Laparoscopic Surgery to Attenuate the Hemodynamic Changes Due to Pneumoperitoneum and Hypercarbia

Gomathi Karmegam[1], Kundhavi Devi[2], Bhavani Vaidyanathan[3], Heber Anandan[4]

[1]Senior Assistant Professor, Government Kilpauk Medical College Hospital, Affiliated to the Tamil Nadu Dr. M. G. R. Medical University, Tamil Nadu, India, [2]Professor, Government Kilpauk Medical College Hospital, Tamil Nadu, India, [3]Assistant Professor, Indira Gandhi Medical College and Research Institute, Puducherry, India, [4]Senior Clinical Scientist, Dr. Agarwal's Health Care Limited, Tamil Nadu, India

Abstract

Background: Laparoscopic surgery has enormous advantages to the patient with regards to the post-operative pain and early discharge. However, it is not without disadvantages due to the hemodynamic swings that occur intraoperatively due to the intra-abdominal pressures. This study was undertaken to determine the efficacy of oral clonidine to attenuate these changes in response to pneumoperitoneum and hypercarbia.

Aim: A comparative study of oral clonidine and placebo in laparoscopic surgery to attenuate the hemodynamic response due to pneumoperitoneum and hypercarbia.

Materials and Methods: A prospective, randomized, double-blind, control study on 30 patients in two groups, one receiving placebo and the other receiving clonidine 5 µg/kg 90 min before induction was carried out. Intraoperative heart rate (HR) and non-invasive blood pressure (BP) were monitored along with post-operative complications such as nausea and vomiting were documented.

Results: Statistical analysis revealed oral clonidine was far beneficial maintaining intraoperative hemodynamic swings during laparoscopic surgery.

Conclusion: Oral clonidine was found beneficial with the ease of administration and control of HR and BP intraoperatively. Preoperatively, sedated and calm patient with a lesser incidence of polypharmacy intraoperatively was added advantages.

Key words: Clonidine, Hypercarbia, Laparoscopic surgery, Pneumoperitoneum, Stress response

INTRODUCTION

Laparoscopy or minimally invasive surgery has made huge advances in the field of surgery. It has a plethora of advantages being reduced pain, therefore, decreased hospital stay, reduction in medical cost with day care admissions, reduction in morbidity and mortality due to minimal handling. Patients may face a stormy intraoperative course if anesthesia fails to maintain the hemodynamics within the normal range during pneumoperitoneum and hypercarbia. Numerous studies have evolved over the years to identify agents capable of maintaining hemodynamics in a balanced spectrum during laparoscopic surgery. Clonidine is a centrally acting alpha 2 agonist used for premedication as it decreases polypharmacy, post-operative nausea, vomiting, and shivering. It has antihypertensive property by decreasing sympathetic outflow.[1] The use of drugs such as oral clonidine as a premedicant given before operation would be desirable to enhance the hypotensive action of inhalational agent without the disadvantages of intravenous (IV) vasodilators.

Corresponding Author: Dr. Gomathi Karmegam, Department of Anaesthesiology, Kilpauk Medical College Hospital, Chennai - 600 010, Tamil Nadu, India. Phone: +91-9444005371. E-mail: g_karmegam@yahoo.co.in

Aim

Comparative study between oral clonidine and placebo in laparoscopic surgery to attenuate the hemodynamic changes due to pneumoperitoneum and hypercarbia.

MATERIALS AND METHODS

A prospective, double-blind study was undertaken in 60 patients: 30 patients in two groups belonging to American Society of Anesthesiologist (ASA) PS I and II. After obtaining approval from the Institute Ethical Committee and due patient consent, Group P (placebo) was given vitamin C 90 min before surgery; Group C (oral clonidine) was given clonidine 5 μg/kg 90 min before surgery. Both the administrator and receiver were blind to the groups allocated. Inclusion criteria were patients aged 20-50 years, ASA PS I and II patients, those undergoing abdominal laparoscopic surgeries, patient weighing 50-65 kg. Exclusion criteria were hypertension/ischemic heart disease/rheumatic heart disease, diabetes mellitus, obesity, anticipated difficult airway, sinus bradycardia/heart blocks/conduction defects, patients on antipsychotics, patients on digitalis, calcium channel blockers and b-blockers, H/o cerebrovascular disease (cerebrovascular accident), chronic renal disease with increased renal parameters, pre-operative hypotension, and patient refusal. The sedation score was assessed preoperatively using the sedation score. Patients were assessed for level of sedation at 30 min, 60 min, and 90 min after premedication. The following score was used to assess the degree of sedation:
Grade 1: Awake and alert patient
Grade 2: Awake and calm lying down quality
Grade 3: Drowsy, arousable on oral commands
Grade 4: Drowsy, arousable on mild physical stimuli
Grade 5: Drowsy, arousable on vigorous physical stimuli only.

Intraoperative heart rate (HR) and blood pressure (BP) were recorded every 5 min from the period of insufflations to release. Intraoperative top ups of fentanyl, propofol, and deepening the plane with sevoflurane were documented.

Pre-operative Assessment

Only those patients in the ASA Class I and II undergoing laparoscopic procedures were taken into this study. Nil oral duration was 8 h. Patients were given the oral premedicant, in a sealed cover 90 min before surgery and shifted to the operation theater with an 18G venflon and maintenance IV fluid. Sedation scoring was done to assess the efficacy of the premedicant. After shifting into the OT, monitors with non-invasive BP, SpO_2, and electrocardiography were connected. Antacid prophylaxis was given with injection. Ranitidine 50 mg and injection

ondansetron 4 mg IV. Premedication was given with injection Glycopyrrolate 10 μ/kg, injection Midazolam 10 μ/kg and injection Fentanyl 2 μ/kg were given in IV. Preoxygenation with 100% O_2 done for 3-5 min. Patient induced with injection. Propofol 2 mg/kg and injection atracurium 0.5 mg/kg after ascertaining good mask ventilation. Maintenance with N_2O and O_2 2:1 and sevoflurane 0.75-2 vol%. Titrated doses of muscle relaxant, fentanyl, and propofol were administered according to the need intraoperatively. Monitoring of HR and BP was done every 5 min during and after intubation, positioning, pneumoperitoneum and during extubation. Pneumoperitoneum was achieved with CO_2 insufflation and intra-abdominal pressure was not allowed to exceed 12-15 mmHg. Time duration from insufflation to release was recorded. Rescue doses of fentanyl or propofol to deepen the plane of anesthesia was taken into consideration. Rescue with injection atropine was used if the HR <30%, injection ephedrine if the BP <30%, and injection nitroglycerin (NTG) infusion was used if the BP exceeded >30% of the patient's baseline. The patient was extubated at the end of surgery. The patients were then shifted to the recovery room and were kept under observation for about 60 min during which the HR, BP, respiratory rate, and SpO_2 were monitored at 30 min intervals for any signs of respiratory depression.

Statistics and Analysis

Data were expressed as mean, standard deviation, or absolute values. Qualitative data were compared with the Chi-square test and Fisher's exact test. Quantitative variables were compared with the Student *t*-test. The level of statistical significance was set at $P < 0.05$.

RESULTS

The mean age in Group C was 26.8 ± 4.40, and in the Group P, it was 26.3 ± 4.08 ($P = 0.649$). The mean weight in Group C was 53 ± 6.81. The mean weight in Group P was 51.13 ± 5.47 ($P = 0.246$). Sex distribution in each group was male = 17, female = 13. Thus, the demographic profile was comparable between the two groups. *P* value not significant.

At the end of 30 min following premedication, 25 patients in Group C were in the sedation score of 2, at the end of 60 min, 26 patients with the score of 3, and after 90 min, 23 patients had a score of 3. It was seen that all the patients in Group P were in the score of 1 till 90 min (Table 1).

9 (30%) patients in Group P supplemental doses of propofol and fentanyl when compared to 2 (6.66%) of Group C.

Table 1: Sedation score of both groups

Score	Grade of sedation and anxiolysis	30 min (%)		60 min (%)		90 min (%)	
		Group C	Group P	Group C	Group P	Group C	Group P
1	Awake and alert	4 (13.33)	30 (100.00)	0	30 (100.00)	0	30 (100.00)
2	Awake, calm, lying quietly	25 (83.33)	0	4 (13.33)	0	3 (10.00)	0
3	Drowsy arousable on oral commands	1 (3.33)	0	26 (86.67)	0	23 (76.67)	0
4	Drowsy arousable on mild physical stimuli	0	0	0	0	4 (13.33)	0
5	Drowsy arousable on vigorous physical stimuli only	0	0	0	0	0	0

i. It is hereby seen that a significantly higher consumption of sevoflurane >1 vol% almost 50% of patients in Group P was required when compared to Group C 2 (6.66%).

ii. 6 (20%) patients in Group P needed NTG infusion (0.1 mg/kg), whereas only 1 (3.33%) patients in Group C needed the same (Table 2).

Cardiovascular Parameters

Mean values of hemodynamic parameters (HR, systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure) were taken at preinduction, at scopy 1 and 5 min thereafter, and with pneumoperitoneum every 5 min intraoperatively for the first 30 min and 15 min thereafter. Hemodynamic stability was remarkable with Group C as seen by the comparisons with Group P (Tables 3 and 4). The equivalent stability was maintained in Group P with additional propofol and fentanyl top-ups and sevo 1-2 vol% and NTG infusion. The pressor response to both intubation and extubation was blunted in the clonidine group Figure 1. Mean duration of surgery was comparable in both groups and not found significant Table 5.

There was no respiratory depression in both the groups, more so in the clonidine group. The patients in both groups had a stable cardiovascular status in the post-operative period.

DISCUSSION

Laparoscopy has been the mainstay in most abdominal surgeries in the past few years. Advantages being its minimal bowel handling and early ambulation of the patients, the disadvantages were CO_2 insufflation, pneumoperitoneum, and hypercarbia. CO_2 absorption causes a trigger in the HR, hypertension, and an increase in systemic vascular resistance. Pneumoperitoneum causes an increase in intra-abdominal pressure causing a biphasic fluctuation in BP.[1,2] Positioning of the patient, namely, trendelenburg and reverse trendelenburg causes changes in the vascular physiology. CO_2 elimination is usually achieved with hyperventilation and deepening the plane of anesthesia which may result in a delay in recovery.[3] Pneumoperitoneum beyond

Table 2: Reduction in requirements of anesthetic drugs and NTG seen in both groups

Drug	30 min %	
	Group C	Group P
Propofol/fentanyl	2 (6.67)	9 (30.00)
Sevoflurane		
1 vol%	2 (6.67)	5 (16.67)
2 vol%	0	15 (50.00)
>2 vol%	0	10 (33.33)
NTG	1 (3.33)	6 (20.00)
Atropine	1 (3.33)	0
Ephedrine	1 (3.33)	0

Table 3: HR during pneumoperitoneum

| Time of observation	Group	HR (Bt/min)	SD	P value
Baseline	Group C	81.166	4.026	0.154
	Group P	79.633	4.213	
Preinduction	Group C	72.8	5.821	<0.0001
	Group P	91.6	3.45	
At Scopy	Group C	75.566	6.463	<0.0001
	Group P	95.098	18.422	
1 min after intubation	Group C	76.601	6.499	<0.0001
	Group P	94.223	2.721	
5 min after intubation	Group C	80.333	7.871	0.130
	Group P	85.396	16.294	
Average intraoperative value	Group C	65.6	8.071	<0.0001
	Group P	79.6	8.298	
During extubation	Group C	69.66	14.406	0.632
	Group P	85.232	18.436	
1 min after extubation	Group C	72.1	10.121	<0.0001
	Group P	89.03	6.206	
5 min after extubation	Group C	75.533	11.578	0.001
	Group P	84.733	5.051	
30 min after extubation	Group C	73.066	15.097	0.052
	Group P	78.795	4.727	
2 h after extubation	Group C	78.333	10.346	0.946
	Group P	78.13	124.3	
4 h after extubation	Group C	80.366	8.176	0.026
	Group P	76.466	4.651	

pressures of 18 mmHg may result in a compartment-like syndrome and a fall in venous return to the heart.[4] Diaphragm being pushed upward reduces the FRC and ineffective ventilation due to increased airway pressures. Absorption of CO_2 into the third spaces causes oozing from surgical sites and blood loss.[5] Studies by Abe *et al.*, conducted on patients were focused on delineating the

Table 4: MAP during surgery

Time of observation	Group	MAP	SD	*P* value
Baseline	Group C	95.77	5.174	0.001
	Group P	92.22	5.276	
Preinduction	Group C	67.766	5.076	<0.0001
	Group P	84.333	6.26	
At scopy	Group C	73.333	5.64	<0.0001
	Group P	91.933	4.346	
1 min after intubation	Group C	76.9	6.676	<0.0001
	Group P	117.9	151.7	
5 min after intubation	Group C	92.077	8.342	0.003
	Group P	98.53	4.261	
Average intraoperative value	Group C	75.51	8.6111	0.070
	Group P	72.511	2.32	
During extubation	Group C	79.866	8.102	<0.0001
	Group P	87.88	3.408	
1 min after extubation	Group C	81.222	10.017	<0.0001
	Group P	90.955	3.833	
5 min after extubation	Group C	82.966	9.47	0.003
	Group P	90.243	4.633	
30 min after extubation	Group C	79.21	7.726	<0.0001
	Group P	89.555	3.358	
2 h after extubation	Group C	88.932	6.313	0.216
	Group P	90.554	3.284	
4 h after extubation	Group C	92.666	4.581	0.7722
	Group P	93	4.321	

Table 5: Duration of surgery

Group	Minutes	SD	*P* value
Clonidine	53.33	±17.137	0.331
Placebo	57.166	±12.844	
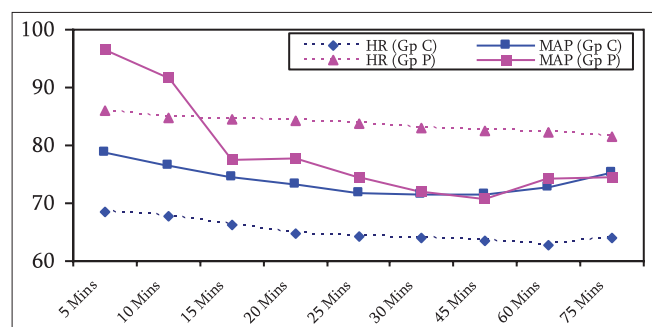
Figure 1: The heart rate and mean arterial pressures throughout the period of laparoscopy

appropriate IAP. Restricting IAP to <12 mmHg reduced hypercarbia and its associated complications.[6] van Zundert *et al.*, conducted studies with thoracic epidural segmental anesthesia as an adjuvant to GA. The good relaxation achieved with the epidural made laparoscopy easier at IAP <12 mmHg.[7] Esmolol, magnesium, IV doses of clonidine and dexmedetomidine were various agents used for hemodynamic stability.[8-11] In this study, oral clonidine was preferred over IV for the ease of administration. Patients were calm and sedated preoperatively. Intraoperative usages of anesthetic drugs were not required, and a good plane

of anesthesia was maintained with minimal sevoflurane inhalant. The increase in HR and BP seen in the placebo group during intubation and insufflation was not seen in the clonidine group. Post-operative nausea/vomiting and respiratory depression were negligible. The advantages of clonidine as a premedicant in laparoscopic procedures can be summarized as follows:

- Excellent sedation and anxiolysis
- Attenuation of stress response to laryngoscopy and intubation
- Maintenance of intraoperative cardiovascular stability
- Good intraoperative analgesia
- Devoid of respiratory depression
- Less distressing side effects such as nausea and vomiting
- Easy administration.

CONCLUSION

Oral clonidine was found to be an excellent premedicant in laparoscopic surgery with a good hemodynamic control. However, it possesses certain limitations in its usage in patients with bradycardia, conduction disturbances, and cardiovascular instability as it is likely to worsen the cardiovascular status. As it may cause excessive sedation, it is better avoided or used with caution in patients with airway obstruction, obesity, and extremes of age. Clonidine at a dose of 5 mcg/kg body weight with a ceiling dose of 300 mcg is tolerated well by the patients without major complications.

REFERENCES

1. Joris J, Chiche JD, Lamy M. Clonidine reduced hemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. Br J Anaesth 1995;74 Suppl: A124-7.
2. Hodgson C, McClelland RM, Newton JR. Some effects of the peritoneal insufflation of carbon dioxide at laparoscopy. Anaesthesia 1970;25:382-90.
3. Lenz RJ, Thomas TA, Wilkins DG. Cardiovascular changes during laparoscopy. Studies of stroke volume and cardiac output using impedance cardiography. Anaesthesia 1976;31:4-12.
4. Blobner M, Felber AR, Gogler S, Weigl EM, Jelen ES. Carbon dioxide uptake from the pneumoperitoneum during laparoscopic cholecystectomy. Anesthesiology 1992;77:A37-40.
5. Richardson JD, Trinkle JK. Hemodynamic and respiratory alterations with increased intra-abdominal pressure. J Surg Res 1976;20:401-4.
6. Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy. Anesth Analg 1993;76:1067-71.
7. Abe H, Ohtomo Y, Idezuki Y. Safe intra - Abdominal pressure of carbon dioxide pneumoperitoneum during laparoscopic surgery. Surgery 1993;114:549-54.
8. van Zundert AA, Stultiens G, Jakimowicz JJ, Peek D, van der Ham WG, Korsten HH, *et al.* Laparoscopic cholecystectomy under segmental thoracic spinal anaesthesia: A feasibility study. Br J Anaesth 2007;98:682-6.
9. Koivusalo AM, Scheinin M, Tikkanen I, Yli-Suomu T, Ristkari S, Laakso J, *et al.* Effects of esmolol on haemodynamic response to CO2 pneumoperitoneum for laparoscopic surgery. Acta Anaesthesiol Scand

1998;42:510-7.
10. Jee D, Lee D, Yun S, Lee C. Magnesium sulphate attenuates arterial pressure increases during laparoscopic cholecystectomy Br J Anaesth 2009;103:484-9.

11. Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. Anesth Analg 1992;75:932-9.