

EFFECT OF PREMEDICATION WITH INTRAVENOUS CLONIDINE ON HAEMODYNAMIC CHANGES IN LAPAROSCOPIC CHOLECYSTECTOMY: A RANDOMISED STUDYSudheer R¹, Karthik G. S², Sahajananda H³, Rangalakshmi S⁴**HOW TO CITE THIS ARTICLE:**

Sudheer R, Karthik G. S, Sahajananda H, Rangalakshmi S. "Effect of premedication with intravenous clonidine on haemodynamic changes in laparoscopic cholecystectomy: A Randomised study". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 24, March 23; Page: 4135-4148, DOI: 10.14260/jemds/2015/596

ABSTRACT: BACKGROUND: Laparoscopic cholecystectomy offers many benefits but significant hemodynamic changes are observed, which can be detrimental especially in elderly and hemodynamically compromised patients. Clonidine was found to inhibit the release of catecholamines and vasopressin and thus modulate the haemodynamic changes induced by pneumoperitoneum. **AIM AND OBJECTIVES OF THE STUDY:** To assess the efficacy of intravenous clonidine premedication in prevention of adverse haemodynamic changes during laparoscopic cholecystectomy. The following parameters were studied. Heart rate and Blood pressure response to induction, intubation and pneumoperitoneum. Requirements of intra-op analgesia like Fentanyl. Incidence of post-op nausea and vomiting Incidence of shivering. **METHODS:** 100 patients undergoing elective laparoscopic cholecystectomy were randomly assigned to one of the two groups to receive either clonidine 4 micrograms per kg or equivalent quantity of normal saline The primary outcome was to assess the efficacy of intravenous clonidine premedication in prevention of adverse haemodynamic changes during laparoscopic cholecystectomy. **STATISTICAL METHODS:** Student t test (two tailed, independent) has been used to find the significance of study parameters (HR, SBP, DBP) on continuous scale between two groups (Inter group analysis) and to test the homogeneity samples based on age (continuous parameters). Chi-square test was used to test the homogeneity of samples based on parameters on categorical scale between two groups. $P < 0.05$ was considered as statistically significant. The statistical software namely SPSS 15.0, Stata 8.0, Med Calc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. **RESULTS:** The result showed that Blood Pressure (SBP, DBP, MAP) and HR in study group fell significantly to lower level within 10 minutes after starting clonidine infusion and remained significantly low during laryngoscopy and intubation, pneumoperitoneum and extubation ($P < 0.001$). **CONCLUSION:** Premedication with 4µg/kg body weight of intravenous clonidine has been found to be safe and effective method that provides stable hemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. It also brings down the incidence of post-operative complications such as nausea, vomiting and shivering

KEYWORDS: clonidine; hemodynamics; laparoscopic cholecystectomy.

INTRODUCTION: Significant hemodynamic changes are observed during laparoscopic cholecystectomy which can be detrimental especially in elderly and hemodynamically compromised patients. Pneumoperitoneum affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular & pulmonary physiology and stress response.^(1,2,3)

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Intravenous clonidine has been used in the past as premedicant in neurosurgical patients, cataract surgeries and orthopedic procedures requiring application of tourniquet but very few studies are available which have used intravenous clonidine as premedicant for preventing adverse hemodynamic changes during laparoscopic cholecystectomy.^(4,5,6) Considering all these observations, the present study is designed to evaluate the efficacy of intravenous clonidine as premedicant in prevention of such hemodynamic changes.

Clonidine reduces sympathetic outflow from the central nervous system and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure.^(7,8) Intravenous doses of 2.5mcg/kg–5mcg/kg have been used in the perioperative period to reduce stress response to intubation, hyperadrenergic & hyperdynamic responses to prolonged tourniquet use in orthopedic surgeries and in the reduction of intraoperative bleeding.^(9,10)

Clonidine attenuates sympathetically mediated hyperdynamic responses, making it a useful adjunct in patients at risk for myocardial ischemia. It can decrease the stress response to laryngoscopy as well as emergence from anesthesia and reduces perioperative catecholamine release overall.^(11,12)

MATERIAL AND METHODS: Pre-anaesthetic evaluation of the patients was done. Ethical Committee approval and informed written consent was obtained. All patients received injection Glycopyrrolate 0.2mg i.m one hour before the induction of anaesthesia. 100 patients between 18-70 years of ASA 1 and 2 undergoing elective laparoscopic cholecystectomy were randomly assigned to one of the two groups to receive either clonidine 4µg/kg based on ideal body weight (IBW), diluted in 20ml normal saline intravenously over 15min (study group) and control group received equivalent quantity of normal saline over 15 min 30 min before induction of anaesthesia. Ideal body weight was estimated using Broca's index: IBW (kg)=Height(cm)-x, where x is 100 for adult males and 105 for adult females.

Patients belonging to ASA 3,4,5, with fixed cardiac output status like Aortic Stenosis, Mitral Stenosis, with history of left ventricular failure, Atrioventricular conduction block, BMI>35 and on drugs like clonidine, beta blocking drugs, MAO inhibitors were excluded from the study. On arrival in the premedication room, baseline values like, Heart rate, SBP, DBP, MAP, SPO₂, ECG and Level of sedation was assessed by Ramsey sedation scale:

1. Awake and anxious.
2. Awake and comfortable.
3. Asleep but arousable.
4. Asleep with brisk response to persistent call or light glabella.
5. Asleep with sluggish response to persistent call or light glabellar tap.
6. No response to call or touch.

Appropriate fluids as deemed required during the procedure was given. The patients received anaesthesia with injection Fentanyl 2µg/kg. Injection Propofol carefully titrated to cause loss of response to oral commands and intubation facilitated by injection Atracurium 0.5mg/kg body weight. Anaesthesia was maintained with Isoflurane 1% in 40% oxygen and nitrous oxide. Additional analgesia was given in the intra-operative period with a Fentanyl bolus of 1µg/kg if an increase of 20% in mean arterial pressure or heart rate from the baseline was observed. All patients were mechanically ventilated to maintain end tidal carbon dioxide 30-40mmHg. Systemic arterial pressure

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including the systolic, diastolic and mean arterial pressure, heart rate, SpO₂, EtCO₂ and electrocardiography (ECG) was recorded at the following points of time:

1. Base line.
2. Every 5mins in pre-op room for 30mins after start of clonidine infusion.
3. 1, 2, 3min after induction.
4. 1, 2, 3, 5min after endotracheal intubation.
5. 5min interval during pneumoperitoneum.
6. 5min after extubation.
7. Every 5mins in post-op room for 30mins

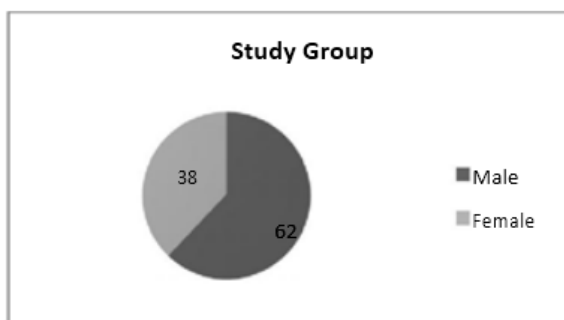
At the end of surgery residual neuromuscular block was reversed by appropriate dose of neostigmine and glycopyrrolate intravenously. In the postanesthesia care unit (PACU) patients were monitored for any evidence of complications or adverse events like bradycardia and hypotension. Degree of sedation was noted.

OBSERVATION AND RESULTS:

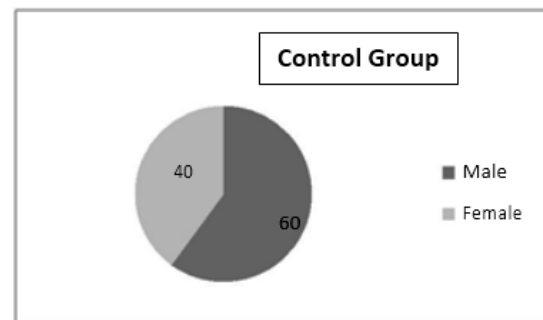
Gender	Control Group		Study Group	
	No	%	No	%
Male	30	60	31	62
Female	20	40	19	38
Total	50	100	50	100

Table 1: Gender distribution of patients studied:

The ratio of male to female patients was similar in both the groups with a P value of 0.582 when compared.



Graph 1: Gender distribution of patient's studied- Study Group.



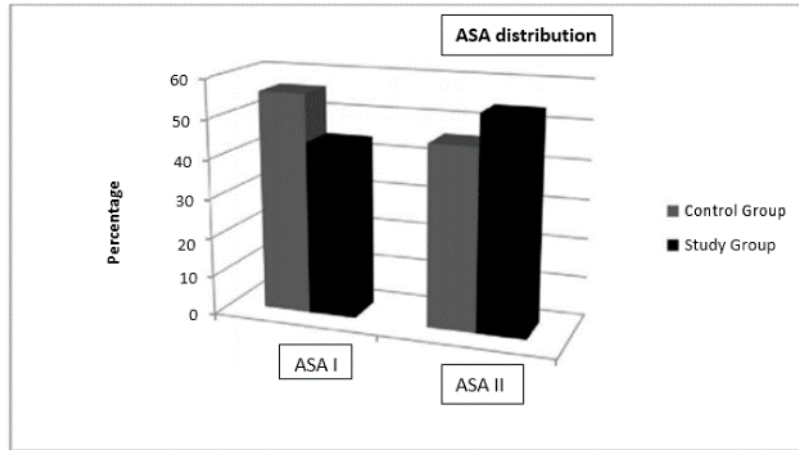
Graph 1.1: Gender distribution of patient's studied-Control

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Gender	Control Group		Study Group	
	No	%	No	%
ASA I	28	56	23	46
ASA II	22	44	27	54

Table 2: ASA distribution of patients studied:

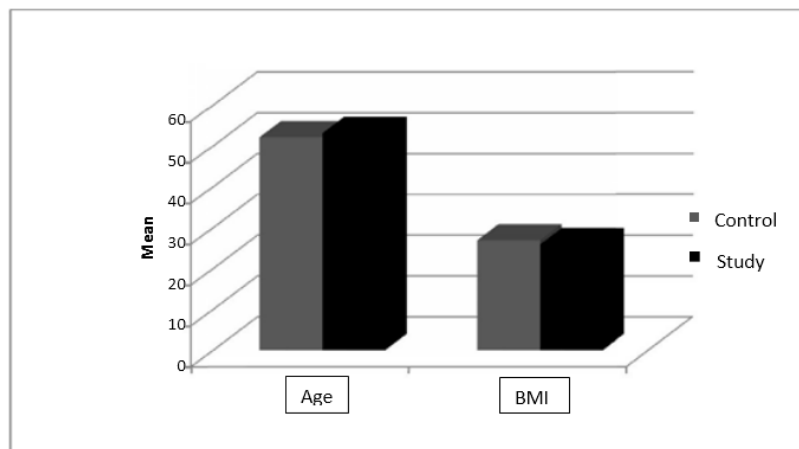
This table shows both groups belong to similar ASA status with a P value of 0.826.



Graph 2: ASA distribution in both groups Group

Other parameters	Control Group		Study Group		P-value
	Mean	SD	Mean	SD	
Age(yrs)	52.1	11.98	53.1	10.98	0.652
BMI	26.9	5.83	25.89	6.1	0.582

Table 3: Comparison of Age and BMI between two groups:

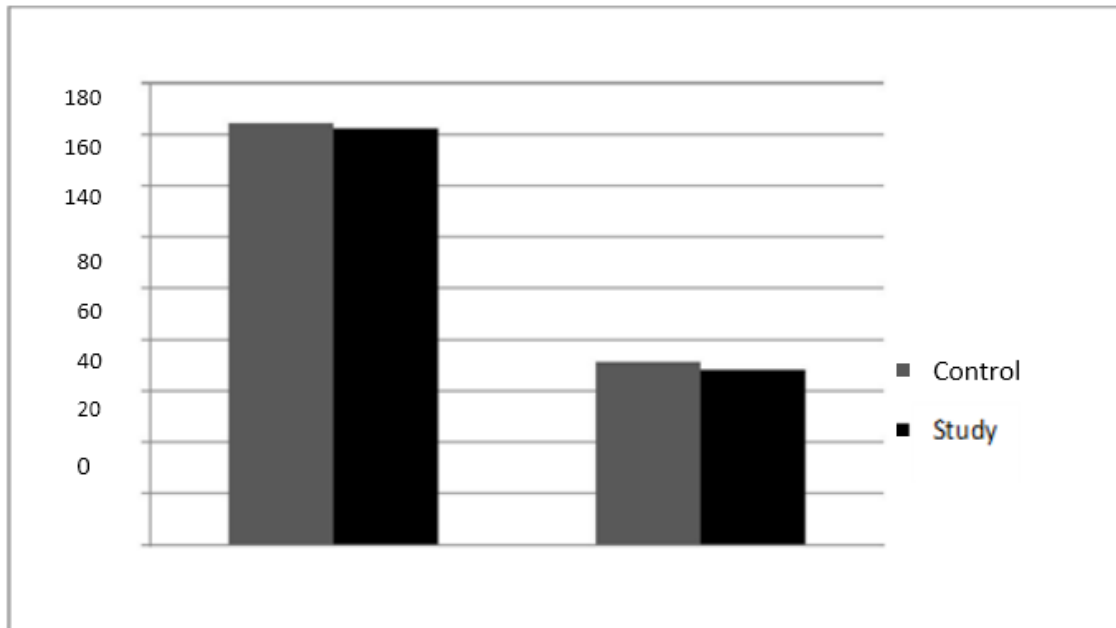


Graph 3

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Other Parameters	Control Group		Study Group		P-value
	Mean	SD	Mean	SD	
Height (cms)	164.44	8.16	162.14	9.99	0.21
Weight (kgs)	71.34	11.33	68.2	11.95	0.181

Table 4: Evaluation of Weight & Height:



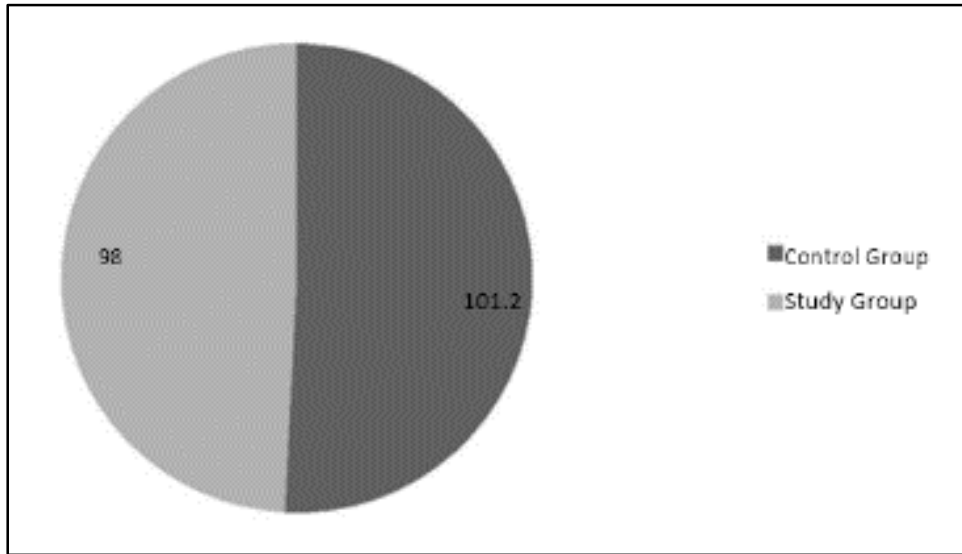
Graph 4

	Control Group		Study Group	
	Mean	SD	Mean	SD
Duration Of Surgery(Min)	101.2	8.24	98	7.28

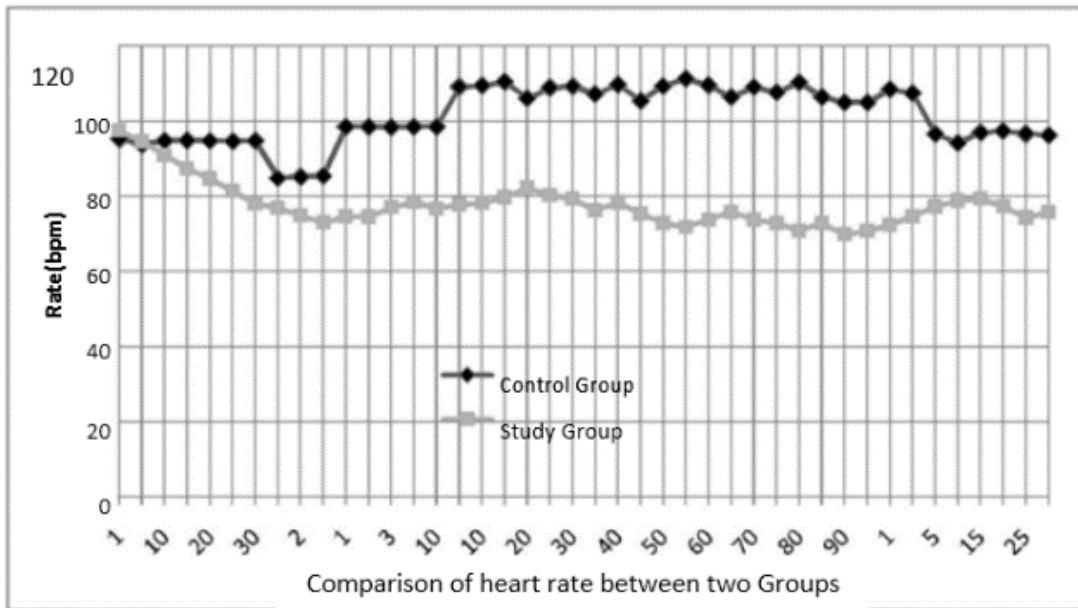
Table 5: Comparison of duration of Surgery between groups:

P value > 0.05.

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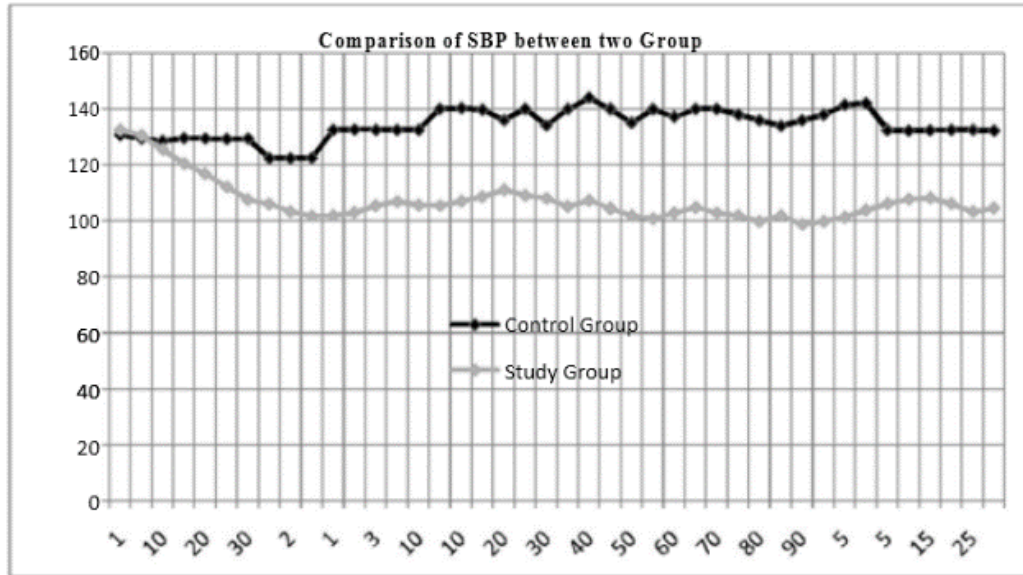
Graph 5: Pictorial representation of duration of Surgery between groups



Baseline values of heart rate were comparable between groups with a P value of 0.388.

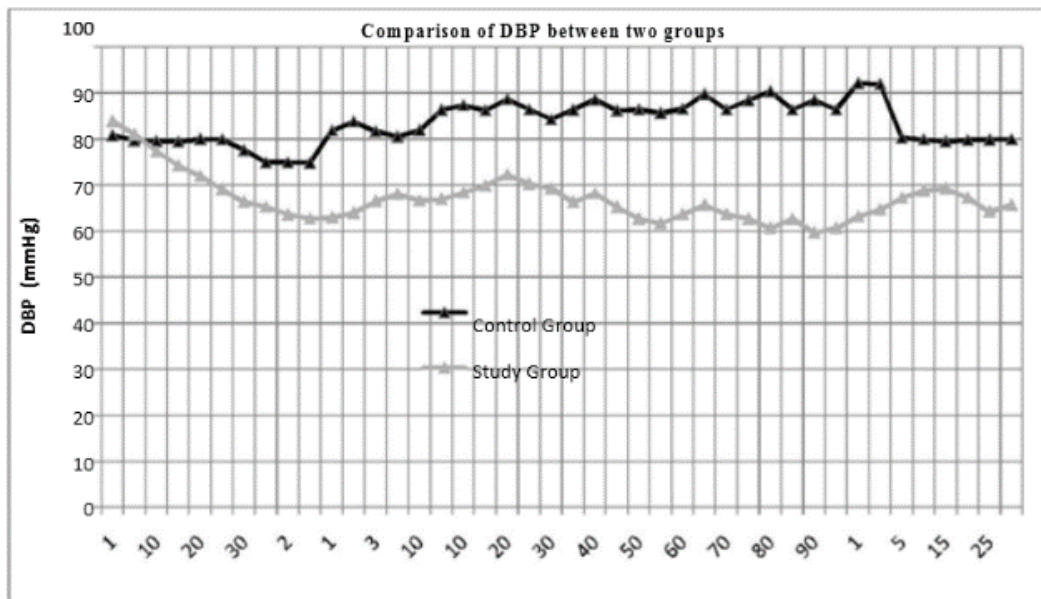
Graph 6: Illustration of heart rate between the groups

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Graph 7: Illustration of SBP between the groups

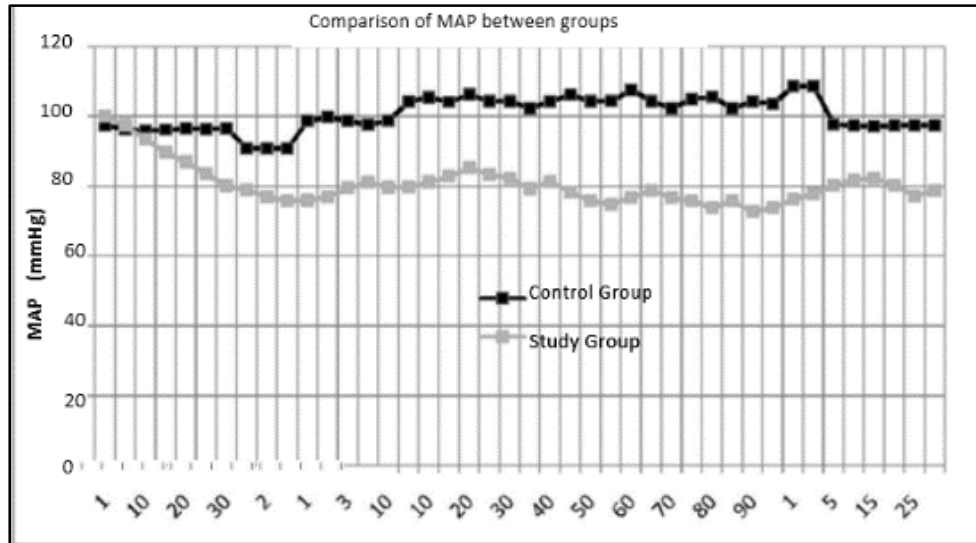
Baseline values of systolic blood pressures were comparable between groups with a P value of 0.560.



Graph 8: Graphical representation of Diastolic BP between the groups

There was no significant difference in base line values of diastolic blood pressures in both the control and the study group with a P value of 0.140.

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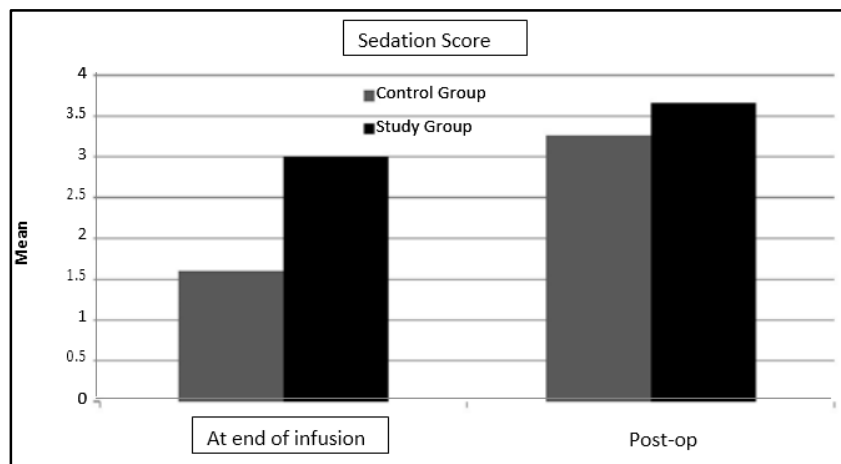


Graph 9: Illustration of Mean Arterial Pressure between the groups

Baseline values of mean arterial pressures were comparable between the groups with a P value of 1.74. The result shows Mean Arterial Pressure in study group fell significantly to lower level ($P < 0.001$) within 10 minutes after starting clonidine infusion and remained significantly low for response to laryngoscopy and intubation, and maintained throughout the procedure as demonstrated by significant P value. Episodes of hypotension were not observed during clonidine infusion in the study.

Sedation Score	Control Group		Study Group		P-value
	Mean	SD	Mean	SD	
At end of infusion	1.6	0.49	3	0.59	< 0.001
post-op after 15min	3.26	0.56	3.66	0.62	0.002

Table 10: Comparison of sedation level at different intervals:



Graph 10: Graphical representation of sedation Levels between groups

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	Control Group		Study Group		P-value
	Mean	SD	Mean	SD	
Total dose- Fentanyl ($\mu\text{g}/\text{kg}$)	2.8	0.54	2.24	0.59	< 0.001

Table 11: Requirements of Fentanyl between groups:

	Control Group		Study Group	
	Yes %	No %	Yes %	No %
Nausea	83	20.8	17	79.2
Vomiting	73.7	17.6	16.3	82.4
Shivering	82.6	22.2	17.3	77.4

Table 12: Comparison of incidence of post-op nausea, vomiting and shivering between two groups:

The incidence of post-op nausea, vomiting and shivering is significantly less in study group when compared to control group, with $P < 0.001$.

DISCUSSION: Alpha2 agonists reduce peripheral noradrenaline release by stimulation of prejunctional alpha2 inhibitory adrenoceptors. They inhibit central neural transmission in the dorsal horn by presynaptic and postsynaptic mechanisms, and directly in spinal pre-ganglionic sympathetic nerves. Traditionally, they have been used as antihypertensive drugs, but doses based on sedative, anxiolytic, analgesic properties are being developed.^(13,14,15)

We studied 100 adult patients with similar Demographic profiles like Age, Height, Weight, BMI, Sex, ASA physical status I and II and scheduled for elective laparoscopic cholecystectomy under general anaesthesia.

Aho⁽¹⁶⁾ et al using clonidine 3 or 4.5 $\mu\text{g}/\text{kg}$ or saline intramuscularly 30 to 45 min prior to induction of anaesthesia in gynec laparoscopy. They studied haemodynamic and plasma endorphin responses. They concluded that intramuscular administered clonidine prevents the maximal haemodynamic responses to tracheal intubation and to gynecological laparoscopic procedures.

Jean L Joris and mrimoy das^(17,18) et al used 8 $\mu\text{g}/\text{kg}$ of intravenous clonidine in laparoscopic cholecystectomy and compared the hemodynamic and endocrine changes with the placebo group. They observed clonidine significantly reduced MAP, HR & increase in SVR.

Peter J. Kulka⁽¹⁹⁾ et al, also observed similar effects.

Malek²⁰ et al used 0.15mg clonidine as infusion 15 minutes before laparoscopic cholecystectomy and 0.15 mg clonidine by intramuscular route 60-90 min before surgery and studied the hemodynamic changes and their suppression with clonidine pre-medication. They observed a significant drop in SBP and DBP during procedure after clonidine administration in both routes and recommend intravenous clonidine use as a routine procedure before laparoscopic cholecystectomy.

In our study we observed similar hemodynamic responses during pneumoperitoneum in laparoscopic cholecystectomy with 4 $\mu\text{g}/\text{kg}$ of intravenous clonidine.

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HEARTRATE RESPONSE: In our study during administration of 4 μ g/kg of intravenous clonidine the heart rate fell significantly to lower level within 10min after starting clonidine infusion and remained low till the end of infusion. In the clonidine group the heart rate fell from the base line value of 97.5 \pm 9.14 to 78.10 \pm 7.87 measured at the end of infusion period whereas in the control group the heart rate reduced from 95.28 \pm 9.30 to 94.82 \pm 9.40. When both the groups being compared the heart rate fall was significant in the clonidine group.

After intubation the heart rate increased from 73.04 \pm 7.30 to 74.66 \pm 7.36 in the clonidine group whereas in the control group the heart rate raised from 85.46 \pm 9.49 to 98.54 \pm 9.58. When both the group being compared the heart rate change was significant in control group.

During pneumoperitoneum the heart rate in the control group rose from 98.48 \pm 9.56 to 109.14 \pm 77.80 and remained high throughout the pneumoperitoneum. Whereas, in the study group the heart rate increased from 76.72 \pm 7.17 to 77.80 \pm 7.18. When both the groups being compared the heart rate changes for pneumoperitoneum response was significant in the control group.

After extubation the heart rate increased from 71.84 \pm 7.90 to 72.36 \pm 6.98 in the clonidine group and remained low in the post-op period. In control group the heart rate rose from 104.94 \pm 9.67 to 108.2 \pm 10.6 and settled down to base line values in the post-op period. The heart rate changes were significant in the control group when compared with the clonidine group.

There were no episodes of bradycardia requiring treatment during administration of IV clonidine and in perioperative period during pneumoperitoneum. The inference of our study is that the heart rate changes to stress are minimal during laryngoscopy, pneumoperitoneum and extubation in the clonidine group. This provides stable hemodynamics, preventing adverse effects in laparoscopic cholecystectomy.

BLOOD PRESSURE RESPONSE:

SYSTOLIC BLOOD PRESSURE: We observed that during administration of 4 μ g/kg of intravenous clonidine the systolic blood pressure fell significantly to lower level within 15mins after starting clonidine infusion and remained low till the end of infusion period in the study group. However there was no significant hypotension. The base line value of SBP fell from 132.76 \pm 16.27 to 107.84 \pm 13.96 measured at the end of infusion period. Whereas in the control group we observed minimal changes from the base line value of 130.82 \pm 16.90 to 129.58 \pm 16.29. This shows that there was a significant fall in SBP in clonidine group when compared to control group which is in agreement with Jean L Joris et al and Aho et al.

In our study after intubation the SBP increased from 101.86 \pm 13.17 to 102.0 \pm 13.24. In the control group the SBP rose from 122.60 \pm 16.46 to 132.58 \pm 16.77. When both the groups being compared SBP changes were significant in the control group.

During pneumoperitoneum the SBP changes in the clonidine group were minimal from 105.78 \pm 13.77 to 105.64 \pm 13.76 and remained low throughout the pneumoperitoneum. In control group the SBP rose from 132 \pm 62 to 140 \pm 16.01 and remained persistently high throughout the pneumoperitoneum. When both the groups being compared the SBP changes were significant in the control group.

After extubation there was a minimal change in the SBP from 99.96 \pm 13.63 to 100.44 \pm 13.61 in the clonidine group and remained stable in the post-op period. In the control the SBP rose from

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138.08±16.26 to 141.56±16.88 and settled to base line values in post-op period. When both the groups being compared the SBP changes were significant in control group.

DIASTOLIC BLOOD PRESSURE: In our study during administration of 4µg/kg of intravenous clonidine the DBP fell significantly to lower level within 15min after starting clonidine infusion and remained low till the end of infusion period. The DBP fell from the baseline value of 83.88±9.35 to 66.38 ± 9.38 measured at the end of infusion period. In the control group the DBP reduced from 80.86±11.00 to 77.64±11.07. When both the groups being compared the fall in DBP was significant in the study group. These DBP changes were similar with the studies done by Jean L Joris et al.

In our study after intubation there was a minimal or no response in DBP in the clonidine group. The D BP changes from 62.76 ± 8.93 to 62.96 ± 9.20. In control group the DBP rose from 74.86±11.17 to 81.88±11.18. DBP changes were significant in the control group when compared to clonidine group.

During pneumoperitoneum the DBP in the control group rose from 81.96±11.15 to 86.36±10.99 which remained high throughout the pneumoperitoneum. In the clonidine group the DBP increased from 66.68±9.29 to 66.98±9.45 and remained in the lower side throughout the pneumoperitoneum. Our results were comparable with the studies done by Jean L Joris et al.

The DBP changes after extubation in the clonidine group were from 60.72±9.32 to 63.22±9.28 and remained in the lower side in the post-op period. In control group the changes were significant from 86.44±11.47 to 92.18±11.73 and settled to pre induction values in post-op period. Significant DBP changes were observed in the control group when compared to study group.

Comparison of diastolic blood pressure (mm Hg) between two groups in our study, shows diastolic blood pressure is reduced significantly in the study group in comparison to control group, demonstrated by significant "P" value.

MEAN ARTERIAL PRESSURE: The study of mean arterial pressures reflected the changes seen in the systolic and diastolic pressures. The mean arterial pressure fluctuations in the control group were more than in the study group. While comparing the two groups MAP was found to be statistically significant with p<0.001.

There were no episodes of transient hypertension noted throughout the procedure during the study period. Episodes of prolonged hypotension were not noted during infusion of clonidine and in perioperative and post-operative periods.

REQUIREMENTS OF FENTANYL: In our study all patients received 2µg/Kg of injection fentanyl for induction. Additional analgesia was given in the intra-operative period with a fentanyl bolus of 1µg/Kg if an increase of 20% in MAP or HR from the baseline was observed. In the study group fentanyl requirement was 2.24±0.59 µg/kg whereas in the control group it was 2.80±0.54µg/kg which is significant when compared with p<0.001. This is in agreement with Joan W. Flackeet al,²¹ J. E. Hall et al²², M. De Kock et al.²³

POST-OP NAUSEA, VOMITING AND SHIVERING: All patients were observed for PONV. 83% of the patients had nausea and 73.7% of the patients had vomiting in the control group. Whereas 17% of the

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patients had nausea and 16% of the patients had vomiting in the clonidine group. The incidence of PONV was high in control group as we did not premeditate the patients with antiemetics and those patients who had vomiting received 4mg of injection ondansetron. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system.

Thermoregulatory center. Our study is also comparable with the study of Mrinmoy Das et al, who used 150µg of oral clonidine as premedication in laparoscopic cholecystectomy and observed very less incidence of post-operative shivering.

SEDATION: In the premedication room the patients were assessed for sedation score before and after clonidine administration. The patients in the clonidine group were initially in the Ramsey sedation score of 1.6 ± 0.49 . At the end of clonidine infusion the score went up to 3.0 ± 0.59 . At the end of extubation degree of sedation was again assessed in post-op room. It was seen at the end of 15min after extubation the score in the study group was 3.66 ± 0.62 and in the control group it was 3.26 ± 0.59 . The sedation scores when compared in both the groups were not statistically significant. It was seen that clonidine cause sedation within 15min of intravenous infusion. However in the post-op period there was no incidence of deep levels of sedation. Sedation score in PACU were comparable. This is in agreement with J E Hall et al.²⁴

CONCLUSION: Premedication with 4 µg/kg body weight of intravenous clonidine has been found to be relatively safe as well as effective method that provides stable hemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

Clonidine also affords an added advantage of reduction in requirements of induction agents and requirements of intra op analgesia and also brings down the incidence of post-operative complications such as nausea, vomiting and shivering. It was also observed that clonidine does not cause significant sedation in post-op period.

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AUTHORS:

1. Sudheer R.
2. Karthik G. S.
3. Sahajananda H.
4. Rangalakshmi S.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Anaesthesiology, Raja Rajeswari Medical College & Hospital, Bangalore.
2. Assistant Professor, Department of Anaesthesiology, Raja Rajeswari Medical College & Hospital, Bangalore.

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3. Professor & HOD, Department of Anaesthesiology, Raja Rajeswari Medical College & Hospital, Bangalore.
4. Professor, Department of Anaesthesiology, Raja Rajeswari Medical College & Hospital, Bangalore.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Sudheer R,
560, 2nd B Main, 2nd Stage, 11th Block,
Nagarbhavi, Bangalore-560072.
E-mail: sudheer_mys@yahoo.co.in

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