HAEMODYNAMIC CHANGES DURING LAPAROSCOPIC CHOLECYSTECTOMY: EFFECT OF CLONIDINE PREMEDICATION

Mrinmoy Das¹, Manjushree Ray², Gauri Mukherjee³

Summary

Clonidine has been shown to reduce perioperative haemodynamic instability. The aim of the study was to investigate the clinical efficiency of oral clonidine premedication in prevention of haemodynamic response associated with pneumoperitoneum.

Sixty adult patients of ASA physical status I & II, scheduled for elective laparoscopic cholecystectomy were recruited for a prospective randomized, double-blinded comparative study. They were randomly allocated to one of the two groups to receive either oral clonidine 150 µg (Group C) or ranitidine 150 mg (Group P), 90 minute before induction of anaesthesia.

Significant rise in heart rate was observed following pneumoperitoneum in Group P as compared to Group C (99.23±14.02 Vs 81.26±8.40 bpm). Similarly, rise in systolic arterial pressure (143.63±19.60 Vs 119.6±10.06 mm Hg), diastolic arterial pressure (99.23±14.02 Vs 81.26±8.40 mm Hg) and mean arterial pressure (114.13±16.57 Vs 93.83±8.107 mm Hg) was more in Group P following pneumoperitoneum. Nitroglycerine drip was started in 33.3% patients in Group P to control intraoperative hypertension. Incidence of postoperative nausea-vomiting and shivering was also less in Group C.

To conclude, clonidine premedication provides perioperative haemodynamic stability, hence it can be recommended as a routine premedication for laparoscopic procedure.

Key words Laparoscopic cholecystectomy; Pneumoperitoneum, Haemodynamic response; Clonidine premedication.

Introduction

Laparoscopic cholecystectomy has revolutionized gall bladder surgeries and it has now become the “gold standard” of cholelithiasis. It offers many benefits than conventional cholecystectomy, and has been promoted, as a “gentle surgery”. However, this procedure is not risk free. In fact it produces significant haemodynamic changes specially in elderly and haemodynamically compromised patients.

Pneumoperitoneum (Pnp) affects several homeostatic systems leading to alteration in acid-base balance, cardiovascular, pulmonary physiology and stress response. The extent of cardiovascular changes associated with pneumoperitoneum include an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which in turn compromise tissue perfusion.

Various pharmacological agents were chosen to prevent haemodynamic changes associated with pneumoperitoneum. Nitroglycerine was used to correct the reduction of cardiac output associated with increased pulmonary occlusion pressure and systemic vascular resistance.¹

Aho et al² used α₂ adrenergic receptor agonist for prevention of haemodynamic responses associated with laparoscopic surgery. They found that dexmedetomidine effectively reduces the maximum heart rate response after intubation and pneumoperitoneum. Clonidine inhibits the release of catecholamine and vasopressin and thus

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modulates the haemodynamic changes induced by pneu-
moderately.

Considering all these observations, the present study
was designed to evaluate the type and extent of
haemodynamic changes associated with laparoscopic sur-
gery and also to find out the efficacy of clonidine in pre-
vention of such haemodynamic changes.

Methods

This randomized prospective study was carried out
in 60 adult patients of ASA physical status I and II, sched-
uled for laparoscopic cholecystectomy. The study was
approved by the institutional Ethical Committee and writ-
ten informed consent was obtained from all the patients
before being included in the study. Patients with history of
hypertension, ischaemic heart disease, aortic stenosis, left
ventricular failure and atrioventricular conduction block
were excluded from the study. Patients concomitantly tak-
ing clonidine, methyl dopa, beta blocking drugs, benzodiaz-
epines and MAO inhibitors were also excluded from the
study.

All patients received diazepam 5mg orally on the night
before surgery. They were randomly assigned to one of the
two groups to receive either clonidine 150 μg (Group C) or
ranitidine 150 mg (Group P) orally 90 minutes before induc-
tion of anaesthesia. The observer was totally blind about
the groups or medications received by the patients. Group
sizes of 30 were determined by power analysis based on
standard deviation data from previously published reports.

On arrival in the operation theatre, monitors were
attached and baseline parameters such as heart rate, sys-
temic arterial pressure and peripheral oxygen saturation
were noted down. Level of sedation (sedation score) was
assessed by sedation scale : (1) awake and agitated (2)
awake and comfortable (3) asleep but arousable (4) asleep
with sluggish response to persistent call or touch and (5)
no response to call or touch.

After intravenous cannulation, glycopyrrolate 0.2 mg,
was administered intravenously. Patients were induced
with sleep dose of thiopentone sodium. Endotracheal intu-
bation was facilitated by succinylcholine 1.5 mg.kg⁻¹ of body
weight. Anaesthesia was maintained with 33% oxygen in
nitrous oxide, 0.4% halothane and vecuronium bromide 0.1
mg.kg⁻¹. Peroperative analgesia was provided by fentanyl
citrate 1.5 μg.kg⁻¹ body weight. The tidal volume (V₆₀) and
the ventilatory frequency was adjusted and intermittent
positive pressure ventilation (IPPV) was continued by
mechanical ventilator to maintain end tidal carbon dioxide
between 35-45 mm Hg.

Pneumoperitoneum was created by insufflation of
carbondioxide and operation table was tilted about 15° re-
verse Trendelenburg position. Intra abdominal pressure
(IAP) was not allowed to exceed 15 mm Hg throughout
the surgical procedure. After pneumoperitoneum, neces-
ary changes in ventilator setting (tidal volume, respiratory
rate) were made to maintain normocapnia.

Throughout the procedure, any rise in mean arterial
pressure more than 20% from the baseline was treated
with nitroglycerine drip.

Systemic arterial pressure including the systolic, di-
astolic and mean arterial pressure, heart rate, SpO₂, EtCO₂
and electrocardiography (ECG) with ST segment analysis
were recorded at the following points of time : (1) prior to
induction (2) three minutes after endotracheal intubation
(3) before pneumoperitoneum (4) fifteen minutes after
pneumoperitoneum (5) thirty minutes after pneumoperito-
neum (6) ten minutes after release of CO₂ and (7) ten
minutes after extubation.

At the end of surgery residual neuromuscular block
was reversed by appropriate dose of neostigmine and
glycopyrrolate intravenously. Trachea was extubated and
patients were transferred to recovery room. In the
postanaesthesia care unit (PACU) they were monitored
for any evidence of complications or adverse events.
Degree of sedation and intensity of pain were also assessed
by using 10 point visual analogue scale (VAS).

The results obtained in the study are presented in
tabulated manner. Statistical analysis was done by stu-
dents ‘t’ test. Chi square test was performed for non-
parametric values and corresponding P was computed. P
value <0.05 was considered statistically significant.

Results

Two patients were withdrawn from the study be-
cause the proposed laparoscopic cholecystectomy surgery
was converted to open cholecystectomy. Aside from these
two patients, 58 patients completed the analysis.

Demographic profile and preoperative vital parameters
were compared among the two groups of patients and no
significant difference was found (Table 1 & 2). Mean intra-

abdominal pressure was 13.1±1.47 mm Hg in Group P and 12.7±1.15 mm Hg in Group C. Normocapnia was maintained throughout the procedure. EtCO₂ varied from 31.13±3.45 to 35.46±5.36 mm Hg in Group P and 30.66±2.38 to 34.06±3.18 mm Hg in Group C.

Table 1 Demographic profile (Mean ± SD)

<table>
<thead>
<tr>
<th>Demographic Profile</th>
<th>Group C</th>
<th>Group P</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.13±9.47</td>
<td>35.13±8.27</td>
<td>0.196</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>57.06±5.98</td>
<td>59.83±7.15</td>
<td>0.109</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M : F)</td>
<td>5 : 25</td>
<td>8 : 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA Grading</td>
<td>Grade I = 26</td>
<td>Grade I = 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II = 4</td>
<td>Grade II = 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Preoperative vital parameters (Mean ± SD)

<table>
<thead>
<tr>
<th>Vital Parameters</th>
<th>Group C</th>
<th>Group P</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Rate (bpm)</td>
<td>79.4±7.81</td>
<td>84.4±11.21</td>
<td>0.357</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>94.7±7.22</td>
<td>91.7±9.02</td>
<td>0.151</td>
<td>NS</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>96.4±4.127</td>
<td>96.3±1.20</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sedation Score</td>
<td>1.23±0.43</td>
<td>1.33±0.52</td>
<td>0.065</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3 Changes in pulse rate in two groups

<table>
<thead>
<tr>
<th>Pulse Rate (bpm)</th>
<th>Group P (Mean±SD)</th>
<th>Group C (Mean±SD)</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Premedication</td>
<td>81.43±11.21</td>
<td>79.1±7.81</td>
<td>0.3540</td>
<td>NS</td>
</tr>
<tr>
<td>Before Induction</td>
<td>88.53±14.02</td>
<td>75.16±9.93</td>
<td>0.085</td>
<td>S</td>
</tr>
<tr>
<td>After Intubation</td>
<td>107.76±14.06</td>
<td>87.26±11.34</td>
<td>0.0069</td>
<td>HS</td>
</tr>
<tr>
<td>Before Pneumoperitoneum</td>
<td>86.56±16.75</td>
<td>76.26±9.42</td>
<td>0.052</td>
<td>S</td>
</tr>
<tr>
<td>After Pneumoperitoneum (15 minutes)</td>
<td>96.06±21.81</td>
<td>75.76±10.07</td>
<td>0.008</td>
<td>HS</td>
</tr>
<tr>
<td>After Pneumoperitoneum (30 minutes)</td>
<td>94.73±19.79</td>
<td>75.53±10.15</td>
<td>0.0044</td>
<td>HS</td>
</tr>
<tr>
<td>After Release of Carbon dioxide</td>
<td>84.57±15.15</td>
<td>74.1±8.71</td>
<td>0.0026</td>
<td>HS</td>
</tr>
<tr>
<td>After Extubation</td>
<td>113.17±13.53</td>
<td>93.6±7.93</td>
<td>0.0048</td>
<td>HS</td>
</tr>
</tbody>
</table>

Table 4 Changes in systolic blood pressure in two groups

<table>
<thead>
<tr>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Group P (Mean ± SD)</th>
<th>Group C (Mean ± SD)</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Premedication</td>
<td>118.96±12.07</td>
<td>121.5±8.45</td>
<td>0.376</td>
<td>NS</td>
</tr>
<tr>
<td>Before Induction</td>
<td>121.73±11.14</td>
<td>111.03±9.42</td>
<td>0.00017</td>
<td>HS</td>
</tr>
<tr>
<td>After Intubation</td>
<td>143.6±21.54</td>
<td>120.56±6.58</td>
<td>0.0061</td>
<td>HS</td>
</tr>
<tr>
<td>Before Pneumoperitoneum</td>
<td>123.9±14.46</td>
<td>113.6±9.64</td>
<td>0.0018</td>
<td>HS</td>
</tr>
<tr>
<td>After Pneumoperitoneum (15 minutes)</td>
<td>143.6±19.60</td>
<td>119.6±10.06</td>
<td>0.00015</td>
<td>HS</td>
</tr>
<tr>
<td>After Pneumoperitoneum (30 minutes)</td>
<td>140.75±18.52</td>
<td>119.03±8.22</td>
<td>0.0028</td>
<td>HS</td>
</tr>
<tr>
<td>After Release of Carbon dioxide</td>
<td>125.64±13.77</td>
<td>116.23±9.48</td>
<td>0.0032</td>
<td>HS</td>
</tr>
<tr>
<td>After Extubation</td>
<td>139.35±9.53</td>
<td>124.13±8.10</td>
<td>0.018</td>
<td>S</td>
</tr>
</tbody>
</table>

NS = Not significant; S = Significant; HS = Highly Significant
Ten patients (33.3%) in Group P received nitroglycerine infusion (0.5 μg.kg⁻¹.min⁻¹) for treatment of intraoperative hypertension. It was not required in Group C patients, because they remained haemodynamically stable. Intensity of pain was less in Group C as compared to Group P (VAS 1.9±1.688 Vs 5.214±2.114) during early postoperative period.

Incidence of nausea-vomiting, hypertension, shivering and shoulder pain were 35.70%, 35.70%, 10.7% and 14.3% in the Group P, while only 6.89% patients suffered from nausea vomiting in Group C. Sedation was common in Group C (33.3%). Other complications were not ob-

### Table 5 Changes in mean arterial pressure in two groups

<table>
<thead>
<tr>
<th>Mean Arterial Pressure (mm Hg)</th>
<th>Group P (Mean ± SD)</th>
<th>Group C (Mean ± SD)</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Premedication</td>
<td>91.7±9.02</td>
<td>95.39±6.98</td>
<td>0.0883</td>
<td>NS</td>
</tr>
<tr>
<td>Before Induction</td>
<td>95±10.42</td>
<td>85.57±9.06</td>
<td>0.00059</td>
<td>HS</td>
</tr>
<tr>
<td>After Intubation</td>
<td>113.56±16.33</td>
<td>93.7±7.33</td>
<td>0.00018</td>
<td>HS</td>
</tr>
<tr>
<td>Before pneumoperitoneum</td>
<td>98.6±14.74</td>
<td>90.28±7.26</td>
<td>0.0129</td>
<td>S</td>
</tr>
<tr>
<td>After Pneumoperitoneum (15 minutes)</td>
<td>114.13±16.57</td>
<td>93.83±8.107</td>
<td>0.00182</td>
<td>HS</td>
</tr>
<tr>
<td>After Pneumoperitoneum (30 minutes)</td>
<td>108.60±15.11</td>
<td>93.64±8.40</td>
<td>0.033</td>
<td>S</td>
</tr>
<tr>
<td>After Release of Carbon dioxide</td>
<td>97.25±11.34</td>
<td>90.63±8.96</td>
<td>0.01625</td>
<td>S</td>
</tr>
<tr>
<td>After Extubation</td>
<td>108.42±8.07</td>
<td>97.37±7.63</td>
<td>0.041</td>
<td>S</td>
</tr>
</tbody>
</table>

NS = Not significant; S = Significant; HS = Highly Significant

### Table 6 Changes in diastolic blood pressure in two groups

<table>
<thead>
<tr>
<th>Diastolic Blood Pressure (mm Hg)</th>
<th>Group P (Mean ± SD)</th>
<th>Group C (Mean ± SD)</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Premedication</td>
<td>78.93±8.22</td>
<td>81.67±7.11</td>
<td>0.018</td>
<td>NS</td>
</tr>
<tr>
<td>Before Induction</td>
<td>82.1±9.99</td>
<td>72.93±9.98</td>
<td>0.00075</td>
<td>HS</td>
</tr>
<tr>
<td>After Intubation</td>
<td>98.76±13.15</td>
<td>80.83±8.09</td>
<td>0.0006</td>
<td>HS</td>
</tr>
<tr>
<td>Before pneumoperitoneum (15 minutes)</td>
<td>83.43±12.09</td>
<td>77.76±9.58</td>
<td>0.073</td>
<td>NS</td>
</tr>
<tr>
<td>After Pneumoperitoneum (30 minutes)</td>
<td>99.23±14.02</td>
<td>81.26±8.40</td>
<td>0.0015</td>
<td>HS</td>
</tr>
<tr>
<td>After Pneumoperitoneum (30 minutes)</td>
<td>94.5±14.82</td>
<td>80.93±9.15</td>
<td>0.00015</td>
<td>HS</td>
</tr>
<tr>
<td>After Release of Carbon dioxide</td>
<td>82.60±12.18</td>
<td>77.66±9.79</td>
<td>0.093</td>
<td>NS</td>
</tr>
<tr>
<td>After Extubation</td>
<td>92.14±8.84</td>
<td>83.86±8.86</td>
<td>0.00138</td>
<td>HS</td>
</tr>
</tbody>
</table>

NS = Not significant; S = Significant; HS = Highly Significant
served in Group C. None of the patient showed any evidence of ischaemia or arrhythmia intraoperatively

**Discussion**

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum.

This double blind prospective study was carried out in 60 adult patients, to evaluate the effect of clonidine premedication in attenuating haemodynamic stress response associated with pneumoperitoneum.

Clonidine, an imidazoline derivative is a selective $\alpha_2$ adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased SVR and cardiac output. 150 $\mu$g (2.7 $\mu$g.kg$^{-1}$) clonidine was administered orally, 90 minutes before surgery in this series. Dose of clonidine varied from 2 to 5 $\mu$g.kg$^{-1}$ in different studies. Higher dose of clonidine (5 $\mu$g.kg$^{-1}$) is usually required for potentiation of postoperative analgesia by intrathecal morphine. A small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting haemodynamic stability. Aho et al$^2$ used 3 $\mu$g.kg$^{-1}$ and 4.5 $\mu$g.kg$^{-1}$ clonidine for suppression of haemodynamic response to pneumoperitoneum. Rise in blood pressure and heart rate was less in both the groups but 4.5 $\mu$g.kg$^{-1}$ clonidine produced greater fall in mean arterial pressure before induction. Joris et al$^3$ used very high dose of clonidine (8 $\mu$g.kg$^{-1}$) for reducing the level of catecholamine and vasopressin following pneumoperitoneum. Malek et al$^4$ used 150 $\mu$g of clonidine as i.v. infusion and intramuscularly while Sung et al$^7$ and Yu et al$^8$ used 150 $\mu$g of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.

Following pneumoperitoneum with carbon dioxide, patients were hyper ventilated to maintain normocapnia. Every effort was made to maintain intra abdominal pressure (IAP) below 14 mm Hg. Mean intra-abdominal pressure was 13.1±1.47 mm Hg in Group P and 12.7±1.15 mm Hg in Group C.

Haemodynamic changes associated with pneumoperitoneum was first recognized in 1947. Diamant et al$^9$ reported 35% decrease in cardiac output in dog with a raised intra abdominal pressure of 40 mm Hg. Ishizaki et al$^{11}$ tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery. They observed significant fall in cardiac output at 16 mm Hg of intra-abdominal pressure. Haemodynamic alterations were not observed at 12 mm Hg of intra-abdominal pressure. Based on all these observations the current recommendation is to monitor intra-abdominal pressure and to keep it as low as possible.

Cunningham et al$^{12}$ and Dorsay et al$^{13}$ assessed the ejection fraction (EF) of left ventricle by trans esophageal echocardiography during pneumoperitoneum. No significant change in ejection fraction was reported up to 15 mm Hg of intra-abdominal pressure. Considering all these facts intra abdominal pressure was kept below 14 mm Hg.

In spite of maintaining normocapnia and keeping intra-abdominal pressure below 14 mm Hg significant rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed in Group P. Rise in systolic, diastolic and mean arterial pressure was more than 20% from the baseline. Slight fall in systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed following premedication with clonidine. Following intubation and pneumoperitoneum, increase in arterial pressure was noticed but it never crossed the base line value. Hence clonidine premedication was able to achieve haemodynamic stability during pneumoperitoneum.

Similar findings were reported by Aho et al$^2$, Joris et al$^3$, Malek et al$^4$, Sung et al$^7$, Yu et al$^8$ and Laisalmi et al$^{14}$.

Aho et al$^2$ observed that 4.5 $\mu$g.kg$^{-1}$ of clonidine significantly decreased the mean arterial pressure before induction of anaesthesia. So they recommended 3 $\mu$g.kg$^{-1}$ of clonidine for perioperative haemodynamic stability. Joris et al$^3$ used higher dose of clonidine for reduction of catecholamine and vasopressin associated with pneumoperitoneum. Clonidine significantly reduced the concentration of catecholamine but not vasopressin and cotisol concentration. Similarly Sung et al$^7$ observed haemodynamic stability during pneumoperitoneum with 150 $\mu$g oral clonidine. Requirement of isoflurane was also less by 30% in the clonidine group. Esmolol, labetalol and nifedipine were used...
to control hypertension in control group. Finally Yu et al. recommended the routine use of clonidine premedication in laparoscopic patients.

The adverse effects in the postoperative period were less in the patients who had clonidine premedication in comparison with placebo premedication. There was incidence of shivering in 10.70% patients in the placebo group compared to none in the clonidine group.

This finding corroborates the finding of Nicolaou et al, where they concluded that clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centers. Thus he opined that clonidine can be used as an effective agent for inhibition of perioperative shivering which can adversely increase metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence.

Thirty five percent of patients of the Group P suffered from nausea and / or vomiting, while only 6.89% of the patients receiving clonidine had any such episode. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system. Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts warrants further investigation.

In conclusion, premedication with 150 µg oral clonidine, has been found to be relatively safe as well as effective method that provides stable haemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Clonidine also affords an added advantage of reduction in postoperative complications such as nausea-vomiting and shivering.

Hence 150 µg oral clonidine can reasonably be recommended as premedicant for all laparoscopic procedures in otherwise healthy patients. However further study is required to find out its efficacy in patient with compromised cardiovascular system.

References