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A Comparative Study of Oral Clonidine and Midazolam Premedication on Haemodynamic Changes during Laparoscopic Cholecystectomy

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ABSTRACT

Laparoscopic cholecystectomy has revolutionized gall bladder surgeries and it has now become the "gold standard" of cholelithiasis. The present study is aimed to observe the changes in heart rate and blood pressure, if any associated with this procedure by the use of oral clonidine and midazolam as a premedication and to study the effect on end tidal carbondioxide.

Methods: The patients posted for laparoscopic cholecystectomy were randomly divided into three groups of thirty patients each and oral premedication was given sixty minutes before surgery. Group I: Received 150mcg of oral clonidine. Group II: Received 7.5mg of oral midazolam. Group III: Control group without any premedication. The observer was totally blind about the groups or medications received by the patients. Statistical analysis was done by students 't' test. Chi square test was performed for non-parametric values and corresponding P value <0.05 was considered statistically significant.

Result: In our study, we found that Clonidine decreases heart rate (P <0.05), mean arterial blood pressure (P <0.05) and EtCO2 (P <0.05), while midazolam causes increase in heart rate (P <0.05), mean arterial blood pressure (P <0.05) and EtCO2 (P <0.05).

Conclusion: Clonidine orally can be reasonably recommended as a premedicant for all laparoscopic procedures in otherwise healthy individuals.

Keywords: Laparoscopy; Cholecystectomy; Clonidine; Midazolam; EtCO2 (end tidal carbondioxide)

INTRODUCTION

Laparoscopic cholecystectomy has revolutionized gall bladder surgeries and it has now become the "gold standard" of cholelithiasis. Philips Mouret performed the first laparoscopic cholecystectomy in 1987 in France.[1] However this procedure is not risk free. In fact, it produces significant haemodynamic changes especially in elderly and cardiovascular compromised patients.

Laparoscopic cholecystectomy combines the benefits of completely removing the gall bladder with the advantages of shorter hospital stays, more rapid return of normal activities, less pain associated with small limited incision and less postoperative ileus compared with the open laparotomy technique.

Peritoneal insufflation of CO_2 during most operations contribute to significant hemodynamic changes associated with laparoscopy. Despite considerable depth of anaesthesia, peritoneal CO_2 insufflations induced a significant and immediate increase in blood pressure and systemic vascular resistance, while $EtCO_2$ gradually increases. These hemodynamic

changes may be detrimental for the patients, so the drugs that prevent these changes need to be used.

Clonidine, an imidazoline derivative is a selective α_2 adrenergic agonist. It produces a fall in heart rate and blood pressure associated with decrease in systemic vascular resistance and cardiac output.[2]

Midazolam is a benzodiazepine characterized by rapid onset and short duration of action. It is a sleep inducing agent and has anticonvulsant, anxiolytic and muscle relaxant properties. Premedication by oral administration of midazolam is safe and an effective method of sedation that significantly reduces anxiety.[3]

The present study is aimed

- To observe the changes in heart rate and blood pressure, if any associated with this procedure and by the use of oral clonidine and midazolam as a premedication.
- To study the effect on end tidal carbon dioxide consequent to the use of these drugs in laparoscopic cholecystectomy.

MATERIALS AND METHODS

Selection of patients

The present study was conducted on ninety adult patients of either sex admitted to St. Stephen's Hospital, Delhi. Necessary approval of hospital ethical committee was taken for the patients undergoing elective laparoscopic cholecystectomy under general anaesthesia.

Setting- Department of Anaesthesia, St. Stephen's Hospital, Delhi, India

Study period - From 01/06/2009 to 30/05/2010.

Study Design

The study was a randomized, control, prospective, double blind and observational study. Randomization was done using computer generated random numbers.

Inclusion Criteria:

1. Adult patients of either sex between 25-50 years and between 40-60 kilograms.
2. ASA class 1 and 2.
3. Elective cases posted for laparoscopic cholecystectomy.

Exclusion criteria:

1. ASA III and IV
2. Patients concomitantly taking clonidine, methyldopa,beta-blocking drugs,benzodiazepines and MAO inhibitors.
3. Those patients who will be converted to open cholecystectomy.

Pre-anaesthetic management

A detailed pre anaesthetic checkup was done in all the patients, which included a detailed history and through physical examination. The following investigation were carried out in all the patients: Routine haemogram, blood sugar, blood urea nitrogen, serum creatinine, serum electrolyte, chest x-ray, ECG.

An informed consent was taken from all the patients. The patients were asked to restrict oral intake overnight or at least six hours before surgery.

Allocation of groups

The patients were randomly divided into three groups of thirty patients each and oral premedication was given sixty minutes before surgery.

Group I: Received 150mcg of oral clonidine.

Group II: Received 7.5mg of oral midazolam.

Group III: Control group without any premedication.

The observer was totally blind about the groups or medications received by the patients.

Baseline monitoring

On arrival in the operation theatre, monitors comprising of ECG (lead II), non-invasive automated blood pressure, pulse oximeter and end tidal carbondioxide were applied to all the patients and baseline parameters such as heart rate, blood pressure and spo2 were recorded.

A suitable peripheral vein was secured in all the patients 10 minute prior to induction of anaesthesia and total amount of fluid required intraoperatively was calculated on a per kg basis in all patients. 50% of the total fluid required was given in the first hour, 25% in the second hour and the rest 25% in the third hour. Maintenance fluid was continued till the patient started taking orally.

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Anaesthetic technique

Through intravenous cannulation, glycopyrrolate 0.2 mg was administered intravenously. Patients were induced with a sleep dose of thiopentone sodium. Endotracheal intubation was facilitated by succinylcholine 1.5mg.kg-1 of body weight. Anaesthesia was maintained with 33% oxygen nitrous oxide, 0.4% halothane and vecuronium bromide 0.1mg.kg-1. Preoperative analgesia was provided by fentanyl citrate 1.5 mcg.kg-1 body weight. The tidal volume (VT) 6ml to 8ml per kg and the ventilatory frequency 12 to 14 per minute was adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator. Pneumoperitoneum was created by insufflation of carbon dioxide and operation table was tilted about 15° reverse Trendelenburg position. Intra-abdominal pressure (IAP) was not allowed to exceed 15 mm Hg throughout the surgical procedure. After pneumoperitoneum, necessary changes in ventilator setting (tidal volume, respiratory rate) were made and $EtCO_2$ was not allowed to cross beyond 50mmHg in any group. Throughout the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with nitroglycerine drip. Including the systolic, diastolic and mean arterial pressure, heart rate, SpO_2, $EtCO_2$ 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 pneumoperitoneum (6) ten minutes after release of CO_2 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. Oxygen saturation was noted down and was recorded.

Statistical analysis

The results obtained in the study are presented in tabulated manner. Statistical analysis was done by students “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’

In conclusion, the results of the present study indicate that:

In laparoscopic cholecystectomy in control group (Group III), there was significant rise in haemodynamic parameters like heart rate(Table2), blood pressure(Table3) and increased end tidal carbondioxide(Table4).

Premedication with 150 mcg oral clonidine in Group I, has been found to be relatively safe as well as effective method to provide stable haemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy(Table2and3) and prevents increase in end tidal carbondioxide as compared to patients receiving 7.5mg oral midazolam (Table 4).

DISCUSSION

The study was performed in 90 patients of ASA physical status I and II divided randomly into three groups. Group I received tab clonidine 150mcg while group II received tab midazolam 7.5mg oral premedication 60 minutes before induction and group III without any premedication. In all the three groups' pre induction heart rate and mean arterial blood pressures were taken (Table1). Intra operative values of heart rate, mean arterial blood pressure and $EtCO_2$ values were compared at different time intervals.

In our study, in group I we used oral clonidine 150 mcg which caused statistically significant ($p<0.05$) fall in heart rate which was seen 10 minutes after intubation and onwards upto reversal (Table 2). Clonidine decreases heart rate by parasympathetic stimulation. Our findings are supported by Malek et al[4] who used 150 µg of clonidine as intravenous infusion and intramuscularly as premedication for maintenance of haemodynamic stability during pneumoperitoneum. In another study Yu et al[5] used 150 µg of oral clonidine as premedication and concluded that clonidine preserves heart rate variability for patients undergoing laparoscopic cholecystectomy.

In our study, in clonidine group out of 30 patients 23 patients (76%) had increased heart rate after

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intubation due to intubation response. 10 minutes onwards after intubation fall in heart rate was statistically significant ($p < 0.05$). In our study we observed that the fall in heart rate was statistically significant at 80 to 90 minutes because clonidine reaches to its peak plasma concentration after 2hrs. At reversal, slight increase in heart rate was seen due to light plane of anaesthesia and intravenous atropine.

In group II we used oral midazolam tab at the dose of 7.5mg. Statistically significant ($p<0.05$) rise in heart rate was seen just after intubation upto reversal (Table 2).

In control group, there was statistically significant ($p<0.05$) rise in heart rate just after intubation upto reversal. At the time of intubation increase in heart rate was because of intubation response. After that rise in heart rate was due to pneumoperitoneum. Pneumoperitoneum induced hypercarbia causes sympathetic stimulation[6,7] which leads to increased heart rate (Table 2).

Statistically significant ($p<0.05$) difference in heart rate between clonidine and midazolam was seen after 15 minutes of intubation upto reversal as clonidine decreases heart rate while midazolam increases heart rate (Table 2).

On comparing clonidine group to control group statistically significant difference in heart rate was seen after intubation upto reversal. At the time of intubation both groups showed rise in heart rate. This rise in heart rate was due to intubation response. Clonidine decreases heart rate by stimulating parasympathetic outflow, which may contribute to the slowing of heart rate as a consequence of increased vagal tone and diminished sympathetic drive. While in group III from 5 minutes onwards rise in heart rate was due to sympathetic stimulation as a consequence of pneumoperitoneum (Table 2).

At the time of intubation rise in heart rate due to intubation response was seen with midazolam and also with control group. Statistically significant difference in mean heart between midazolam group and control group was seen at 5 minutes after intubation upto 30 minutes. Although midazolam causes increase in heart rate but it restricts the increase in heart rate compared to control group (Table2).

In Group I clonidine in their tested doses lead to a significant decrease in mean arterial pressure to their preinduction level (Table 3). However this decrease in mean arterial pressure by midazolam is not significant as compared to group I. Clonidine produces fall in blood pressure associated with decreased cardiac output and SVR. Our findings are consistent with Sung et al[8] who used oral clonidine as premedication and suggested that clonidine provides perioperative hemodynamic stability.

Midazolam causes transient decrease in mean arterial pressure by decreasing systemic vascular resistance (SVR), venodilation,[9] and a transient change in portal blood flow[10]which combines to reduce cardiac filling. Midazolam also decreases myocardial contractility by direct action.

In control group there was a significant rise in the mean arterial pressure which may be due to intubation response, hypercarbia and baroreceptor stimulation which is due to reduced venous return and cardiac output combined with reverse Trendelenberg's position and pain (Table 3). The rise in mean arterial blood pressure was significantly higher in control group than in clonidine and midazolam group.

In clonidine group there was significant decrease in $EtCO_2$ which persisted upto reversal where as in midazolam group there was significant increase in $EtCO_2$ (Table 4). The decrease in blood pressure can decrease lung perfusion, which may lead to fall in $EtCO_2$. But it is proven that both drugs do not have any direct effect on $EtCO_2$. In placebo group significant ($p<0.05$) rise in $EtCO_2$ persisted upto reversal due to pneumoperitoneum (Table 4).

Hence we have seen in our study that clonidine is more effective than midazolam to prevent change in hemodynamic parameters induced by CO_2 insufflation in laparoscopic cholecystectomy. Earlier studies have also shown similar kind of results but this kind of comparative study was lacking. However in this study the patient population is very small so generalization of the results of this study over our population needs more validation.

CONCLUSION

Oral clonidine can reasonably be recommended as a premedicant for all laparoscopic procedures in otherwise healthy patients.

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Table 1: Preoperative vital parameters (Mean + SD)

Vital parameters	Group I	Group II	Group III	P Value	Significance
Pulse Rate (bpm)	99.8±20.1	90.5±10.6	104.5 ± 14.8	0.304	NS
MAP (mm Hg)	82.4±15.1	78.9±10.6	78.2±13.2	0.318	NS
SpO2 (%)	99.7±0.9	99.9±0.4	99.8±0.4	0.489	NS

NS = Not significant **bpm=beats per minute**

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Table 2: Changes in pulse rate (Mean SD)

Pulse Rate(bpm)	Group 1	Group 2	Group 3	P Value	Significance
Before Induction	75.9±13.7	80.2±11.5	84.7±14.1	0.013	S
After Intubation	96.5±20.8	102.2±21	107±21.5	0.019	S
Before Pneumoperitoneum	81.7±12.6	84.1±12.2	89±20.2	0.007	HS
After Pneumoperitoneum (15 min.)	91.1±15.2	96.9±14.3	103±19.6	0.014	S
After Pneumoperitoneum (30 min.)	86±16.6	95.5±9	103.5±18	0.004	HS
After Release of Carbon dioxide	95.6±18.9	97.0±9.3	100±14.5	0.001	HS
After Extubation	101±12.6	102±10.8	105.8±14	0.031	S

S= significant HS= Highly significant

Table 3: Changes in Mean arterial pressure (Mean±SD)

Mean Arterial Pressure (mmHg)	Group I	Group II	Group III	P Value	Significance
Before Induction	97.5±9.5	102.4±5.2	106.2±10.5	0.006	HS
After Intubation	100.4±13.9	104.4±13.2	109.1±17.6	0.003	HS
Before Pneumoperitoneum	79.1±15.5	94.7±18.2	100.3±18.8	0.002	HS
After Pneumoperitoneum (15 min.)	96.9±10.9	104.7±12.4	105.3±25.8	0.015	S
After Pneumoperitoneum (30 min.)	93.2±11.5	99.7±11.3	105.7±14.6	0.004	HS
After Release of Carbon dioxide	92.4±12.5	101.1±8	108.2±13.7	0.002	HS
After extubation	94±12.4	100.4±11.1	107.3±11	0.001	HS

S=Significant HS= Highly Significant

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Table 4: Changes in ETCO2 (mm Hg) (Mean + SD)

ETCO2 (mm Hg)	Group I	Group II	Group III	P Value	Significance
Before Induction	35.1±2.2	32.8±3	34.5±2.9	0.4	NS
After Intubation	34.7±2.6	33.3±3.4	35.2±3.3	0.03	S
Before Pneumoperitoneum	37.3±2.5	36.3±4	37.8±2.7	0.02	S
After Pneumoperitoneum (15 min.)	35.9±3.1	40.5±4	43.6±3.6	0.006	HS
After Pneumoperitoneum (30 min.)	36±4.1	44.8±3.5	45.8±2.2	0.001	HS
After release of Carbon dioxide	32.7±7	47.5±7.1	48.6±2.5	0.007	HS
After Extubation	33.7±5.1	48.8±3.6	50.6±5.5	0.002	HS

S= Significant HS=Highly Significant

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