

EFFECTS OF METOPROLOL ON HAEMODYNAMIC RESPONSE TO CARBON DIOXIDE PNEUMOPERITONEUM FOR LAPAROSCOPIC SURGERY

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ABSTRACT: BACKGROUND: Carbon dioxide pneumoperitoneum for laparoscopic surgery increases arterial pressures, heart rate and systemic vascular resistance. In this randomized double-blind placebo-controlled clinical study, we investigated the efficacy of metoprolol to provide perioperative haemodynamic stability in patients undergoing laparoscopic cholecystectomy. **METHODS:** Fifty patients, of either sex (20-40 yrs of age) undergoing elective laparoscopic cholecystectomy were randomly allocated in two groups containing 25 patients each. Group M received bolus dose of 10mg intravenous metoprolol before pneumoperitoneum. Group S received 0.9% saline of same volume. **RESULTS:** Mean arterial pressure and heart rate in Group M were significantly less throughout the period of pneumoperitoneum. Intravenous labetalol was required in 52% (13 out of 25) patients in group S to control intraoperative hypertension and it was clinically significant in comparison to group M. **CONCLUSION:** Metoprolol attenuates the adverse haemodynamic response to pneumoperitoneum and provide haemodynamic stability during laparoscopic surgery. **KEYWORDS:** Metoprolol, pneumoperitoneum, haemodynamics, laparoscopic surgery.

INTRODUCTION: Carbon dioxide is commonly used to create pneumoperitoneum for laparoscopic surgical procedures.^{1,2} Both carbon dioxide and pneumoperitoneum cause adverse cardiovascular effects.³ Adverse cardiovascular changes are characterized by elevation of arterial pressure and systemic vascular resistance and decreased cardiac output.⁴ These haemodynamic responses are mainly due to increased release of catecholamines, vasopressin or both.^{5,6} Attenuation of adverse haemodynamic response to pneumoperitoneum is usually done by opioids,⁷ vasodilators⁸ and alpha₂ adrenergic agonists.^{9,10}

Metoprolol, a cardioselective beta1 adrenoceptor antagonist, has been used to control tachycardia and hypertension. Esmolol, an ultrashort-acting cardioselective beta1 adrenoceptor antagonist, also blunts adrenergic responses to perioperative noxious stimuli effectively.¹¹ Vucevic M and colleagues¹² have shown that esmolol is effective in attenuating the adverse haemodynamic response to laryngoscopy and endotracheal intubation.¹²

Therefore due to the similar pharmacodynamics of metoprolol (Being a cardio-selective beta1 adrenoceptor antagonist like esmolol), the researchers hypothesized that a bolus dose of metoprolol administered before pneumoperitoneum would be able to attenuate the adverse haemodynamic response to laparoscopic surgery.

METHODS: The study protocol was approved by the Institutional Ethics Committee and informed consent was obtained from the individual patients. Fifty American Society of Anesthesiologists' (ASA) grade I and II patients, aged 20-40 years, undergoing elective laparoscopic cholecystectomy under

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general anesthesia were randomly assigned to of the two groups of 25 patients each: Group M (Metoprolol group) and Group S (Control group). Before performing the study it was hypothesized, based on the review of the published literature and our clinical experience, that the hemodynamic effects pneumoperitoneum (Hypertension, tachycardia) will be evident in at least 70% of the patients. Considering an absolute improvement in the primary outcome by 40% in the study group by the addition of metoprolol (i.e. not more than 30% patients will have hypertension and tachycardia following pneumoperitoneum) can be considered as clinically relevant and based on a type I error level of 0.05; type II error level of 0.2, and a two sided test, we needed 21 patients in each treatment groups. Therefore to accommodate the probable drop outs a number of 25 patients in each group were included.

Patients with pre-existing hypertension, bronchial asthma, diabetes, sinus bradycardia and severe hepatic, renal, endocrine and cardiac dysfunction were excluded from the study. Patients were then randomly allocated (Using computer derived random number sequence) into two groups (n=25) to receive one of the following regimens: metoprolol 10mg in 10ml (Group M) or saline 0.9% 10ml (Group S). Identical syringes containing the study drug or saline were prepared and kept in sealed envelopes by another investigator blinded to the randomization. The anesthesiologist who administered anesthesia to the patient was unaware of the nature of study drug administered.

All the patients were given diazepam 10mg and ranitidine 150mg orally on the night before surgery and tab. Ranitidine was repeated on the day of surgery, two hours before induction, with sips of water. On arrival to operation theatre, routine ASA monitoring (Electrocardiography, pulse oxymetry, noninvasive blood pressure) was started and baseline vital parameters e.g. heart rate (HR), mean arterial blood pressure (MAP) and arterial oxygen saturation (SpO₂) were recorded. An intravenous line was started. Patients were induced with fentanyl 2µg/kg and propofol 2mg/kg intravenously (IV). Endotracheal intubation was facilitated by muscle relaxant rocuronium 0.7 mg/kg. Anesthesia was maintained with 33% O₂ in N₂O, 0.6% isoflurane and intermittent bolus dose of rocuronium. Patients received top-up of IV fentanyl 1µg/kg at half hourly intervals. Group M patients received metoprolol 10mg intravenously as a bolus dose before pneumoperitoneum and those allocated in Group S received same volume of 0.9% saline. CO₂ was insufflated into the peritoneal cavity to create pneumoperitoneum. Intra-abdominal pressure (IAP) was maintained up to 12mm Hg throughout the laparoscopic procedure. All the patients were positioned in a head-up tilt of 15°. The patients were mechanically ventilated to keep end-tidal carbon dioxide (EtCO₂) between 35-45 mmHg. Inj. Paracetamol 1000 mg was infused IV in every patient.

In cases of acute and severe haemodynamic fluctuations, the following medical interventions were taken: i) bradycardia (Heart rate <60 beats/min), bolus dose of 0.6mg atropine IV; ii) hypotension (MAP<60mm Hg), increased rate of infusion of IV fluid and/or bolus dose of phenylephrine 100mcg IV and; iii) hypertension (MAP>110mm Hg) bolus dose of labetalol 5mg IV.

At the end of the surgery, ondansetron 4mg was administered IV for prophylaxis against nausea and vomiting. Residual neuromuscular block was reversed with appropriate doses of neostigmine and glycopyrrolate and tracheal extubation was performed. HR and MAP were recorded at the following points of time:

1. Prior to induction.
2. 3 minutes after endotracheal intubation.
3. Before pneumoperitoneum.
4. 15 minutes after pneumoperitoneum.

5. 30 minutes after pneumoperitoneum.
6. 10 minutes after release of pneumoperitoneum.
7. 10 minutes after extubation.

Patients were observed for adverse events e.g. bradycardia, hypotension, hypertension during postoperative period in post-anesthesia care unit.

STATISTICAL ANALYSIS: The numerical data obtained from the study were expressed as Mean±SD. Student's t test was employed to calculate the statistical differences in continuous variables between the groups, categorical variables were compared with Chi-square test (or Fisher's exact test; as applicable). A 'p' value of <0.05 was considered to be statistically significant. SPSS; version 16.0 (SPSS, Chicago, IL) was used for analysis.

RESULTS: The patients allocated in the Group M and Group S were comparable with respect to age, distribution of gender, body weight and the duration of surgery (Table 1). No significant difference was found between the preoperative MAP and the MAP values following intubation ($p>0.05$, Table 2). Prior to the induction of anesthesia, following the endotracheal intubation and before the initiation of pneumoperitoneum, the MAP and HR values were comparable between the groups ($p>0.05$). However following pneumoperitoneum both the MAP and HR values in Group M were significantly lower compared to Group S, at 15 min, 30 min, following the release of CO₂ and after extubation ($p<0.05$, Tables 3, 4).

No patient of either of the Groups suffered from hypotension and bradycardia in our study. Hypertension occurred in 13 patients (52%) of group S whereas no patient of group M suffered from hypertension.

DISCUSSION: In the study, we observed the effects of metoprolol, administered before pneumoperitoneum, on haemodynamics in patients undergoing laparoscopic cholecystectomy.

In laparoscopic surgery, CO₂ is routinely used to create pneumoperitoneum.^{1,2} Immediately after pneumoperitoneum, plasma levels of catecholamines and vasopressin are increased. Increased catecholamine level activates the renin-angiotensin-aldosterone-system (RAAS) leading to some of the characteristic haemodynamic alterations like elevated arterial pressure and increased systemic/pulmonary vascular resistance.^{4,5} Vasopressin also contributes to elevation of arterial pressure by increasing the systemic vascular resistance.⁶ Drugs like clonidine,⁹ dexmedetomidine¹⁰ and magnesium sulphate¹³ have been successfully used for attenuating the rise in MAP and HR in response to pneumoperitoneum during laparoscopic surgery.

Metoprolol, a short acting cardioselective beta-adrenoceptor antagonist, has been used to control tachycardia and hypertension in the perioperative period. It is the prototype of cardioselective (β_1) blockers. Onset of action of IV metoprolol is immediate. Half-life varies from 2.8 to 7.5 hours. Since catecholamines released during pneumoperitoneum have positive chronotropic and inotropic actions, β_1 receptor antagonist like metoprolol slows the heart rate and decreases myocardial contractility. When tonic stimulation of β receptors is low, this effect is correspondingly modest. However, when sympathetic nervous system is activated as during pneumoperitoneum during laparoscopic surgery, metoprolol may attenuate the expected rise in heart rate and arterial pressure.

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Esmolol is an ultrashort-acting cardioselective β_1 adrenoceptor antagonist and is found effective to attenuate adrenergic responses to perioperative noxious stimuli.^{11,12,14} Koivusalo A.M. and colleagues¹⁵ have used esmolol in an initial bolus of 1mg/kg before pneumoperitoneum and followed by an infusion of 200mcg/kg/min. They observed that esmolol was effective in attenuating the rise of heart rate and arterial pressure during laparoscopic surgery.¹⁵ Based on the results of studies using esmolol, we planned to conduct our study using metoprolol as both the drugs are cardioselective β_1 blocker and metoprolol is much cost effective than esmolol.

There are very few studies on the efficacy metoprolol to attenuate adverse haemodynamic response during perioperative period. Magnusson J and colleagues¹⁶ conducted a study to find out the efficacy of metoprolol to attenuate the stress response to microlaryngoscopy. They administered 200 mg metoprolol orally as slow release tablet for 4days before surgery including the morning of the surgery and 10mg IV as bolus dose before induction. They observed that metoprolol decreased heart rate and general level of arterial pressure during anesthesia but did not affect the fluctuations in arterial pressure.¹⁶ Based on the IV bolus dose of metoprolol used in the above study, we have selected the IV bolus dose of 10mg metoprolol and observed its efficacy to attenuate the adverse haemodynamic response to pneumoperitonium.

Baseline MAP and MAP after intubation and before pneumoperitoneum was comparable between the two groups. But MAP was significantly lower throughout the period of CO₂ pneumoperitonium and after extubation in patients of group M compared to patients of group S. We observed the similar finding in case of heart rate too. So bolus dose of metoprolol administered intravenously before pneumoperitoneum was effective in attenuating the increase in mean arterial pressure (MAP) and heart rate (HR) during CO₂ pneumoperitoneum.

Diamant et al¹⁷ reported 35% decrease in cardiac output in dogs with a raised IAP of 40mmHg. Ishizaki et al¹⁸ tried to evaluate the safe IAP during laparoscopic surgery. They observed significant fall in cardiac output at 16 mm Hg of IAP and haemodynamic alterations were much less at 12mmHg of IAP. So in our study, we kept IAP 12mm Hg. In spite of maintaining normocapnia and keeping IAP 12mmHg, there was significant rise of MAP and HR in patients of Group S during pneumoperitoneum. However in Group M, haemodynamic responses to pneumoperitoneum were effectively blunted and both the MAP and HR were remained at a significantly lower level compared to Group S.

As far as the adverse effects are concerned, no patient of either group suffered from hypotension and bradycardia in our study. Hypertension occurred in 13 patients (52%) of Group S for which they had to be treated with inj. labetalol whereas no patient of Group M suffered from hypertension.

CONCLUSION: Metoprolol attenuates the elevation of mean arterial pressure and heart rate during and after pneumoperitoneum and thereby provides haemodynamic stability during laparoscopic surgery.

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Table 1 Patient's characteristics and duration of surgery (Mean ± SD)			
	Group M (n=25)	Group S (n=25)	P Value
Age (Years)	30.4 ± 5.12	31.4 ± 5.36	0.45
Sex (M/F)	9/21	11/19	
Weight (kg)	45.24 ± 8.16	47.88 ± 9.4	0.51
Duration of surgery (min)	45.4 ± 6.24	44.36 ± 5.26	0.54

Table 2 Changes in Mean Arterial Pressure (Mean ± SD)			
	Group M	Group S	Statistical Significance
Preoperative	88.4 ± 8.6	89.32 ± 6.8	P>0.05; NS
After intubation	100.4 ± 10.6	102.4 ± 11.2	P>0.05; NS
Before pneumo- Peritoneum (PP)	97.6 ± 10.8	98.6 ± 11.24	P>0.05; NS
15 min after PP	95.4 ± 10.4	109 ± 12.7	P<0.05; S
30 min after PP	96.6 ± 11.6	108 ± 12.6	P<0.05; S
After release of PP	90.4 ± 9.2	101.8 ± 11.4	P<0.05; S
After extubation	94.8 ± 10.36	104.6 ± 10.6	P<0.05; S

S –Significant; NS –Not Significant

Table 3 Changes in Heart Rate (Mean ± SD)			
	Group M	Group S	Statistical Significance
Preoperative	80.2 ± 6.3	81.34 ± 4.6	P>0.05; NS
After intubation	97.6 ± 10.44	100.2 ± 11.6	P>0.05; NS
Before pneumo- Peritoneum (PP)	86.6 ± 9.4	88.4 ± 8.8	P>0.05; NS
15 min after PP	78.2 ± 8.8	93.4 ± 11.4	P<0.05; S
30 min after PP	80.4 ± 10.4	94.8 ± 11.6	P<0.05; S
After release of PP	79.4 ± 9.6	90.2 ± 10.4	P<0.05; S
After extubation	85.2 ± 10.4	98.84 ± 11.6	P<0.05; S

S –Significant; NS –Not Significant

Adverse effects	Group M	Group S	Statistical Significance
Bradycardia	0	0	-
Hypotension	0	0	-
Hypertension	0	13	P< 0.05, S

S = Significant, NS = Not significant

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