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A prospective randomized double-blind controlled trial on evaluating the Efficacy of Inj.Metoprolol 50µgm/Kg. I.V., in attenuating the hemodynamic response to laryngoscopy, intubation and carbon dioxide pneumoperitoneum in patients undergoing laparoscopic appendicectomy

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Abstract

Introduction: We evaluated the efficacy of inj.Metoprolol 50 µgms/kg. i.v. given 5 minutes before induction of anesthesia in attenuating the hemodynamic response to intubation and CO_2 pneumoperitoneum.

Materials and Method: We conducted a randomized double-blind controlled study on 60 patients. Five minutes before induction of anesthesia, either inj. Metoprolol 50µgm/kg diluted to 10 ml or 10ml normal saline given intravenously. Heart Rate(HR) and MAP recorded at basal, one, five minutes after Intubation, 15 minutes after establishing pneumoperitoneum, before and after extubation were analyzed with Descriptive statistics.

Results: In Both the groups no significant increase was observed in HR at 1 minute and 5 minutes after intubation compared to the basal HR. But the MAP at 1 and 5 minutes after intubation increased significantly in control group, whereas no significant increase occurred in Metoprolol group. HR and MAP recorded at 15 minutes after pneumoperitoneum showed significant increase from both basal and pre pneumoperitoneum values in control group but no significant increase was observed in Metoprolol group. During Extubation also no significant increase in HR and MAP observed in Metoprolol group compared to pre extubation values whereas Control group showed significant increase in HR and MAP after extubation compared to pre extubation values.

Conclusion: Intravenous Metoprolol 50 µgms/kg. i.v. given 5 minutes before induction of anesthesia reduces adverse hemodynamic changes during intubation and pneumoperitoneum during laparoscopic surgeries. There are no significant adverse effects during surgery or 8 hours post operatively.

Keywords: Laparoscopic surgery, Metoprolol, Pneumoperitoneum, Intubation response, Hemodynamic response

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Introduction

Laparoscopic procedures offer specific advantages to the patient like less post-operative pain, and quicker recovery, shorter hospital stay, early ambulation, less morbidity and smaller scars. Carbon dioxide pneumoperitoneum produced during these procedures causes similar hemodynamic changes as in airway manipulation.[1,2] Tachycardia and hypertension either due to intubation or due to pneumoperitoneum may cause hemodynamic instability in patients with cardiovascular disease. This may be due to increased intra-abdominal pressure, Neurohumoral responses and absorbed carbon dioxide leading to hypercarbia.[3] Many pharmacological techniques using adrenoreceptor blockers,[4-11] opioids,[10] vasodilators[12] were used to attenuate these responses. Metoprolol, a selective β1 adrenergic blocking agent acts by,[13,14] competitive antagonism of catecholamines at peripheral(especially cardiac) adrenergic neuron sites, leading to decreased blood pressure; Central effect leading to reduced sympathetic outflow to the periphery; Suppression of renin activity. These properties of metoprolol make it suitable for suppressing the stress response. Moreover, the elimination halftime of Metoprolol[13] being 3.5 hours allows it to be administered as a single dose covering the duration of surgery. Short acting drugs like esmolol require continuous infusion throughout the surgery which is less cost effective than single-dose metoprolol. Thus in this study, we evaluated the efficacy of injection metoprolol 50 micrograms/kg. i.v. in attenuating stress responses to intubation and pneumoperitoneum.

Aim of the Study

To study the efficacy of Inj.Metoprolol 50 micrograms/kg i.v. given 5 minutes before induction of anesthesia in attenuating hemodynamic stress response to laryngoscopy, intubation, and carbon dioxide pneumoperitoneum in laparoscopic appendicectomies and to observe for any complications related to inj.Metoprolol during intraoperative period and 8 hours postoperatively.

Materials and Method

After obtaining hospital ethical committee approval 60 ASA Class I & II patients, with airway Mallampatti classification 1 & 2, in the age group of 15 to 45

undergoing laparoscopic appendicectomy were selected for the study.

Study design: Prospective randomized double-blind controlled study. Randomization was done using a set of computer generated random numbers. The anesthesia provider and the observer were blinded. Another person other than the anesthesia provider and the observer loaded either inj. Metoprolol or normal saline as per the random numbers and gave it to the anesthesia provider. The syringes were labeled only with the serial no. assigned to the patient. Descriptive statistics were done for all data and were reported in terms of mean values and percentages. Continuous variables were analyzed with the unpaired t test and ANOVA. Categorical variables were analyzed with the Chi-Square Test and Fisher Exact Test. The P value of less than 0.05 is taken as significant.

Thorough preoperative assessment with history, physical examination and investigations carried out (Hb%, Total count, differential count, renal function tests, blood routine, ECG, Chest X-ray). Patients with Hypertension, Ischemic heart disease, rhythm other than sinus, any degree of heart block, diabetes mellitus, COPD, bronchial asthma, peripheral vascular disease were excluded from study. When we took more than 1 attempt at intubation and patients who were converted to open surgery after laparoscopic visualization were excluded from the study.

Anesthesia: All the 60 patients were given Tablet Alprazolam 0.25mg, Cap.Omeprazole 20mg, Tablet Ondansetron 4 mg night before surgery. On the morning of surgery, while the patient was at rest in the ward Heart Rate and Blood Pressure recorded and these were taken as basal values for the patient. For all the patients Inj.glycopyrolate 0.2mg i.m. given 1 hour before surgery. In the operation theater, patients connected to ECG monitor, Non Invasive Blood Pressure Monitor, Pulse oximeter and End-tidal carbon dioxide, Urine Output were monitored. All baseline values recorded. Intra venous access established. Five minutes before induction of anesthesia, the contents of the syringe (either inj.Metoprolol 50µgm/kg diluted to 10 ml or 10ml normal saline) given intravenously over a period of 3 minutes. All the 60 patients received inj.Fentanyl 2 µ/kg for analgesia and additional 0.5 µ/kg every hour for the duration of surgery. They were induced with inj.Propofol 2mg/kg., inj. Succinylcholine 1.5mg/kg for muscle relaxation and intubated 60seconds after succinylcholine injection with an appropriate size cuffed endotracheal tube. Intubation was done by the same person in all the cases. Anesthesia was maintained with nitrous oxide-oxygen mixture, with isoflurane 1 MAC and Inj.Vecuronium for muscle relaxation. ET CO2 maintained between 25 to 35 mm of Hg by adjusting the minute ventilation**.** Intra-abdominal pressure maintained at 12 mm of Hg by CO2 insufflation. Inj.Neostigmine and inj.glycopyrolate were used for reversal of muscle relaxation. Heart Rate, SpO2, ETCO2 monitored continuously and Blood Pressure (systolic, diastolic, MAP recorded every 5 minutes, before intubation, one min, five minutes after intubation, before extubation and after extubation and as often required. Episodes of hypertension (i.e. blood pressure >20% of the baseline) were managed with additional inj.Fentanyl 0.25microgram/kg. Episodes of hypotension (i.e. blood pressure <20% of the baseline) were managed by fluid boluses and vasopressors. Incidences of bradycardia (heart rate less than 60/minute) were noted down. Patients were monitored 8 hours postoperatively for ECG Changes, arrhythmias, bradycardia, hypotension and bronchospasm.

Measurements taken at the following timings were noted: Basal, one and five minutes after intubation, before pneumoperitoneum, every 15 minutes after establishing pneumoperitoneum**,** before extubation and after extubation. In addition, duration of the laryngoscopy and duration of pneumoperitoneum were also recorded.

Results

Metoprolol group (group M) and Control group (group C) were compared in respect to age, sex, weight, Airway Class, Duration of laryngoscopy and Duration of Pneumoperitoneum. Heart Rate(HR) and Mean Arterial Pressure(MAP) values recorded at one and five minutes after intubation were compared with the basal values of the patient in both the groups. HR and MAP recorded 15 minutes after establishing pneumoperitoneum were compared with Baseline and pre pneumoperitoneum values in both the groups. In addition Heart rate and Mean Arterial Pressure, values recorded after extubation were compared with pre-extubation values. Both Metoprolol group(group M) and control group(group C) were similar in respect to age, sex and weight distribution. There was no significant difference in duration of laryngoscopy and duration of pneumoperitoneum between the two groups.

In our observation during intubation, mean Heart Rate in Metoprolol group at 1 minute(81.16 ±7.87) and 5 minutes (81.46 ± 7.04) after intubation compared to Basal Heart Rate(81.581.5 ± 7.65) showed no significant increase. In control group also Mean Heart Rate at 1 minute(86.13 ± 9.5) and 5 minutes(85.93±8.37) after intubation compared to Basal Heart Rate (82.83±8.62) showed no significant increase in response to intubation. In Metoprolol group Mean Arterial Pressure(MAP) at 1 minute(91.46 ± 3.98 mm of Hg) and 5 minutes (91.96 ± 4.99) after intubation compared to Basal MAP (93.96 ± 2.76) showed no significant increase. Though Metoprolol group showed statistically significant decrease in MAP(91.46 ± 3.98) at one minute after intubation, clinically the decrease was insignificant. But in Control group MAP at 1 minute(98.46±7.31) and 5 minutes(99.76±7.99) after

intubation was significantly higher than the Basal MAP(93.76±3.18) (p = 0.018).

Heart Rate and Mean Arterial Pressure in Metoprolol group at 15 minutes after pneumoperitoneum (HR-81.83 ± 7.26, MAP-94.2 ± 8.43) compared to basal (HR-81.5 ± 7.65, MAP-93.96 ± 2.76) and pre pneumoperitoneum (HR-80.23 ± 6.81, MAP-93.06 ± 5.63) showed no significant change. In Control group 15 minutes after pneumoperitoneum (HR-88.53 ± 10.79, MAP-104.63 ± 13.75) compared to basal (HR-82.83 ± 8.62, MAP-93.76 ± 3.18) and pre pneumoperitoneum (HR-77.9 ± 6.65, MAP-91.03 ± 4.77) showed significant increase in both Heart Rate and Mean Arterial Pressure (p < 0.01).

In Metoprolol group Heart Rate and Mean Arterial Pressure after extubation (HR-85.86 ± 9.03, MAP-96.76 ± 3.97) compared to pre extubation (HR-83.73 ± 6.84, MAP-95. 16 ± 3.59) showed no significant increase (p=0.30, p=0.10). Whereas in Control group Heart Rate and Mean Arterial Pressure after extubation(HR-96.73 ± 9.9, MAP-108.96 ± 8.93) compared to pre extubation (HR-86.33 ± 6.79, MAP-100.83 ± 6.67) showed significant increase in both Heart Rate and Mean Arterial Pressure (p < 0.01).

Table 1: Heart rate and Blood Pressure response to intubation 1 and 5 minutes after intubation compared with baseline Heart rate in both groups

Time	Group M			Group C		
	Mean ± Standard deviation	Standard error	P Significance	Mean±SD	Standard error	P Significance
Basal HR	81.5 ± 7.65	1.39		82.83±8.62	1.57	
HR 1 minute after Intubation	81.16 ± 7.87	1.43	0.86 Not Significant	86.13±9.51	1.73	0.16 Not significant
HR 5 Minutes after intubation	81.46 ± 7.04	1.28	0.98 Not significant	85.93±8.37	1.52	0.16 Not significant
Basal MAP	93.96 ± 2.76	0.50		93.76±3.18	0.58	
MAP 1 minute after intubation	91.46 ± 3.98	0.72	0.006 Significant decrease	98.46±7.31	1.33	0.018 Significant
MAP 5 minutes after intubation	91.96 ± 4.99	0.91	0.06 Not Significant	99.76±7.99	1.45	0.018 Significant

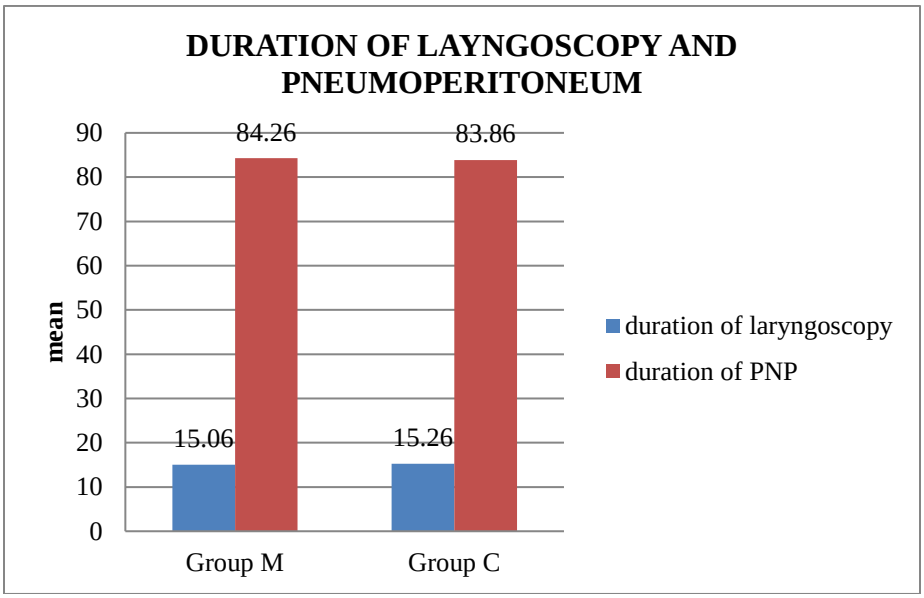
Table 2: Heart Rate and Mean Arterial Pressure readings measured at 15 minutes after establishing pneumoperitoneum were compared with basal and pre pneumoperitoneum readings in both the groups

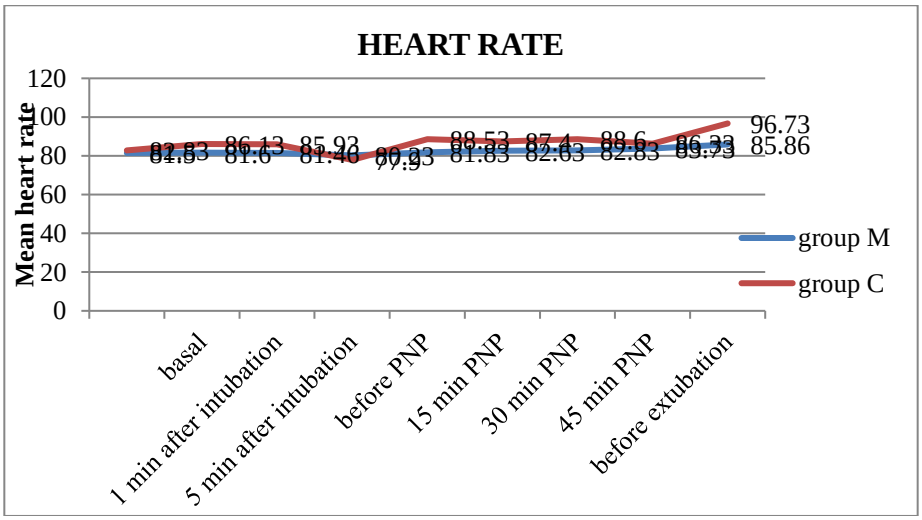
Time	Group M			Group C		
	Mean ± Standard deviation	Standard error	P Significance	Mean ± Standard deviation	Standard error	P Significance
Basal HR	81.5 ± 7.65	1.39	0.86 Not Significant	82.83 ± 8.62	1.57	0.02 Significant
HR 15 minutes after PNP	81.83 ± 7.26	1-32		88.53 ± 10.79	1.97	
Basal MAP	93.96 ± 2.76	0.50	0.88 Not Significant	93.76 ± 3.18	0.58	<0.01 Significant
MAP 15 minutes after PNP	94.2 ± 8.43	1.54		104.63 ± 13.75	2.51	
HR Before PNP	80.23 ± 6.81	1.24	0.38 Not Significant	77.9 ± 6.65	1.21	<0.01 Significant
HR 15 Minutes after PNP	81.83 ± 7.26	1.32		88.53 ± 10.79	1.97	
MAP Before PNP	93.06 ± 5.63	1.02	0.54 Not Significant	91.03 ± 4.77	0.87	<0.01 Significant
MAP 15 minutes after PNP	94.2 ± 8.43	1.54		104.63 ± 13.75	2.51	

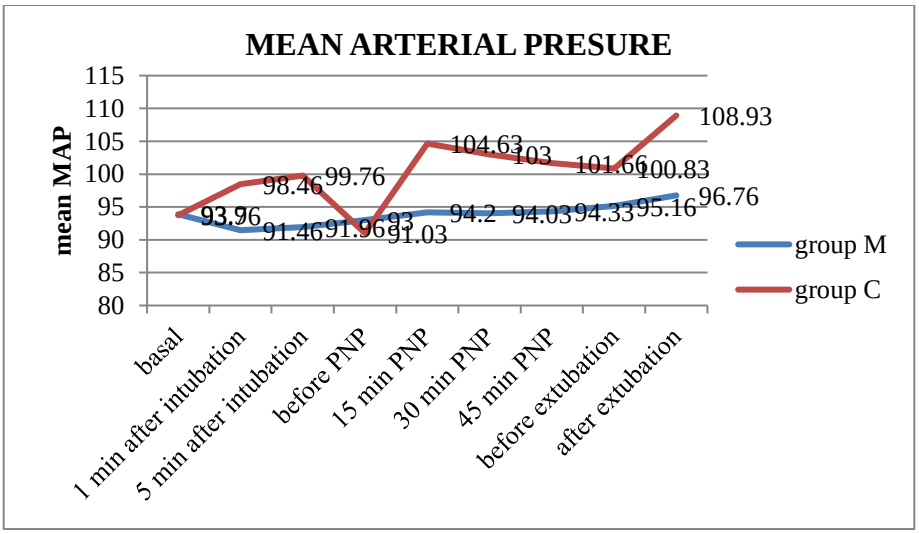
HR=Heart Rate MAP=Mean Arterial Pressure PNP=Pneumoperitoneum

Table 3: Heart Rate and Mean Arterial Pressure readings measured before and after extubation

Time	Group M			Group C		
	Mean ± Standard deviation	**Standard error**	**P Significance**	**Mean ± Standard deviation**	**Standard error**	**P Significance**
Before Extubation HR	83.73 ± 6.84	1.25	0.30 **Not Significant**	86.33 ± 6.79	1.24	<0.01 **Significant**
After Extubation HR	85.86 ± 9.03	1.64		96.73 ± 9.93	1.81	
Before Extubation MAP	95.16 ± 3.59	0.65	0.10 **Not Significant**	100.83 ± 6.67	1.21	<0.01 **Significant**
After Extubation MAP	96.76 ± 3.97	0.72		108.96 ± 8.93	1.63	







Discussion

Demographic profile: Both Metoprolol group (group M) and control group (group C) were similar in respect to age, sex and weight distribution. There was no significant difference in duration of laryngoscopy and duration of pneumoperitoneum between the two groups.

Hemodynamic response to intubation: There was no significant difference in heart rate at 1 and 5 minutes after intubation compared to basal heart rate in both the groups. It may be that our anesthetic technique and short duration of laryngoscopy effectively prevented an increase in heart rate. However, there was a significant increase in Mean Arterial Pressure (MAP), at 1 and 5 minutes after intubation compared to basal MAP in control group. But in Metoprolol group compared to the basal MAP, 1 minute after intubation there was a small but significant (clinically insignificant) decrease in MAP, 5 minutes after intubation there was no significant difference in MAP. From these observations, Metoprolol seems to be effective in attenuating the stress response to intubation. These observations are similar to the findings of Kumar M; Tikkle AC et al,[5] who studied the effect of inj.Metoprolol, i.v.3mgm given 5 minutes before induction of anesthesia and concluded Metoprolol effectively attenuated the cardiovascular response to laryngoscopy and intubation. These observations also correlate with the study of J. Manusson, M.D., T. Thulin, O. Werner et al of Sweden,[6] who studied the effect of pretreatment with Metoprolol in patients undergoing surgery and concluded metoprolol significantly reduced arterial pressure both during undisturbed anesthesia and during intubation and extubation. Metoprolol's efficacy in attenuating the stress response to intubation in our study is similar to Nitroglycerin, demonstrated by Mikawa K, Hasegawa M, Suzuki T, Obara H et al.[12] Results of this study regarding the efficacy of Metoprolol in attenuating the stress response to intubation is also similar to that of propranolol demonstrated by Maharajan et al.[7] Metoprolol's efficacy is also comparable with esmolol's efficacy demonstrated by Arthi Rathore, Dr. H.K. Guptha et al.[11]

Hemodynamic response during CO2 pneumoperitoneum: There was a significant increase in Heart Rate and Mean Arterial pressure in Control group 15 minutes after pneumoperitoneum compared to both basal and pre pneumoperitoneum values. But in Metoprolol group there was no significant difference in Heart Rate and Mean Arterial Pressure compared to basal and pre pneumoperitoneum values. From the observations it seems, Metoprolol is effective in attenuating the stress response induced by pneumoperitoneum. In attenuating the stress response to pneumoperitoneum results with metoprolol in this study are similar with the various other medications used for this purpose, as found in the following studies: Propranolol, Maharajan SK et al,[7] who demonstrated propranolol is effective in decreasing the stress response due to airway manipulation and CO2 pneumoperitoneum in patients undergoing laparoscopic surgeries; Esmolol, Koivusalo AM, Schejnin M, Tikkannen I et al[4] who demonstrated that esmolol blunts the pressor response to induction and maintenance of pneumoperitoneum; Clonidine, JL. Jonis, JD Chiche et al,[9] who found that clonidine is effective in attenuating the stress response to pneumoperitoneum.

Response to extubation: In the Metoprolol group, there was no significant difference in Heart rate and Mean Arterial Pressure measured before and after extubation. But in Control group, there was a significant increase in both HR and MAP compared to the pre-extubation values. Our observations correlate with the study of J. Manusson, M.D., T. Thulin, O. Werner et al of sweden[6], whose study also proves metoprolols efficacy. The results are also similar to that of propranolol in the study of Maharajan SK et al.[7]

Perioperative events: All the patients were monitored intraoperatively and 8 hours postoperatively for any

complications, and the following observations were made.

Hypertensive Episodes: Highest Mean Arterial Pressure observed in Metoprolol group was 126mm of Hg, In Control group it was 134 mm of Hg. Both occurred during the first 15 minutes of CO2 pneumoperitoneum. In Metoprolol group 2 patients developed hypertensive episodes, they were managed with supplementing additional fentanyl. In control group 10 patients had hypertensive episodes, all of them were given additional fentanyl; Five among them required an increase in Isoflurane concentration to control blood pressure. It is clear that opioid requirement and Isoflurane requirement are more in the Control group compared to the Metoprolol group.

Hypotensive Episodes: One patient in Metoprolol group and two patients in control group developed hypotensive episodes. Lowest Mean arterial pressure was 62 mm of Hg. in Metoprolol group and 65 mm of Hg. in Control group. All of them responded to fluid boluses and none of them required any vasopressors. Others: Two patients in each group developed sinus bradycardia. Only one patient in the Metoprolol group developed a heart rate less than fifty(47), it responded promptly to inj. Atropine 0.6mg i.v.. Other three patients who developed bradycardia had heart rates between 50 and 60, not associated with any hypotension and they did not require any treatment. There was no other ECG abnormalities or bronchospasm in any of the patients in both the groups. There were no significant complications during the 8 hours postoperatively in both groups of patients, other than post-operative nausea and vomiting. Three patients in the Metoprolol group and four patients in the Control group had postoperative nausea and vomiting, all of them occurred during the first-hour post-operatively. There was no significant difference in the average hourly urine output between the two groups. In this study, there was no significant difference in the incidence of complications between the Metoprolol group and the Control group.

Conclusion

Inj.Metoprolol 50µgm./kg. i.v. given 5 minutes before induction of anesthesia effectively attenuates the hemodynamic response to laryngoscopy, intubation, and carbon dioxide pneumoperitoneum. There were no significant complications associated with inj.Metoprolol 50µgm./kg/i.v during intraoperative period and 8 hours postoperatively. Inj. Metoprolol can be used as a cost effective alternative for attenuating stress response to pneumoperitoneum in laparoscopic surgeries.

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