Original Research Paper

Volume - 14 | Issue - 02 | February - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Anaesthesiology

EFFECTS OF ORAL METOPROLOL AND ATENOLOL ON ANALGESIC AND ANESTHETIC REQUIREMENTS IN LAPAROSCOPIC CHOLECYSTECTOMY: A PROSPECTIVE RANDOMIZED DOUBLE BLIND CONTROLLED STUDY

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ABSTRACT **Introduction:** Laparoscopic surgery is a procedure in which small incisions are given over the abdomen and the operation is performed through them. Reduced postoperative pain is one of the biggest advantages of laparoscopy compared with open surgery. However, postoperative pain is not completely disappeared and is still considerable, and is the primary reason for prolonged hospitalization after laparoscopic cholecystectomy. Metoprolol reduces the requirements of propofol and attenuate hemodynamic stress response. Without modifying the depth of anesthesia atenolol has shown to reduce the doses of various anesthetic drugs by suppressing cerebral cortical electrical activity, resulting in a burst-suppression pattern. **Material And Methods:** We have conducted this prospective, randomised, double blind, placebo controlled study conducted in the Surgical Gastroenterology operation theatres of Sri Venkateswara Institute of Medical Sciences. This study was registered in Clinical Trials Registry [CTRI/2020/07/026617] before enrolment of the first patient in our study. Blinding was ensured by allotting a random number to each patient using a sealed opaque envelop technique. Oral atenolol [25mg], metoprolol [50mg] or a sugar cube of same and colour were given to the patients by an independent anesthesiologist as per their random group allocation. The independent anesthesiologist was not a part of the study protocol. **Results:** With respect to ASAPS grade in the placebo group, there were equal number [13] of ASAPS grade I and II patients. In the atenolol group, ASAPS grade I patients were a majority, that is; 69.23% [18] and 30.77 % [8] were ASAPS grade II patients. ASAPS grade I patients were 57.69% [15] and grade II were 42.31% [11] in the metoprolol group. Majority of the patients belong to ASAPS 1 [46/78] and were uniformly distributed across the 3 groups. All the three groups were comparable with respect to the distribution of patients in ASAPS grades I and II. $p = 0.360$ and there was no statistical significance. There was a significant difference among the groups in occurrence of tachycardia, hypertension and hypotension. The incidence of tachycardia, hypertension were more in placebo group compared to patients who received either atenolol or metoprolol. The incidence of hypotension was more in patients who received atenolol or metoprolol. **Conclusions:** Our study concluded that administration of oral atenolol and metoprolol preoperatively in patients undergoing laparoscopic cholecystectomy could reduce the isoflurane but not the intraoperative fentanyl requirements. Therefore the use of long acting beta blockers as a single oral dose on the day of surgery cannot be suggested based on our study results.

KEYWORDS : Metoprolol, Atenolol, Analgesic, Laparoscopic cholecystectomy

INTRODUCTION

Hundreds of years ago, the ideas for laparoscopic surgery were thought upon, and a framework was made for this new procedure. George Kelling was the pioneer in laparoscopic examination.[1] Phillipe Mouret in 1987 first performed laparoscopic cholecystetomy.[2] Laparoscopic surgery is a procedure in which small incisions [0.5 cm - 1.5 cm] are given over the abdomen and the operation is performed through them.[3]

Reduced postoperative pain is one of the biggest advantages of laparoscopy compared with open surgery. However, postoperative pain is not completely disappeared and is still considerable,[4]and is the primary reason for prolonged hospitalization after laparoscopic cholecystectomy.[5,6] Patients frequently complain of back, shoulder region pains and discomfort of port site incisions.[7] Shoulder and sub-diaphragmatic pain occurs in about 12% to 60% of patients.[8] The etiology for pain include the peritoneal insufflation with CO_2 and phrenic nerve irritation in the peritoneal cavity. [9-11] Additional contributing factors include sociocultural status, and individual factors.

Laparoscopy places many challenges in the cardiac system, the increase in multiple pressor responses have effect on preload, inotropy, rhythm, afterload and increase in myocardial oxygen demand. The stimulation of autonomic nervous system causes release of catecholamines, activation of the renin–angiotensin system, and release of the neurohypophysial hormone vasopressin.[12]

Insufflation of CO_2 and surgery is associated with a significant sympathetic response and the resulting tachycardia and hypertension is controlled by increasing the concentration of inhalational anesthetic and aliquots of opioids. Blunting of the surgical stress response and reduction in anaesthetic doses has been observed with beta blocker premedication.[13] One possible way of preventing adverse cardiac events is the use of perioperative beta blockers.[14] Catecholamine surges cause excitotoxic effects and occur with pneumoperitoneum. These can be attenuated with perioperative beta blockers and thus myocardial injury is reduced.[15]

Beta blockers exert an analgesic effect by inhibiting the G protein coupled potassium channels on the cell membranes.[16] Cells of the periaqueductal gray region in the midbrain mediate pain transmission and are under the control of GABAergic neurons. An increase in GABA release interrupts pain transmission and activation of B1 receptors suppressed GABA release.[17] Increasing GABA levels in the brain by selective blockade of B1 receptors play a role in the management of acute and chronic pain. There is reduced requirements for volatile anesthetics because beta blockers also accentuate the uptake and increase the effects of inhalational agents.[18]

Metoprolol reduces the requirements of propofol and attenuate hemodynamic stress response.[19] Without modifying the depth of anesthesia atenolol has shown to reduce the doses of various anesthetic drugs [20] by suppressing cerebral cortical electrical activity, resulting in a burst-suppression pattern.

Therefore we have compared the efficacy of perioperative use of cardioselective beta blockers metoprolol and atenolol versus placebo on intraoperative analgesic and anesthetic requirements in patients undergoing elective laparoscopic cholecystectomy.

MATERIAL AND METHODS

We have conducted this prospective, randomised, double blind, placebo controlled study conducted in the Surgical Gastroenterology operation theatres of Sri Venkateswara Institute of Medical Sciences. This study was registered in Clinical Trials Registry [CTRI/2020/07/026617] before enrolment of the first patient in our study.

All patients undergoing scheduled elective laparoscopic cholecystectomy under general anesthesia were screened for participation in the study.

The inclusion criteria are
1.Patients aged 18-60 years.
2.Patients of either sex.
3.Patients belonging to American Society of Anesthesiologists Physical Status [ASAPS] I,II.

The exclusion criteria are
1.Patients allergic to study drugs.
2.Patients with severe cardiovascular, renal and respiratory co-existing diseases
3.Patients unwilling to participate in the study.
4.Patients unable to give informed consent.
5.Patients who are on beta blockers.
6.Hypertensive patients on treatment.
7.Pregnant and lactating women.

Blinding :
Blinding was ensured by allotting a random number to each patient using a sealed opaque envelop technique. Oral atenolol [25mg], metoprolol [50mg] or a sugar cube of same and colour were given to the patients by an independent anesthesiologist as per their random group allocation. The independent anesthesiologist was not a part of the study protocol.

Group Allocation:
1]Group A : [n = 26] Patients received tablet atenolol 25 mg orally 90 minutes before surgery
2]Group M : [n = 26] Patients received tablet metoprolol 50 mg orally 90 minutes before surgery
3]Group P : [n= 26] Patients received placebo 90 minutes before surgery

Preoperative Visit:
A thorough preanesthetic checkup was done. Written, informed consent was obtained from all patients willing to participate in the study.

All patients received tab. alprazolam 0.25 mg orally on the night before surgery and tab.pantoprazale 40mg orally 2 hours before the surgery.

The following parameters were recorded during the study period.
1.Hemodynamic parameters [Heart rate, SBP, DBP, MAP] was monitored throughout the surgical procedure – baseline, after induction, after intubation, every 15 minutes throughout the surgery and at the time of extubation
2.Total amount of isoflurane consumed in [ml]
3.Total amount of additional inj fentanyl required.

The total amount of isoflurane consumed was based on Avagadro's law which states that 1g molecular weight of a substance would occupy 22.4 litres at standard temperature and pressure.

Therefore 184 g of isoflurane would occupy 22.4 litres

1 g of isoflurane would occupy = 22400/184 = 121.73 ml .

Since the density of isoflurane is 1.495 g/ml

A total volume of 1ml liquid isoflurane would provide 182ml of vapour [121.73 x 1.495].

Statistical Analysis
All collected data was represented in excel chart and double checking was done for any clerical errors. Data was analysed using IBM SPSS version 20.0. The variability in data obtained was expressed either as median with range for non parametric data or mean with standard deviation for normally distributed data. The normal distribution of continuous variables was evaluated by the Shapiro-Wilk test.

1.Continuous data like age, height, weight, BMI were analysed by one way ANOVA test .

2.Categorical data like gender, ASAPS grading were analysed with Chi-square test.

3.Total dose of isoflurane consumed, additional amount of fentanyl required during maintenance was compared using one way ANOVA test.

4.Incidence and frequency of adverse haemodynamics like hypotension, hypertension, tachycardia, bradycardia were compared using Fisher exact or Chi square test

5.p-value of < 0.05 was considered statistically significant

RESULTS

The present study was conducted among 78 ASA grade I and II patients. The patients were of both sex and age was between 18 -60 years. These 78 patients undergoing laparoscopic cholecystectomy were randomly divided into 3 groups Metoprolol group [group-M], Atenolol group [group-A] and Placebo group [group-P].

Table 1 : Demographic Data Of The Patients In Study

Variable	Group A [n=26]	Group M [n=26]	Group P[n=26]	p Value
Age [years]	40.73 ± 10.31	43.04 ± 10.44	47.19 ± 10.19	0.079
Weight [kg]	63.88 ± 13.43	64.61 ± 13.61	62.53 ± 12.73	0.849
Height [cms]	160.53 ± 7.17	159.03 ± 9.18	158.30 ± 7.96	0.60
BMI [kg/m^2]	24.73 ± 4.83	25.48 ± 4.65	24.92 ± 4.62	0.83
Sex [M/F] [n]	15/11	10/16	16/10	0.203
ASA Grade [I/II] [n]	18/8	15/11	13/13	0.365

n=number of patients, BMI=Body mass index, M = Male, F = Female
ASA=American Society of Anesthesiologist's Physical Status grading.
Data are represented as mean ± SD

Group A – Atenolol, Group M – Metoprolol, Group P - Placebo,

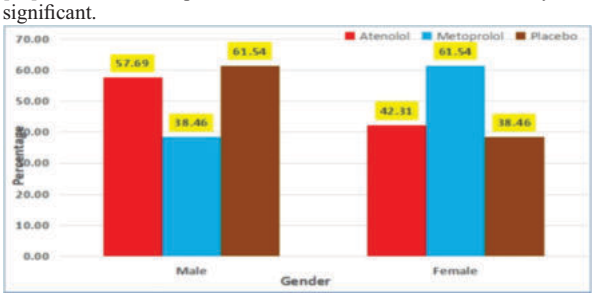
Table 1 shows comparison of mean age of the patients in group A, was 40.73 ± 10.31, in the group M it was 43.04 ± 10.44; and in group P it was 47.19 ± 10.The age of the patients in the three groups was comparable, with a p value of 0.079.

The mean weight of the patients in metoprolol group [group M] was 64.61 ± 13.61 kg; Atenolol group [group A] was 63.88 ± 13.43 kg and placebo group [group P] was 62.53 ± 12.73 kg. The mean weight of the patients in the three groups was comparable and showed no statistically significant difference. The p value was 0.84.

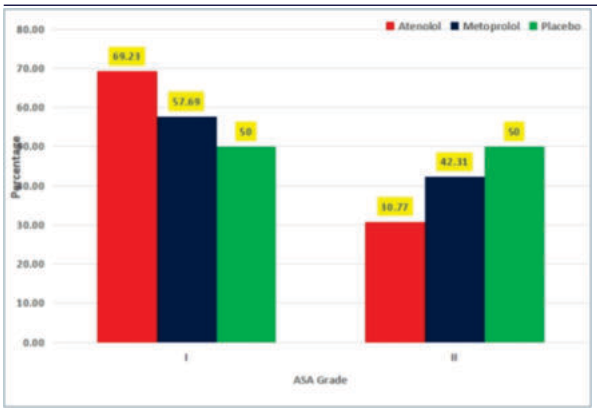
The average height of the patients in Atenolol group [group A] was 160.53 ± 7.17 cms; metoprolol group [group M] was 159.03 ± 9.18 cms and the placebo group [group P] was 158.30 ± 7.96 cms. Patients in the three groups were comparable with respect to height. There was no statistically significant difference with a p value of 0.60.

The body mass index was calculated by dividing weight of the patient in kilograms with square of the height in meters. The BMI of the patients in group A was 24.73 ± 4.83 kg/m^2; metoprolol group [group M] was 25.48 ± 4.65 kg/m^2 and the placebo group [group P] was 24.92 ± 4.62 kg/m^2. Patients in the three groups were comparable with respect to BMI with a p value 0.83.

The total number of patients in the three groups were 78 belonging to both sex. The total number of male patients were 41 and total number of female patients were 37. Among this, in the atenolol group 57.6 % [15] patients were males and 42.3% [11] patients were females. In the metoprolol group, 38.4 % [10] were males and 61.5 % [16] were females. The placebo group had 61.5 % [16] male patients and, 38.4 % [10] were females. p value was 0.200 which is statistically not significant.



Graph 1: Comparison Of Gender Between The Three Groups



Graph 2 : Comparison Of ASA Physical Status Between The Three Groups

With respect to ASAPS grade in the placebo group, there were equal number [13] of ASAPS grade I and II patients. In the atenolol group, ASAPS grade I patients were a majority, that is; 69.23% [18] and 30.77 % [8] were ASAPS grade II patients. ASAPS grade I patients were 57.69% [15] and grade II were 42.31% [11] in the metoprolol group. Majority of the patients belong to ASAPS 1 [46/78] and were uniformly distributed across the 3 groups. All the three groups were comparable with respect to the distribution of patients in ASAPS grades I and II. p = 0.360 and there was no statistical significance.

Table 2 : Comparison Of Additional Amount Of Inj Fentanyl Administered To The Patients In The Intraoperative Period

	Group A [n=6]	Group M [n=4]	Group P [n=23]	P value
Additional amount of Inj. Fentanyl given [ug] [mean ± SD]	21.67 ± 7.53	25.00 ± 17.32	33.04 ± 11.05	0.075

Group A – Atenolol ; Group M – Metoprolol ; Group P – Placebo

Table 2 compares the additional fentanyl used intraoperatively among the 3 groups. Fewer patients required additional amount of fentanyl and the quantity required was also lesser, in the groups A and M. The number of patients who needed additional fentanyl intraoperatively were 6, 4 and 23 from group atenolol, metoprolol and placebo respectively. The mean quantity of fentanyl received by the atenolol group was 21.67 ± 7.53 ug, metoprolol group was 25.00 ± 17.32 ug, and the placebo group was 33.04 ± 11.05 ug. While comparing the three groups there was no statistically significant difference in the additional amount of intraoperative fentanyl given. p =0.075

Table 3 : Comparison Of The Total Amount Of Isoflurane Consumed [ml] In The Study Groups

	Group A [n=26]	Group M [n=26]	Group P [n=26]	P
Total Amount of Isoflurane consumed [ml/hr]	21.38 ± 3.66*	20.84 ± 4.55*	33.79 ± 8.00	0.000

Group A – Atenolol ; Group M – Metoprolol ; Group P – Placebo
*p < 0.05 in comparison to placebo

Total amount of isoflurane consumed was calculated to compare the anesthetic requirement in the three groups. The mean amount of isoflurane used was comparatively lesser in the patients who were given metoprolol or atenolol preoperatively than in patients who didn't receive any beta receptor blocking drug. In the atenolol group the mean amount of isoflurane required was 21.38 ml, whereas the consumption in the metoprolol and the placebo groups was 20.84 ml and 33.79ml respectively. There was statistically significant difference in the amount of isoflurane consumed when the placebo group was compared with atenolol and metoprolol groups [p value = 0.00]. But there was no such statistically significant difference in the amount of isoflurane consumed between the atenolol and metoprolol groups [p value = 1.00].

Table 4 : Comparison Of The Incidence Of Adverse Events In The Study Groups

Adverse Events	GROUP A [n=26]	GROUP M [n=26]	GROUP P[n=26]	P
Bradycardia	3	4	0	0.130
Tachycardia	6	4	23	0.000
Hypertension	5	4	20	0.000
Hypotension	14	16	3	0.000

There was a significant difference among the groups in occurrence of tachycardia, hypertension and hypotension. The incidence of tachycardia, hypertension were more in placebo group compared to patients who received either atenolol or metoprolol. The incidence of hypotension was more in patients who received atenolol or metoprolol.

DISCUSSION

In the current study we did find that both metoprolol and atenolol premedication reduced the mean amount of intraoperative isoflurane consumption by 12-13 ml/h.[Table 3].However unlike the Yamakage et al [21] study we observed a higher incidence of hypotension in the beta-blocker treated group. This could be because of difference in techniques of anaesthesia induction as most of the incidences of hypotension were observed immediately after induction. The earlier study used an inhalational induction method where as the current study used propofol for anaesthesia induction and it's a well-known fact that propofol induction may result in a hypotension in as much as 60% of study subjects

In our study three patients from atenolol and four patients from metoprolol group compared to none from control group had bradycardia but this difference did not reach statistical significance. In our study apart from the uniform bolus dose at the time of induction the subsequent dose were determined by the heart rate and blood pressure response during the surgery. Table 4 indicates that patients from control group should have consumed more fentanyl in contrast to study group[metoprolol and atenolol] because more number of tachycardia and hypertensive responses but the analysis did not reveal a significant difference in fentanyl consumption among three groups though the control group consumed more mean fentanyl dose. This could be because the first line treatment for such haemodynamic response [tachycardia and hypertensive] was increment of isoflurane concentration to increase the depth of anaesthesia followed fentanyl bolus. As majority of these responses were controlled with increased isoflurane dial setting we could a see a significant difference in isoflurane consumption but not in fentanyl consumption.

The mechanism by which beta blocker use reduces opioid consumption is not clear. Zaugg and colleagues[22] demonstrated that though intraoperative atenolol administration do not have any impact on level nociceptive stress hormones like neuropeptide Y, norepinephrine, epinephrine, or cortisol in the perioperative period but still was able to reduce the consumption of morphine. This implies the analgesic potentials of beta blockers goes beyond simple attenuation of nociceptive hormones and may include central analgesia as induced by clonidine by activating G-Proteins[23] ; by eliciting a reduction in hepatic blood flow and thus altering hepatic extraction ratio of drugs like fentanyl which depend on liver for its metabolism.[24]

The metoprolol dose used in our study is far less than that by Indranil et al [25mg versus 100mg] and even than we could demonstrate a significant reduction in isoflurane requirement in the betablocker treated group [Table 3].The blunted haemodynamic response is well evidenced from table 4 where almost 50% of the study subjects from the beta blocker treated group had hypotension during the study period. A higher dose of metoprolol[100mg] resulted in a higher incidence of bradycardia [6.6%] in Indranil et al [25] study compared to the current study where the combined incidence of bradycardia in beta blocked group was 11.6% despite use of low dose metoprolol and atenolol. This difference could be because of our study cohort included laparoscopic cholecystectomy and apart from the beta blockade effect, the stretching of bile duct and abdominal viscera could also have resulted in bradycardia.

In our study there was significant hypotension and higher incidence of bradycardia in the metoprolol group which was however insignificant. This could be due to the increased duration of action of metoprolol. Erdivanlı et al. [26] observed in their study patients in the MT group had no adverse hemodynamic effects. Thus the amount of desflurane consumed by those patients was also lesser when compared to the R group. In contrast, in the R group dose adjustments had to be made to treat adverse events like hypotension and bradycardia. They recommended that single IV doses of metoprolol could be chosen due to the simplicity of administration and monitoring without profound hypotension or bradycardia.

CONCLUSIONS

Our study concluded that administration of oral atenolol and metoprolol preoperatively in patients undergoing laparoscopic cholecystectomy could reduce the isoflurane but not the intraoperative fentanyl requirements. Both atenolol and metoprolol administration reduced the incidence of hypertension and tachycardia in the intraoperative period but the incidence of hypotension was more in patients who received atenolol and metoprolol treatment compared to placebo. Therefore the use of long acting beta blockers as a single oral dose on the day of surgery cannot be suggested based on our study results.

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