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COMPARISON OF PRE-EMPTIVE MEDICATION OF PREGABALIN, CLONIDINE AND MELATONIN IN ATTENUATION OF PRESSOR RESPONSE TO LARYNGOSCOPY AND INTUBATION IN ABDOMINAL LAPAROSCOPIC SURGERIES.

Anaesthesiology

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ABSTRACT

Background & Aims: Laryngoscopy and intubation cause various noxious stimuli leading to hypertension, tachycardia and arrythmias. The pneumoperitoneum further aggravates these disturbances. Although various studies have been performed to study efficacy of drugs on attenuating such responses, search for better agent continues. So far with best of our knowledge, no single study has been conducted, comparing efficacy of oral pregabalin, clonidine and melatonin. Hence the purpose of this study. **Methods:** Total 90 patients were randomly divided into three equal groups, Group M (Melatonin): received 6 mg of melatonin orally, Group P(Pregabalin): received 150 mg of pregabalin orally, Group C(Clonidine): received clonidine 200 µg orally. The study drugs were administered 2 hours prior to surgery. On arrival at the operating room all standard monitoring was attached. Anaesthesia induction was done using standard technique. The haemodynamic variables were noted at various points of time during laryngoscopy and after intubation. Sedation and analgesia were assessed in post operative period. Statistical analysis was done as appropriate. **Results:** All three drugs were effective in preventing increase in heart rate and blood pressure. However, clonidine was more effective than melatonin and pregabalin was least effective. Post operative sedation and pain scores were comparable. **Conclusion:** Hence, we conclude that oral melatonin(6mg), oral clonidine(200 µg) and oral pregabalin(150mg) are equally effective in attenuating stress response to laryngoscopy and intubation in patients undergoing abdominal laparoscopic surgeries. All three drugs provide adequate analgesia and minimal sedation.

KEYWORDS

Clonidine, haemodynamic, laryngoscopy, laparoscopic, melatonin,pregabalin.

INTRODUCTION:

Laryngoscopy and endotracheal intubation are routine procedures during administration of general anaesthesia. However, it causes various noxious stimuli leading to cardiovascular changes such as hypertension, tachycardia and arrythmias.[1] This is known as stress response or pressor response. This haemodynamic response is a result of stimulation of adrenergic fibers and increase in level of circulating catecholamines which leads to stimulation of cardio-accelerator fibers. This effect is transient and lasts for short period. [2] Although it is well tolerated routinely by normotensive patients but it may be life threatening in patients with associated co-morbidities and may increase morbidity and mortality.

Although abdominal surgeries were routinely performed via open approach but since the advent of laparoscopy, majority of the procedures are done via laparoscopic approach. But the pneumoperitoneum created by insufflating carbon dioxide gas further adds several alterations in homeostatic balance due to stimulation of peritoneal receptors and increased intrabdominal pressure. As a result, there is tachycardia and hypertension, followed by hypotension due to obstruction of venous return and decreased pre load. Hence, there is greater importance of attenuation of vasopressor responses to laryngoscopy and intubation during laparoscopic procedures.

Pregabalin is a gabapentin like compound which produces an inhibitory effect on neuronal excitability in amygdala, neocortex and hippocampus. [3] It also has properties like analgesic, anticonvulsant and anxiolytic which are due to the reduction in neurotransmitters like glutamate, nor adrenaline, serotonin, dopamine and substance P. Clonidine is an α-2 adrenoreceptor agonist which acts by central sympatholytic action. [4] Melatonin is a pineal gland hormone which maintains the circadian rhythm and also has sedative, analgesic, anxiolytic and anti-inflammatory properties. [5]

Although various studies have been performed to analyze efficacy of drugs on attenuating haemodynamic stress response to laryngoscopy and endotracheal intubation, so far with best of our knowledge no single study has been done on comparison of efficacy of oral pregabalin, clonidine and melatonin in attenuating haemodynamic stress response at the time of laryngoscopy and intubation in abdominal laparoscopic surgeries.

METHODS:

This prospective, randomized, double blinded comparative study was conducted in the Department of Anaesthesiology and Critical Care at a tertiary care hospital. The approval was obtained from the institutional Ethical committee. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013.

A written informed consent was obtained from all patients fulfilling the inclusion criteria of the study. A total of 90 patients aged between 20 and 60 years with American Society of Anesthesiologists grade I and II patients scheduled to undergo elective laparoscopic surgery under general anaesthesia with endotracheal intubation were included in the study. Patients were randomly divided into three equal groups, as follows: -

Group M (Melatonin): received 6 mg of melatonin orally
Group P(Pregabalin): received 150 mg of pregabalin orally
Group C(Clonidine): received clonidine 200 µg orally.

The study drugs were administered 2 hours prior to taking the patient in the operating room. Anesthetic technique was standardized in all the 3 groups. On arrival at the operating room, electrocardiogram, pulse oximetry, and non-invasive arterial blood pressure were applied as routine monitoring. Vital signs were obtained and subsequent values were recorded throughout the surgical procedure at frequent intervals as per the prescribed proforma. Then an intravenous 18G or 20G cannula was inserted and preloaded with 500 ml of balanced salt solution as intravenous fluid. The patients were preoxygenated for 3 minutes and were administered inj. glycopyrrolate 0.004 mg.kg-1, inj. fentanyl 1.5-2 µg.kg-1, and injection midazolam0.2 mg.kg-1 iv. Anaesthesia induction was achieved with inj. propofol 1.5-2.5 mg.kg-1 iv in incremental doses till loss of verbal contact and inj. succinyl choline 1 mg.kg-1 intravenously was administered for facilitating endotracheal intubation.

Laryngoscopy was attempted 30 seconds after induction of anaesthesia by an experienced anesthetist. The patients who required more than 1 attempt at intubation or in whom laryngoscopy and intubation took more than 30 seconds, were excluded from the study. After confirmation of endotracheal tube position, anaesthesia was maintained using 50% O2: air; and isoflurane (1.2- 1.5%). Recovery from anaesthesia was obtained by discontinuation of isoflurane and reversal of neuromuscular blockage by injection glycopyrrolate 0.02 mg.kg-1 and neostigmine 0.05 mg.kg-1. Intraoperative analgesia was attained by administering inj. paracetamol 1gm iv infusion slowly,

after creation of pneumoperitoneum. Then extubation was done after the airway reflexes were regained. Duration of surgery was defined as the time from surgical incision till closure of the wound. The following variables (SBP, DBP, MAP, HR, SpO2) were recorded just before medications (baseline), after induction, just before intubation, 1 min, 3 min, and 5 min after the intubation. Also, haemodynamic parameters were recorded at the start of pneumoperitoneum and then at 15 min, 25 min, 35 min following extubation. Ramsay sedation score was noted at 60 min, 2h, 4 h, 6h and 12h after extubation. Visual analogue scale was noted at 60 min, 2h, 4h and 6h. Time to requirement of first rescue dose of analgesic was noted. The rescue analgesia was administered as injection paracetamol 15 mg.kg-1 intravenous infusion. Patients were continuously monitored for development of any adverse event such as tachycardia, bradycardia, arrhythmias, hypertension, hypotension, respiratory depression, headache, nausea, vomiting, restlessness or stridor. Hypertension was defined as SBP >30% of baseline value or > 140 mmHg and hypotension was defined as a decrease in the systolic arterial pressure 30% from baseline values. Similarly, tachycardia and bradycardia defined as variations in HR 30% above or below the baseline values, respectively.

Primary Objective was to compare the heart rate and mean blood pressure among the three groups at laryngoscopy and intubation. Secondary objectives were to compare the sedation scores (RSS-Ramsay sedation score) and to assess the pain scores (VAS- Visual analogue scale) among the three groups, in the post- operative period.

The quantitative data were expressed as mean ± standard deviation and analyzed using student t test. ANOVA test was used for analysis of variance. The qualitative data were expressed as numbers, ratios and percentage. The chi square test was used for analyzing such data. The compiled data was sent for statistical analysis. SPSS (IBM SPSS Statistics Inc., Chicago, Illinois, USA) version 23 software was used for statistical analysis. P value less than 0.05 was considered statistically significant.

Sample Size: Our estimated sample size based on mean blood pressure difference among groups. For the sample size calculation, we have defined mean difference of 3.37 with 4.7 Standard Deviation. We have calculated sample size with 95% confidence interval, 80% power and alpha level of 0.05.

Pooled standard deviation=

$$\sqrt{(S_1^2 + S_2^2)/2}$$

Where S1 is standard deviation of group 1, and S2 is standard deviation of another group.

Comparison of two mean formula

N=size per group;
SD= Standard Deviation= 4.7

δ =mean difference = 106.87-103.5=3.37 (SBP at 10 min)
$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ — From Z table at type I error of 5
$Z_{\beta} = Z_{0.20} = 0.84$ — at 80% power

$$N = 2 \times \frac{(Z_{\alpha/2} + Z_{\beta})^2}{(\delta_0)^2} \times SD^2$$

$= 2 (1.96+0.84)^2 (4.7)^2 / (3.37)^2$
$= 15.68 * 22.09 / 11.35$
$= 346.37 / 11.35$
$= 30.51$
$= 30$
Hence the sample size can be taken as 30 in each group.

RESULTS:

Our study comprised a total of 90 patients scheduled to undergo elective laparoscopic surgery under general anaesthesia All the three groups were demographically comparable. [Table 1] The study drugs averted significant rise in heart rate. However, in group C heart rate was lower when compared with group M while group P had least lowering effect on heart rate. There was slight increase in heart rate at the time of laryngoscopy and intubation in all the three groups as compared with base line but was within physiological limits and this too touched the baseline within 3 minutes. [P=0.000] Throughout the procedure, heart rate was maintained within physiological limits at various points of time. [Graph 1]

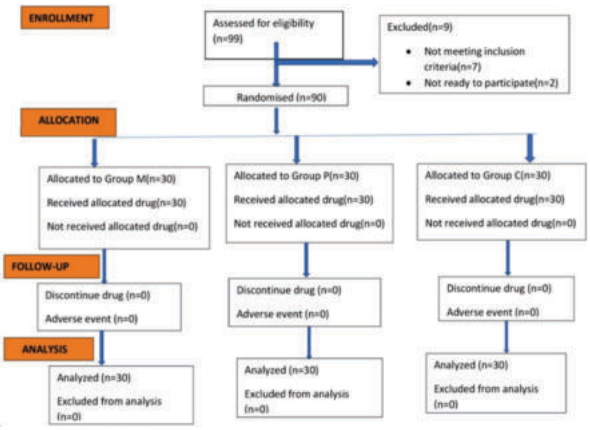


Figure 1-Consort diagram

Likewise, all the 3 study groups efficiently attenuated mean blood pressure. However, group C showed more attenuation of mean blood pressure as compared to group M and group P had least effect. There was a very slight rise of mean blood pressure at the time of laryngoscopy and intubation, but it was also within physiological limits and returned to baseline just after 1 minute of laryngoscopy and intubation. Also, all the 3 study groups showed significant attenuation of mean blood pressure throughout the procedure. [Graph 2]

The Ramsay Sedation Score [RSS] values depicts that all the study groups showed score of 3 to 4 in immediate post-operative period, and further reduction with time. [Graph 3]

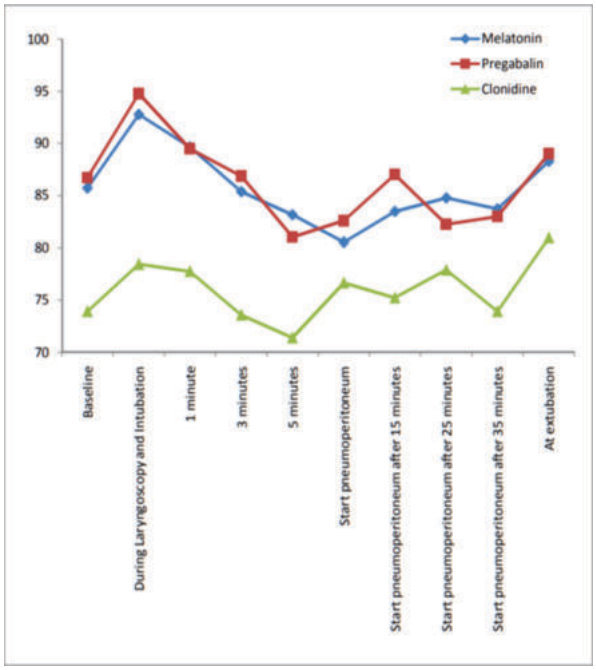
The pain, as assessed by visual analogue scale [VAS] showed score of 1 to < 3 till 2 hours of post-operative period in all the three study drugs. However, after 4 hours VAS score was 4 to 6 and group P showed low VAS score as compared to group M and group C. [Graph 4]

OBSERVATION

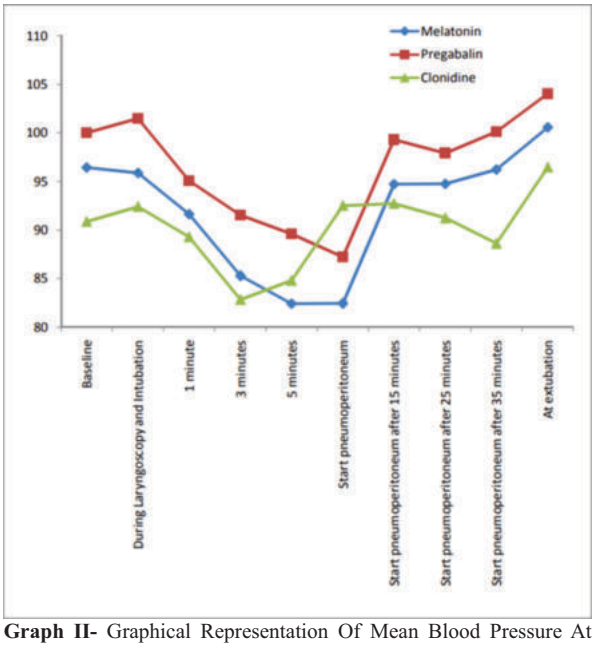
Table1. Demographic Variables

S. No.	Variables	Group M	Group P	Group C	P value
1.	Age in yr [Mean ±SD]	39.33± 12.27	41.30± 10.82	41.20± 10.07	0.742
2.	Gender M/F	37.5/31.8	41.7/30.3	20.8/37.9	0.303
3.	ASA I/II	30.2/40.7	31.7/37.0	38.1/22.2	0.329

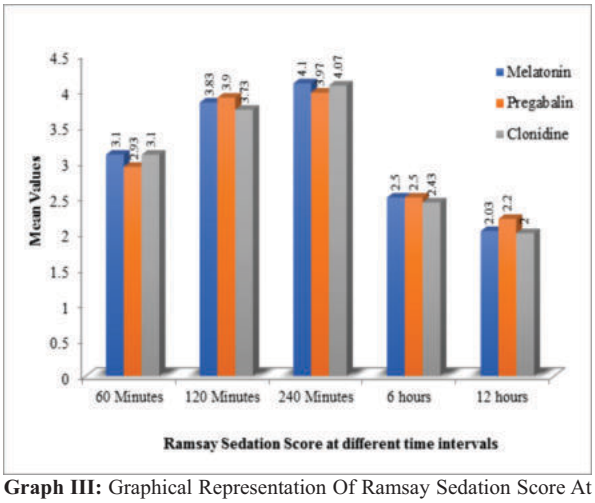
NS = Not significant;M/F= Male/Female; ASA= American Society of Anaesthesiologist.



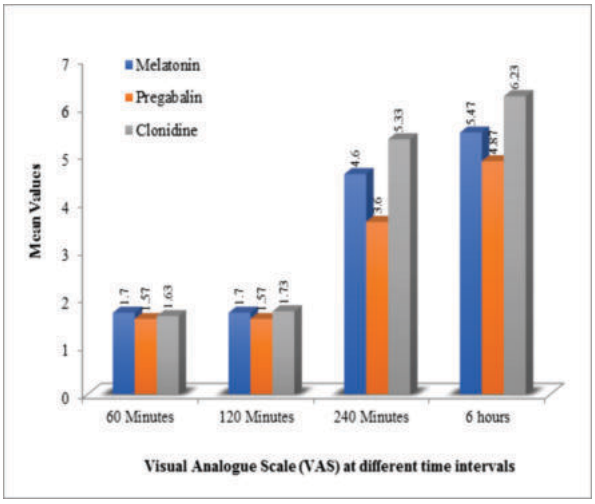
Graph I- Graphical Representation Of Heart Rate At Various Interval Of Time



Graph II- Graphical Representation Of Mean Blood Pressure At Various Interval Of Time



Graph III: Graphical Representation Of Ramsay Sedation Score At Different Time Intervals



Graph IV: Graphical Representation Of Visual Analogue Scale At Different Time Intervals

DISCUSSION:

Airway management is one of the core skills of an anesthesiologist, which aims with least possible airway manipulation and without disturbing the haemodynamic parameters.

Pregabalin, melatonin and clonidine have been used to attenuate haemodynamic disturbances in response to laryngoscopy and intubation. But no such study is available which has compared all the three drugs in a single study. Hence, the relevance of our study.

We observed significant attenuation of heart rate at laryngoscopy, endotracheal intubation and so also at various other points of time of expected pressor responses i.e., during pneumoperitoneum and at the time of extubation. [Graph 1] This effect of preventing the rise in heart rate is most probably due to the sympatholytic effect of melatonin. The mechanism of this action is probably by interfering with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholamine levels. Pregabalin is a new synthetic molecule and a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid. This justifies the effects of attenuation of heart rate, observed at various points of time in our study in the group P. Clonidine, an alpha receptor agonist, has specificity towards the presynaptic α_2 receptors in the vasomotor centre in the brainstem. This binding has a sympatholytic effect, suppresses release of norepinephrine, ATP, renin, and neuropeptide Y. Clonidine may also cause bradycardia, theoretically by increasing signalling through the vagus nerve. The net result is decrease in heart rate as well as prevention of increase due to sympathetic stimulation. This was also observed in our study that heart rate was lowest at the time of receiving the patient in operating room, in patients administered clonidine pre operatively.

Odeberg S et al studied the haemodynamic effects of pneumoperitoneum and influence of posture during anaesthesia in laparoscopic surgeries found that there is increase in haemodynamic parameters, after intrabdominal insufflation of carbon di oxide for creation of pneumoperitoneum. [6] In a study conducted by Chandra DK et al [7] who used melatonin [6mg] and pregabalin [150mg] with placebo group found significant changes [P<0.05] in preventing the rise in the heart rate at different time intervals. Similarly, a study conducted by Chandra A et al [8] found similar significant changes [P<0.05] in stabilizing the heart rate at different time intervals by using pregabalin and clonidine drugs.

All three study drugs proved to attenuate mean arterial blood pressure at various time intervals i.e., laryngoscopy, intubation, at pneumoperitoneum and at extubation and significant attenuation of mean blood pressure was noted at all intervals. [Graph 2]

The mechanism of action of hypotensive effect of melatonin is complex and unclear. It may interfere with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholamine levels. In addition, it may induce relaxation of the smooth muscle of the arterial walls by increasing nitric oxide availability. The net effect is reduction in blood pressure. Pregabalin binds potently to the alpha2-delta subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters, including glutamate, noradrenaline, serotonin and dopamine; this is the basis of the attenuation of hypertensive responses.

Clonidine causes hypotension by stimulating presynaptic α_2 receptors in the vasomotor centre in the brainstem. This binding has a sympatholytic effect, suppresses release of norepinephrine, adenosine triphosphate, renin, and neuropeptide Y which if released would increase vascular resistance. Thus, it decreases peripheral vascular resistance and lowers blood pressure.

In a study conducted by Chandra DK et al [7] who used melatonin [6mg] and pregabalin [150mg] with placebo group found significant changes [P<0.05] in attenuation of mean blood pressure at different time intervals. Gupta K et al [9] compared control group with pregabalin 150mg and clonidine group 200mcg with placebo group and concluded that both the drugs statistically reduce mean arterial pressure but clonidine being more efficient in attenuation of mean blood pressure.

In our study it was seen that all three study drugs were equally efficacious in producing sedation. As depicted in above table, RSS scores were comparable among all the three drugs at all points of time. [Graph 3] This suggests that melatonin, pregabalin and clonidine have comparable sedative properties and does not cause significant sedation. Similar results were seen in various studies conducted by Chandra DK et al [7] compared melatonin 6mg with pregabalin 150mg

concluded that both drugs caused minimal sedation. Similarly, Gupta K et al studied oral clonidine [200µg] and pregabalin [150mg] and concluded that both the drugs have efficient sedative property. [9]

Analgesic scores were favourable among all the three drugs until 120 minutes after extubation. [Graph 4] This suggests that melatonin, pregabalin and clonidine provide effective post operative analgesia. Similar results were seen in studies conducted by Parveen S et al in which he compared clonidine 0.3mg [300 µg] and pregabalin 150mg and found that both the study drugs had an efficient analgesic property. [10] Bhagat N M et al, compared placebo, pregabalin [300mg] and clonidine [200 µg] concluded that pregabalin was more effective in producing postoperative analgesia. [11]

CONCLUSION:

We conclude that oral melatonin [6mg], oral clonidine [200 µg] and oral pregabalin [150mg] are efficacious in attenuating stress responses at the time of laryngoscopy and endotracheal intubation, when used as pre-medicants for administering general anaesthesia in patients scheduled for laparoscopic abdominal surgeries. However, clonidine has greater effect on reducing heart rate and mean blood pressure than melatonin, whereas pregabalin has lesser effect. All three drugs, in prescribed doses, cause minimal sedation and produce effective post operative analgesia; however, pregabalin has longer duration of analgesic action.

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