



To Evaluate the Various Effects of Low Dose Combination of Oral Melatonin and Alprazolam in Reducing Preoperative Anxiety, Attenuating Adrenergic Response to Laryngoscopy and Intubation and Sedation Score.

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ABSTRACT

Background: preoperative anxiety can lead to hemodynamic instability and increased anaesthetic requirements. Melatonin and alprazolam have independently shown anxiolytic and sedative effects. This study evaluates their combined efficacy.

Methods: this prospective Randomized control study done in Chhattisgarh Institute of Medical Sciences, Bilaspur. After Institutional Ethics Committee approval and written informed consent, 50 patients between age 18-60 years of ASA grade I and II were enrolled in our study. The present study titled "Effect of oral melatonin and alprazolam combination on preoperative anxiety and adrenergic response to laryngoscopy and intubation: A Randomized control placebo trial" was done to assess- The effect on preoperative anxiety, Hemodynamic response (HR, NIBP) to laryngoscopy and intubation, The effect on induction dose of Propofol, The complications in perioperative period.

The patient's history was taken and noted during pre-anaesthetic check-up to include or exclude in the study according to our study criteria. Patients were explained about the Visual analogue scale for anxiety night before surgery. Patients were randomised into two groups, each having 25 patients, using sealed envelope technique based on computer generated random table. Group I- received tablet B complex, 90 min before surgery. Group II- received tablet Melatonin 3mg and

tablet Alprazolam 0.25mg combination, 90 min before surgery.

Results- There was significant reduction in preoperative anxiety in Group II (2.4 ± 0.58) as compared to Group I (3.68 ± 0.85) at 60min after study drug administration with p value (< 0.01). The hemodynamic parameters Heart rate and NIBP were markedly reduced in Group II as compared to Group I during laryngoscopy and intubation. There was significant reduction in induction dose of Propofol in Group II (104.4 ± 17.1) as compared to Group I (116.4 ± 14.97) with p value 0.01. No significant complications observed in perioperative period after study drug administration.

Conclusion- We conclude that low dose combination of Melatonin (3mg) and Alprazolam (0.25mg) administered 90 minutes before surgery is effective in reducing preoperative anxiety. It is effective in reducing induction dose of Propofol. Tablet melatonin(3mg) and alprazolam(0.25mg) combination is effective in attenuating haemodynamic response during laryngoscopy and intubation. The dose and the formulation which we have used in our study produced less side effects like postoperative sedation and respiratory depression. Due to its effectiveness in decreasing preoperative anxiety and adrenergic response during laryngoscopy tablet melatonin(3mg) and alprazolam(0.25mg) can be safely prescribed for patients undergoing surgery under general anaesthesia.



Keywords- melatonin, alprazolam, general anaesthesia, anxiety.

I. INTRODUCTION

Preoperative anxiety is commonly experienced by the patients undergoing any type of surgery. The unpleasant state of uneasiness or tension, fear and preoccupied concern about hospitalization, anaesthesia and surgery is very common^{1,2,3}. Preoperative anxiety can lead to surge of catecholamines which causes tachycardia, hypertension and hemodynamic instability¹. It can lead to undue delay in the surgery, increased duration of surgery, and increased postoperative recovery time².

Efforts at assessing and reducing preoperative anxiety should include timely preoperative visit by the anesthesiologist, and appropriate premedication and psychological preparation of the patient⁴. Anxious patients require larger doses of anaesthetic induction agents, and have increased risk of hemodynamic instability⁵. Further in the OT laryngoscopy and intubation causes hemodynamic responses such as tachycardia, hypertension, arrhythmias and increased circulating catecholamines due to sympathetic stimulation⁶. Hypertension and tachycardia can lead to perioperative cardiac morbidity, prevention of undue responses during laryngoscopy and intubation is very important step for intraoperative patient stability and postoperative patient recovery⁷. In patients with cardiac and cerebral diseases these effects are deleterious.

Various drugs like opioids (fentanyl), calcium channel blocker (verapamil, diltiazem), sympatholytic (clonidine, dexmedetomidine), beta blockers (esmolol, propranolol), benzodiazepines (midazolam, alprazolam), barbiturates, propofol and peripheral vasodilators (sodium nitroprusside, nitroglycerine) have been used to decrease these stress responses, however due to their side effects use of these drugs is limited⁸. Each drug has some limitation such as side effects like respiratory depression, hypotension, tachycardia or allergic reactions⁹. Less side effects and more cost effectiveness make melatonin alprazolam combination more feasible for use as compared to above drugs.

Melatonin (5methoxyNacetyltryptamine) is an endogenous sleep regulating hormone secreted by pineal gland. Exogenous administration of melatonin produces natural sleep pattern. Melatonin has been used as premedication drug for anxiolysis. In higher doses, it provides sedation, reduction in dose of

induction agent, postoperative analgesia and no psychomotor impairment.

Alprazolam is a short acting drug which has anxiolytic, sedative, hypnotic, anticonvulsant, and amnesic properties¹⁰. Alprazolam has also been used as premedication before general anaesthesia to decrease anxiety before surgery as an alternative to midazolam¹¹. Melatonin and alprazolam combination reduces anxiety better than either drug alone. It produces sedation and amnesia similar to that of alprazolam.

Hence, this prospective, randomized, double blind study was conducted to evaluate the various effects of low dose combination of oral melatonin and alprazolam in reducing preoperative anxiety, attenuating adrenergic response to laryngoscopy and intubation and sedation score.

II. MATERIALS AND METHOD

This prospective, randomized double-blind placebo controlled trial was carried out at tertiary care hospital after getting approval from institutional ethics committee [182/1/CIMS/SRRC/2024, 5/10/23]

Total 50 patients of 18-60 years age belonging to ASA grade I and II of either sex, undergoing elective surgery under general anaesthesia were included in the study. Patients with hypersensitivity to any drug used, pregnancy, lactation, patient refusal, posted for head and neck surgery, patient on psychotropic drugs and BMI ≥ 28 were excluded from the study.

The patients willing to participate in this study were informed about the purpose of this study, procedure explained in detail and written informed consent was obtained. One day before surgery, all patients were thoroughly examined and evaluated with regards to history, physical examination and investigations. Patients were explained about VAS scale.

The target sample of 50 was randomly divided into Group I and Group II (25 patients in each Group) based on a computer generated random table. The sequentially numbered sealed opaque envelope method was used for allocation concealment. The study drug or tablet B complex were sealed in envelope by anaesthesiologist not involved in the study. Group I received tablet B complex and Group II received tablet melatonin (3mg) and alprazolam (0.25mg) combination tablet.

On the day of surgery, 90 minutes before surgery, the patients were assessed for preoperative anxiety using VAS score¹⁰. Patients

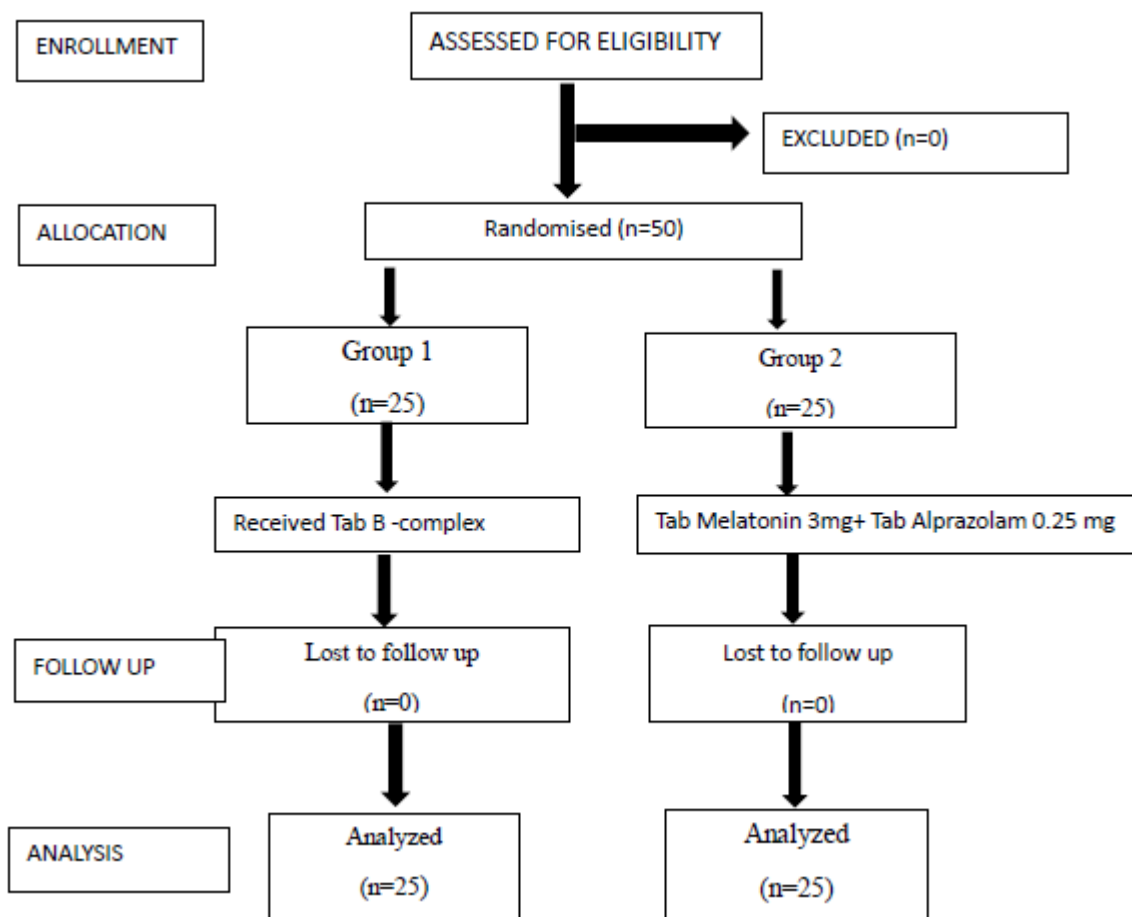


received the drug in sealed envelopes according to the Group to which they belong. Basal vital parameters (HR, RR, SBP, DBP, SPO₂), VAS score and Ramsay sedation score was recorded before giving study drug or placebo, then 30 min and 1 hour after giving study drug or placebo. All the study patients were kept Nil per oral for 8 hours before surgery. All the patients were given inj. Glycopyrrolate 0.2mg IM 30 minutes prior to induction in pre operative room. After shifting patient in the OT, iv line was secured with 18G iv cannula and iv fluid started. Standard monitors (NIBP,

Saturation probe, ECG leads) were attached to the patient and basal readings noted.

Preoxygenation was done with 100% Oxygen for 3 min. Induction done with IV inj. Propofol, and the dose at which eye lash reflex lost was noted. Muscle relaxant IV inj. Succinylcholine 2mg/kg was used. After 1 minutes of controlled ventilation laryngoscopy was performed and endotracheal tube was passed through vocal cords under vision. Patients who required more than one attempt or more than 20 s for laryngoscopy were excluded from the study.

III. CONSORT FLOW CHART



Vitals (HR, NIBP, SPO₂) monitored before laryngoscopy (T₀) and at 1min (T₁), 3min (T₃), 5 min (T₅), 10 min (T₁₀) after intubation and every 10 min till the end of the surgery, and adverse effects if any, were noted. Maintenance of anaesthesia - O₂ + N₂O + Isoflurane (1-2%). Muscle relaxation was attained with inj. Atracurium 0.5mg/kg IV as

loading dose and 0.1mg/kg as maintenance dose. Inj. Paracetamol IV 15mg/kg was given 15 min prior to completion of surgery for postoperative analgesia.

After surgery, residual Neuromuscular blockade was reversed with Inj. Neostigmine 0.05mg/kg IV and Inj. Glycopyrrolate 0.01mg/kg IV and patient was extubated after



fulfilling criteria for extubation and shifted to postoperative recovery unit.

In postoperative period patient was observed for adverse effects, vitals monitoring (HR, NIBP, SPO₂) and sedation score every 1 hour during first four hours and then every four hours for next 20 hours. Sedation score was recorded using Ramsay sedation score (1: anxious, agitated, restless, 2: cooperative, oriented, tranquil, 3: drowsy but responds to commands, 4: asleep, brisk response to light glabellar tap or loud auditory stimulus, 5: asleep, sluggish response to light glabellar tap or loud auditory stimulus, 6: asleep and unarousable). Any adverse events (e.g., respiratory depression, nausea, vomiting, hypotension, bradycardia) were documented.

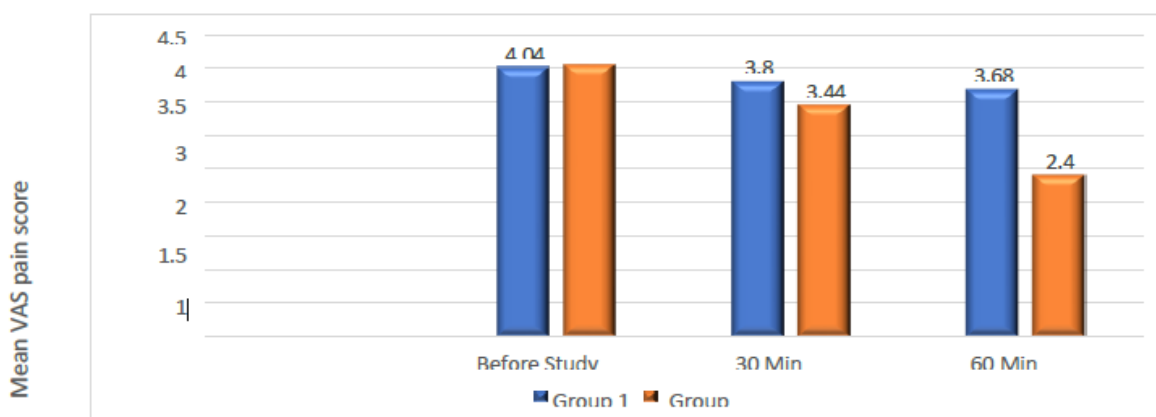
Data was entered in Microsoft Excel and analysed using SPSS (Statistical Package for Social Sciences), version 22. Categorical variables were expressed as frequency and percentage. Continuous variables were expressed as mean and standard deviation. Association between categorical variables were analysed by chi square test, comparison of continuous variable between 2 group was analysed by Student t test . statistical

significance was considered to be present if p value was <0.05.

IV. OBSERVATIONS AND RESULTS

The mean and Standard deviation in the age group is 37.32 ± 13.18 and 37.8 ± 10.1 in Group I and II respectively. In the Group I, 60% participants were female, while in the Group II, 56% participants were female. The mean and SD for weight in Group I and II are 62.4 ± 8.5 and 63.8 ± 7.78 respectively. The mean and SD of Height in Group I and II, are 166.6 ± 8.11 , and 169.16 ± 8.34 respectively. The mean and SD for BMI in Group I and II are 22.52 ± 3.12 , and 22.31 ± 2.51 respectively.

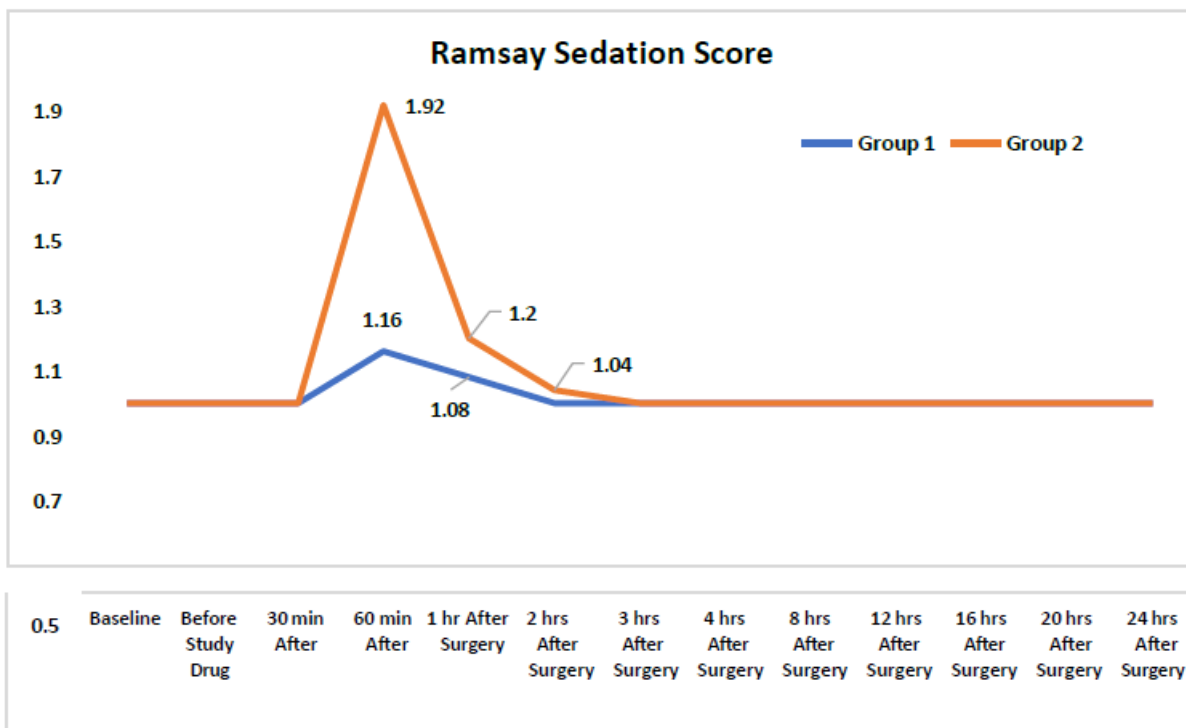
Mean and standard deviation of VAS-A at different time interval. VAS for anxiety was evaluated and recorded before study drug administration then at 30min and 60min after the drug administration. There is significant difference in VAS-A score between Group I and II, at 60min after study drug administration with p value- <0.010. [graph-1]



Graph 1: showing the mean distribution of VAS-A scores in the patient groups at different interval

The mean and SD Of VAS-A scores in Group I and II are 4.04 ± 0.73 , and 4.04 ± 0.84 before study drug, 3.8 ± 0.71 , and 3.44 ± 0.65 , 30minutes after study drug and 3.68 ± 0.85 , and 2.4 ± 0.58 , 60minutes after study drug. Decrease in VAS-A score was highly significant **60 minutes** after giving Tablet Alprazolam and Melatonin as compared with placebo with **p value<0.01**.

Ramsay sedation score among groups at various time intervals. We observed that after administration of study drug at 60min, there was significant difference in Ramsay sedation score between 2 groups with p value-0.005. [graph- 2]



Graph 2: Graph showing mean Ramsay sedation score at different time interval in patient groups, showing significant difference in RSS among groups at 60min after study drug administration

Graph showing Mean RSS scores at different time interval in Group I and II. There is significant difference in Ramsay sedation score between 2 groups at 60 min after study drug administration.

Induction dose of propofol shown in Table 1. There is significant difference in induction dose of propofol in both the groups. The requirement of Induction dose of injection Propofol was significantly reduced in Group II as compared with Group I with p value 0.01.

Induction dose of Propofol- the dose of propofol at which eyelash reflex is lost. Mean

Table 1: Mean induction dose of Injection Propofol (mg) in both the groups

Study group	Induction Dose of Injection Propofol (mg)			
	Min-Max	Median	Mean ± SD	P value
Group 1	90-140	120	116.4±14.97	0.01
Group 2	80-140	110	104.4±17.1	

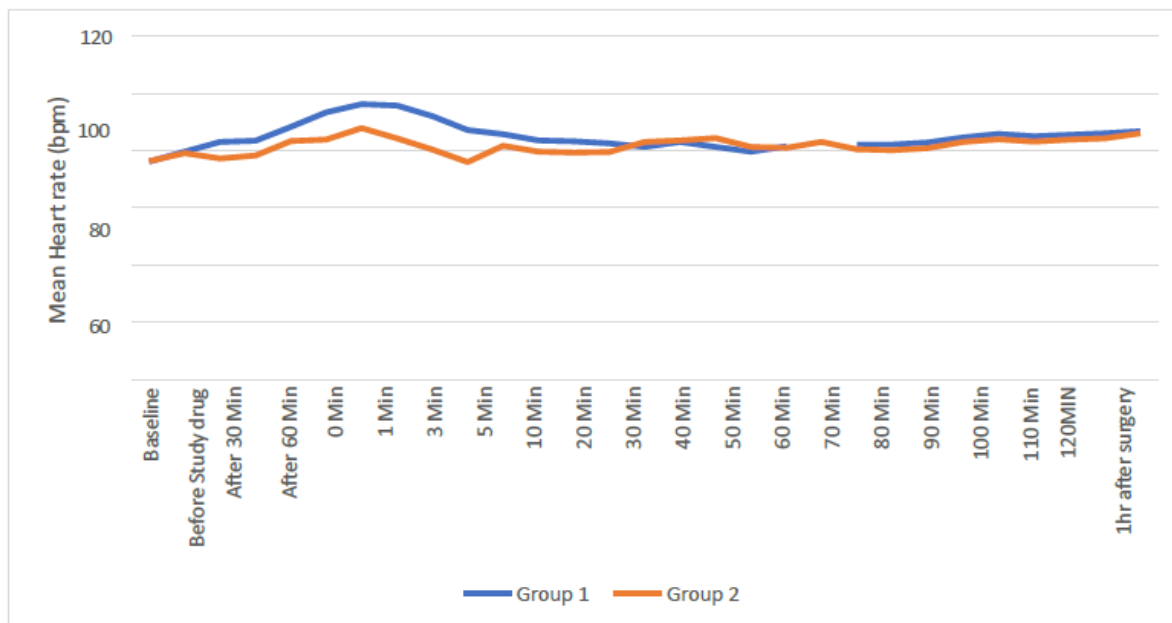
Significant difference in mean induction dose (p=0.01)

Heart Rate-

Heart rate was evaluated and recorded preoperatively as baseline, before study drug administration, after study drug administration at 30min and 60min, during laryngoscopy till 10min, intraoperatively every 10min and postoperatively for 24hrs. Reduction in Heart Rate 30 minutes and 60 minutes after giving Tablet Alprazolam and

Melatonin was highly significant with p value <0.01. [graph- 3]

Heart rate was significantly reduced during laryngoscopy and intraoperatively till 20minutes with highly significant p values of <0.01. Postoperatively there was no significant decrease in heart rate between 2 groups.



Graph 3: Graph distribution of mean Heart rate among groups at different time intervals

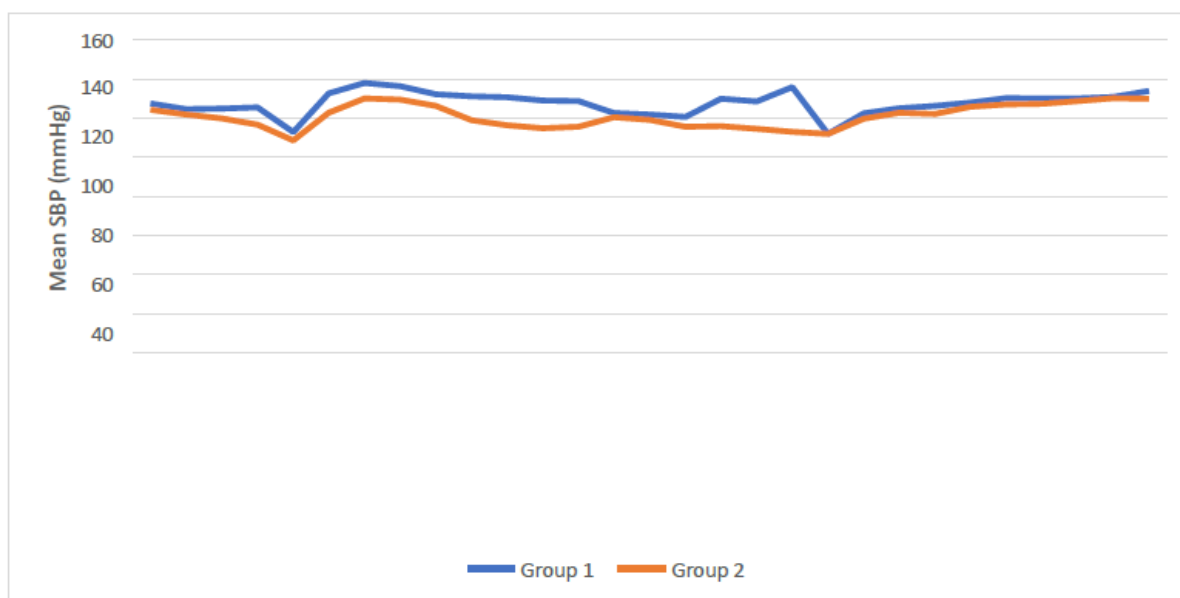
The graph presents mean Heart rate measurements for Group I and II, at various time intervals from before study drug administration to 24Hr postoperatively.

Systolic blood pressure among groups at various time interval.

SBP was evaluated and recorded preoperatively as baseline, before study drug administration, after study drug administration at 30min and 60min, during laryngoscopy till 10min,

intraoperatively every 10min and postoperatively for 24hrs. Reduction in SBP after study drug at 30 minutes was significant in Group II with p value 0.04. After administration of Tablet Alprazolam and Melatonin at 60min reduction in SBP was significant with p value <0.01. [graph- 4]

SBP was significantly reduced during laryngoscopy and intraoperatively till 50minutes with highly significant p values of <0.01. Postoperatively there was no significant decrease in SBP between 2 groups.



Graph 4: Graph distribution of systolic blood pressure at different time intervals in different patient groups

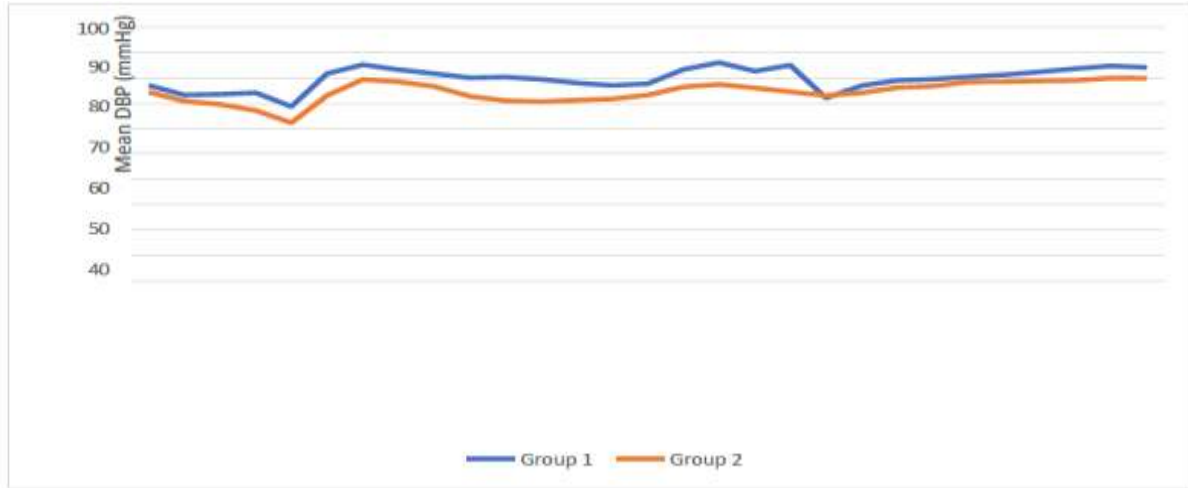


DBP among groups at various time interval.

DBP was evaluated and recorded preoperatively as baseline, before study drug administration, after study drug administration at 30min and 60min, during laryngoscopy till 10min, intraoperatively every 10min and postoperatively for 24hrs. Reduction in DBP at 30 minutes and 60minutes after study drug administration was

significant in Group II with p value 0.04 and <0.01 respectively. [graph- 5]

DBP was significantly reduced during laryngoscopy and intraoperatively till 60minutes with highly significant p values of <0.01. Postoperatively there was no significant decrease in DBP between 2 groups.



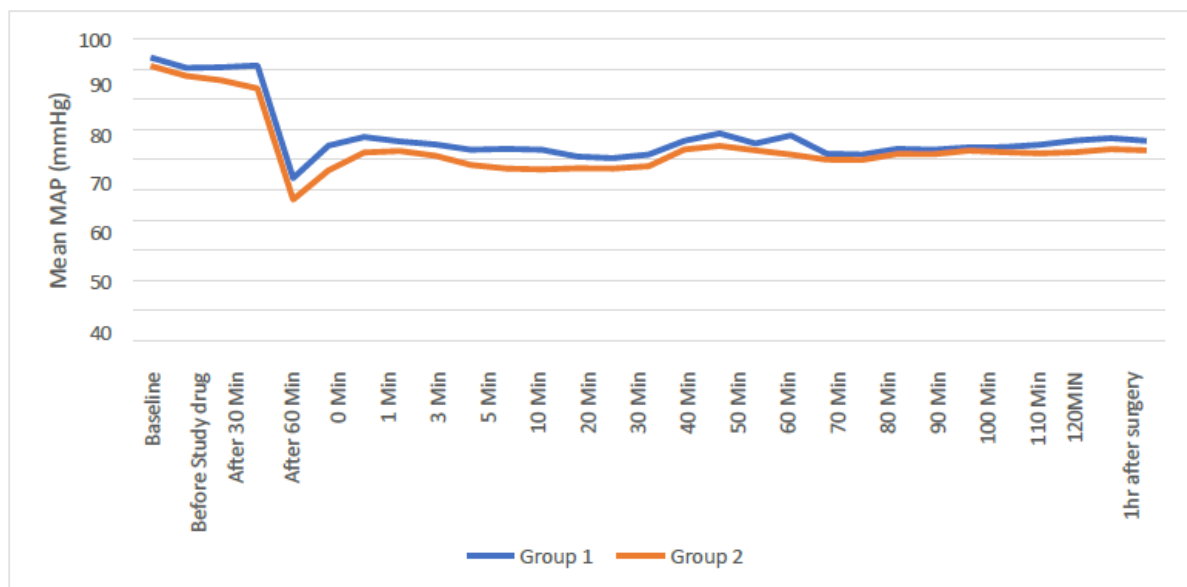
Graph 5: Graph showing mean DBP at different time intervals in different groups

Mean Arterial Pressure among groups at various time interval.

MAP was evaluated and recorded preoperatively as baseline, before study drug administration, after study drug administration at 30min and 60min, during laryngoscopy till 10min, intraoperatively every 10min and postoperatively for 24hrs. Reduction in MAP, 30 minutes and 60

minutes after giving study drug was significant in Group II with p value 0.03 and <0.01 respectively. [graph- 6]

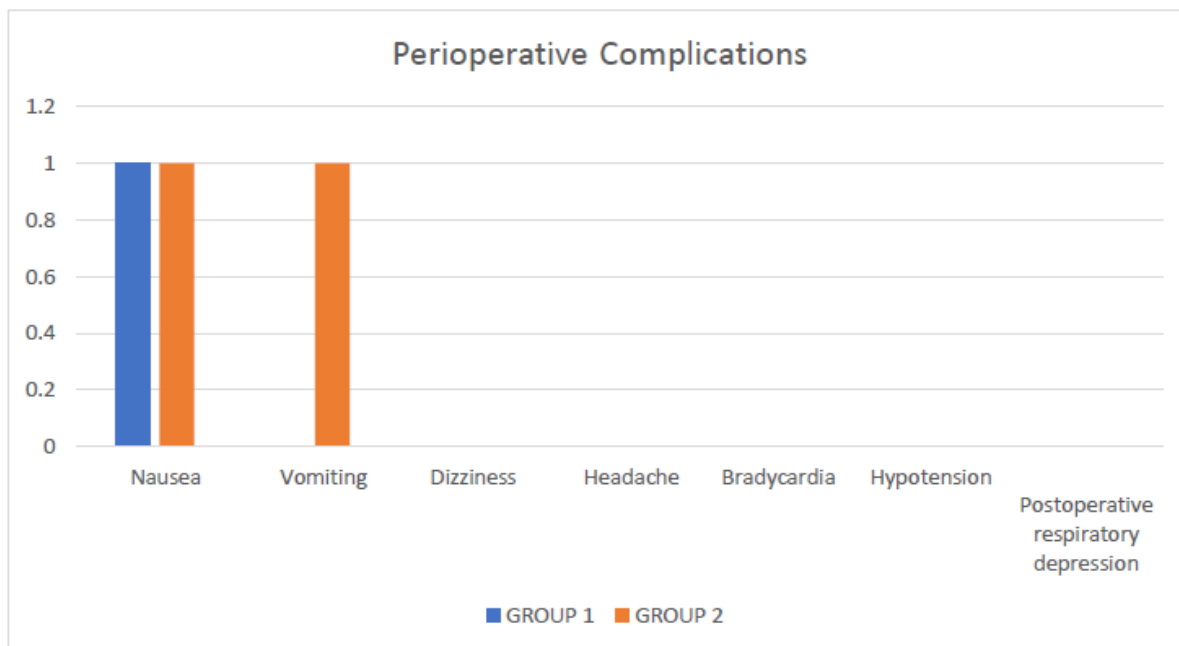
MAP significantly reduced during laryngoscopy and intraoperatively till 60minutes. Postoperatively there was no significant decrease in MAP between 2 groups.



Graph 6: Mean Arterial Pressure at different time interval in different groups



The graph presents mean arterial pressure (MAP) measurements for Group I and II at various time intervals from before administration of study drug to 24Hr postoperatively. [graph- 7]



Graph 7: Graph showing complications among patient groups

The graph presents the perioperative complications among groups. In Group I only 1 patient had nausea. In Group II one patient had nausea and one had vomiting.

Discussion

Demographic data

The demographic data of both the groups were similar in terms of mean values of age, gender, height, weight and BMI.

Preoperative Anxiety

Assessment of preoperative anxiety was done 90 minutes before surgery by using VAS-A score. Then after administration of study drug at 30 minutes and 60minutes. The mean and SD of VAS-A scores before study drug in Group I and II are 4.04 ± 0.73 , and 4.04 ± 0.84 respectively. The mean and SD of VAS-A score at 30 minutes after administration of study drug in Group I and II are 3.8 ± 0.71 and 3.44 ± 0.65 respectively, and 60minutes after administration of study drug are 3.68 ± 0.85 , and 2.4 ± 0.58 respectively. There is a significant statistical difference in VAS-A scores between Group I and II at 60 minutes of administering study drug (P values are <0.01). Our results share similar findings as obtained by Pokhrel K. et al,¹² who compared VAS-A score between combination of Alprazolam and Melatonin and individual drugs with placebo in their study

and they found that at 60min after study drug, reduction in VAS-A score was significant compared to baseline.

Ionescu et al.¹⁵ reported that oral melatonin (3mg) when used as premedication in laparoscopic cholecystectomy produced significant reduction in preoperative anxiety compared to placebo group.

Sedation score

Sedation score was calculated by using Ramsay sedation score before giving study drug, then after administration of study drug at 30 minutes and 60 minutes. In our study, we found that there was significant difference in Ramsay sedation score between Group I (1.16 ± 0.37) and Group II (1.92 ± 0.28) at 60minutes after study drug administration with highly significant p value-0.005.

It was supported by, Khare A. et al¹⁰, they found that both Melatonin (6mg) and Alprazolam (0.5mg) alone caused significant sedation as compared to placebo. Naguib and Samarkandi et al,¹³ also found increased sedation in melatonin (5mg) and midazolam (15mg sublingual) groups as compared to placebo. Induction dose of Propofol.

Induction dose of propofol was calculated as dose at which the eye lash reflex of patient was lost. Our results showed that less dose of propofol was required in Group II as compared to Group I. The requirement of Induction dose of injection



Propofol was significantly reduced in Group II as compared with Group I with **p value 0.01**.

Reduction in preoperative anxiety and attenuation of adrenergic response by melatonin and alprazolam decreases requirement of anaesthetic induction agents. This result was endorsed by the studies done by Mohamed Naguib et al.¹⁴ they found that melatonin premedication significantly decreased the doses of induction agents required. (p value < 0.05). In another study done by Afsanch Nororuzi et al,¹⁶ found that the induction dose of Propofol was lower in melatonin group than in placebo group.

In our study we divided patients randomly. We found that the mean weight and SD of Group I patients was 62.4±8.5 and Group II patient was 63.8±7.78. The mean induction dose of propofol in Group I was 116.4±14.97 and in Group II was 104.4±17.1. we assume that the requirement of mean induction dose of propofol would be much lower if mean weight distribution in both the groups were equal.

Heart Rate

Heart Rate at 30 minutes and 60 minutes, after giving Tablet Alprazolam and Melatonin was significantly reduced in Group II as compared to placebo. The difference in mean HR in Group I (83.04±7.79) and II (77.24±7.36) at 30min after study drug was significant with p value <0.01. Also, at 60 min after study drug, difference in mean HR between Group I (83.44±7.71) and Group II (78.32±7.2) was markedly significant with p value <0.01.

Heart rate was reduced at various time points of laryngoscopy and intubation (p value <0.01). The difference between mean HR in Group I and II during laryngoscopy and intubation at 0min (88.36±7.65 in Group I and 83.32±8.54 in Group II), at 1min(93.4±7.66 in Group I and 83.92±7.35 in Group II), at 3min (96.24±8.58 in Group I and 87.88±8.97 in Group II), at 5min (95.72±10.88 in Group I and 84.24±10.24 in Group II) and at 10min(92±12.29 in Group I and 80.36±7.55 in Group II) was highly significant with p value <0.01.

Intraoperatively there was marked reduction in heart rate in Group II as compared to Group I at various time interval (p values of <0.05) till 50min, after which difference was not significant.

Kumar et al.¹⁷ in their study concluded that melatonin premedication resulted in significant attenuation of postintubation rise in heart rate.

In study done by Choudhary et al.¹⁸, they found that oral melatonin (6mg) premedication is

superior to oral clonidine (0.2mg) in attenuating haemodynamic response to laryngoscopy and intubation. This is in alignment to our study that melatonin has role in attenuation of haemodynamic response to laryngoscopy and intubation.

Systolic Blood Pressure

Systolic blood pressure measured at 30minutes and 60minutes, after giving study drug showed that there was significant reduction in Group II as compared to Group I. The difference in SBP (125.56±9.52 in Group I and 116.72±6.64 in Group II) at 60min after study drug administration was highly significant with p value <0.01.

Also, there was record of considerably low Systolic blood pressure in Group II as compared to Group I during laryngoscopy and intubation (p value <0.01).

During intraoperative period, systolic blood pressure was maintained significantly low till 50 minutes, when measured every 10minutes intraoperatively, in Group II as compared to Group I (p value <0.01).

This result of our study was supported by Gupta P. et al.⁹ They found that in melatonin group, systolic blood pressure was lower than baseline values at all points of time till 10minute after intubation as compared to the control group in which there was significant rise.

In study done by Patil N.M. et al.¹⁹ they found that melatonin group showed significant decrease in SBP in response to laryngoscopy and endotracheal intubation compared to pregabalin group.

Diastolic Blood Pressure

DBP was significantly reduced 30 min after tablet melatonin and alprazolam in Group II as compared to Group II (p value 0.04) in this study. The mean and SD of DBP at 60minutes were 74.08±6.7 and 67.04±5.99 in Group I and II respectively (p value<0.01). DBP was significantly reduced after 1minute, 3minute, 5minute and 10minute after intubation as compared to Group I (p value <0.01, highly significant). Intraoperatively DBP monitored every 10minutes showed significantly low DBP in Group II as compared to Group I till 60 minutes (p value <0.01).

Mohammed AA et al.²⁰ compared the effects of oral melatonin 6mg and 9mg with placebo administered 1 hour prior to surgery. They found that both melatonin groups had lower blood pressure as compared to placebo group. this study corroborates our findings, suggesting a similar pattern.



Mean Arterial Pressure

MAP was significantly reduced 30minute after tablet melatonin and alprazolam was given as compared to placebo group (p value 0.03). MAP was substantially reduced 60minute after study drug in Group II(83.6±5.83) as compared to Group I(91.24±7.43) with p value <0.01. There was highly significant reduction in MAP at 1minute and 3minute after intubation in Group II as compared to Group I (p value <0.01). MAP was significantly reduced 5minute after intubation with p value 0.04 and 10minute after intubation with p value 0.03. Intraoperatively MAP was substantially reduced till 40min with p value <0.01.

In the study by Kumar et al.¹⁷, they found that melatonin premedication resulted in significant attenuation of postintubation rise in MAP.

Complications

There were no significant side effects such as nausea, vomiting, bradycardia, hypotension, dizziness, headache and postoperative respiratory depression.

In our study, in Group I only one patient had nausea. In Group II, one patient had nausea and one had vomiting.

Various studies indicate that melatonin has an excellent safety profile. Nausea, vomiting, dizziness, headache, irritability, hypotension and bradycardia may be seen in some patients with use of very high doses of melatonin.^{9,21}

Alprazolam at dose 0.5mg and higher can cause psychomotor impairment,¹⁰ impaired immediate and delayed recall, recognition and respiratory depression. Absence of these side effects was attributed to lower dose in our study.

V. LIMITATIONS

- We conducted this study in patients undergoing elective surgeries, but patients undergoing emergency surgeries are more anxious and we cannot generalise our findings to these patient groups.
- This study was done on participants of age group 18-60 years, extremes of ages were not included. This study would not be applicable in neonates, infants, paediatric patients and elderly patients.
- We included patients undergoing surgeries under general anaesthesia, exclusively in our study. Therefore, the findings may not be directly applicable to patients receiving other modes of anaesthesia.
- Pregnant and lactating patients were excluded from this study, limiting the generalizability of the findings to these populations.

- We included only ASA grade 1 and 2 patients in our study, patients with any comorbidity or cardiac disease were not included. Cardiac patients are more susceptible for hemodynamic variations, they are the main target group for this study. But we cannot extrapolate results of our study in these population group.
- Patients with difficult intubation were not included in this group.

VI. CONCLUSION

We conclude that low dose combination of Melatonin (3mg) and Alprazolam (0.25mg) administered 90minutes before surgery is effective in reducing preoperative anxiety. It is effective in reducing induction dose of Propofol. Tablet melatonin(3mg) and alprazolam(0.25mg) combination is effective in attenuating haemodynamic response during laryngoscopy and intubation. The dose and the formulation which we have used in our study produced less side effects like postoperative sedation and respiratory depression. Due to its effectiveness in decreasing preoperative anxiety and adrenergic response during laryngoscopy tablet melatonin(3mg) and alprazolam(0.25mg) can be safely prescribed for patients undergoing surgery under general anaesthesia.

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