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Comparison of Oral Melatonin and Alprazolam Alone and In Combination as Premedication on Anxiety and Sedation

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ABSTRACT

Background: Preoperational anxiety is a universal reaction experienced by patients who are admitted in the hospital for surgery. Preoperative anxiety can be defined as- "unpleasant state of uneasiness or tension that is secondary to a patient being concerned about disease, hospitalization, anaesthesia and surgery. This study aims to compare the effects of oral melatonin and oral alprazolam alone and with Combination of both melatonin and alprazolam on perioperative anxiety and sedation.

Aims & Objectives: The objectives of our study were to compare anxiety and sedation, using Hospital anxiety and depression scale and Modified Ramsay Sedation Score.

Material and methods: A total of 90 adult patients were randomly allocated into three groups. Group 1received oral alprazolam0.5 mg, Group 2 received oral melatonin 3 mg, Group 3 received alprazolam 0.5 mg and melatonin 3 mg tablet as premedication.

Results: Three groups were comparable with respect to demographic profile including mean age, sex, weight, and ASA physical status, sedation, and anxiety levels. Sedation was better in Melatonin than Alprazolam and it was further improved on adding Alprazolam and Melatonin (p value<0.5). Anxiety was decrease in Melatonin and slightly decrease in Alprazolam, Adding melatonin to alprazolam reduced anxiety levels more than either of the two drugs given alone (P value 0.0004).

Conclusion: Combination of alprazolam 0.5mg and melatonin 3mg significantly reduced the patient's level of anxiety with sedative effect, which helped in smoother induction of anaesthesia.

Key Words: *Alprazolam, Melatonin, Sedation, Anxiety*

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INTRODUCTION

Preoperational anxiety is a universal reaction experienced by patients who are admitted in the hospital for surgery because of many reasons such as fear of surgery, resultant postoperative pain, doubts about anaesthesia, outcome of disease and surgical procedure, separation from family.

Preoperative anxiety can be defined as- "unpleasant state of uneasiness or tension that is secondary to a patient being concerned about disease, hospitalization, anaesthesia and surgery. The preoperative distress can trigger a set of behavioral and systemic manifestations in the form of increased sympathetic output (increased heart rate, blood pressure, cardiac contractility, perspiration, cold clammy skin), increased baroreceptor response, which make anesthetic management difficult in terms of delayed induction, increased intraoperative anesthetic requirements, haemodynamic instability, more requirement of analgesics. Interventions to reduce preoperative anxiety include pharmacological therapy [1], provision of information [2], distraction, attention focusing, and relaxation procedures [3].

Benzodiazepines, Opioids and NSAIDs are traditionally being used to treat preoperative anxiety [4] but these drugs are associated with their side effects.

Melatonin causes sedation and anxiolysis [5, 6] due to its inhibitory action on central nervous system. It may also have minor side effects but has no postoperative residual effects. It also has analgesic, anti-inflammatory, anti-oxidative and chronobiotic effects besides anxiolytic, sedative and hypnotic properties which makes it a desirable drug to be used as a premedicant alternative to benzodiazepines.

MATERIALS AND METHODS

This study was carried out at the Department of Anaesthesia and Critical care, Government medical college Kota from June 2021 to Nov 2022. After getting approval from the institutional research ethics committee and written informed consent, ninety patients were studied.

Study Design: Randomized Comparative Prospective Analyticalstudy.
Sample Size: 3groups of 30 subjectsin each
Duration of study: January 2021 to March 2022
Sampling Method: Simple random sampling

Inclusion criteria:

- ASA Grade I & II status.
- Age between 18-60 years of either sex.
- Patients scheduled to undergo elective surgical procedures under general anaesthesia.

Exclusion criteria:

- Pregnant and lactating females
- Patients with history of psychiatric disorders or on any anti psychotic drugs.
- Patients with language or communication difficulties.
- Patients with sleep disorders.
- Patients with severe renal or hepatic derangement.
- Patients having inability to read and write basic alphabets.
- Hypersensitivity to melatonin or alprazolam.
- Patient taking opioids, benzodiazepines, other drug/alcohol abuse.
- Anticipated difficult airway and difficult intubation.

Details of the study

With the help of computer generated random numbers, patients were assigned in one of the three groups. On the pre anesthetic visit one day prior to surgery, the patients were explained about the nature of the study and aboutvarious scales. All patients were electively kept nil by mouth for 6 hours before surgery.

Group 1: Alprazolam 0.5mg tablet given orally with sip of water.
Group 2: Melatonin 3mg tablet given orally with sip of water.
Group 3: Combination of 0.5mg alprazolam and 3mg melatonin tablet given orally with sip of water.

The patient's level of anxiety and sedation were assessed and various haemodynamic parameters including heart rate (HR), noninvasive blood pressure (NIBP), and oxygenation (SpO_2) were recorded before given study medications. The study medications were given to the patient 120 min before induction of general anaesthesia.

Parameters recorded

Anxiety scores, sedation score done by the investigator, before giving the premedication, after 1hour of drug administration, and just before operation theater. Post-operative6 hours and 24 hours.

Occurrence of side effects of melatonin like headache, nausea, enuresis, depression and dizziness.
Occurrence of side effects of alprazolam like dry mouth, headache, hiccups, nausea, vomiting, blurred vision, and dizziness.

Hospital Anxiety and Depression Scale (HADS): is comprises of two sub-scales, Depression and Anxiety. Each sub-scale has a score ranging from 0-21. HADS items are rated on a 4-point Likert-type scale ranging from 0-3, with higher scores representing greater symptoms of severity. Score of 0-7 indicate normal levels of anxiety, 8-10 indicates borderline abnormal anxiety and 11-21 suggests abnormal levels of anxiety. The anxiety sub-scale questions are numbered as 1, 3, 5, 7, 9, 11 & 13 and these were used in present study. This scale is a valid and reliable self-rating scale that measures anxiety and depression in both hospital and community settings. This scale has high sensitivity and specificity.

MODIFIED RAMSAY SEDATION SCALE

I	Anxious, agitated, restless.
II	Cooperative, oriented, tranquil.
III	Responds to commands only.
IV	Brisk response to light glabellar tap or loud noise.
V	Sluggish response to light glabellar tap or loud noise.
VI	No response.

RESULTS

Table no 1: Age, Weight, Sex and ASA wise distribution of patients

Variables	Group 1 (MEAN +/- SD)	Group 2 (MEAN +/- SD)	Group3 (MEAN +/- SD)
Age	43.1+/-8.69	33.4+/-8.21	29.53+/-9.14
Weight	60.93+/-7.50	59.3+/-5.84	54.03+/-6.19
Sex			
Male	18	19	24
Female	12	11	6
ASA			
Grade I	25	27	25
Grade II	5	3	5

The three groups were comparable with respect to demographic profile including mean age, sex, weight, and ASA physical status.

Table No 2: Observation of changes in sedation with Modified Ramsay Sedation Scale

Modified Ramsay Sedation Scale	Group 1	Group 2	Group 3	p vaule
	Mean ±SD	Mean ±SD	Mean ±SD	
Baseline	1.5±0.50	1.36±0.49	1.4±0.49	0.562
After 1 hr	2.03±0.18	2.2±0.40	2.43±0.50	0.0006
Just before OT	2.13±0.34	2.43±0.50	2.56±0.50	0.0014
After 6 hr	1.63±0.49	1.43±0.50	1.6±0.49	0.2541
After 24 hr	1.6±0.49	1.36±0.49	1.5±0.50	0.1979

Table No: 2 shows Comparison of three groups with Modified Ramsay Sedation Scale at baseline, after 1 hour, just before OT, after 6hours, and after 24hours of drug administration. Study depicts significant better sedative effect in Group 3 as compare to Group 1, and Group 2at one hour and just before OT.

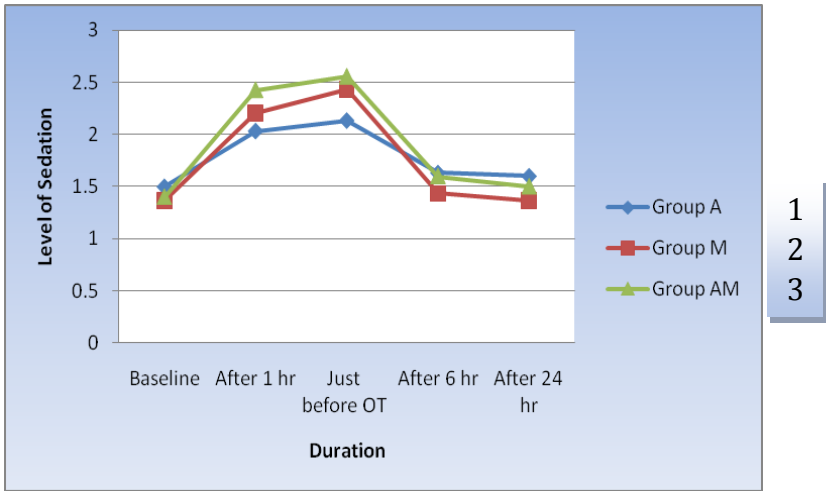
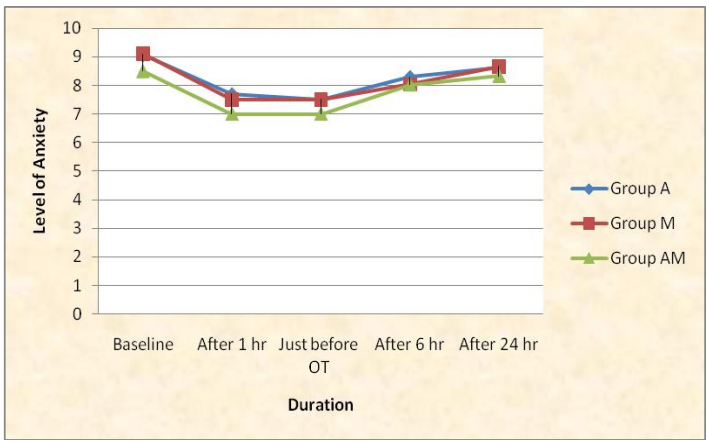


Table No 3: Observation of changes in Anxiety with Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)	Group 1	Group 2	Group 3	p value
	Mean ±SD	Mean ±SD	Mean ±SD	
Baseline	9.06±1.01	9.1±1.18	8.5±1.07	0.0634
After 1 hr	7.7±0.53	7.5±0.66	7±0.81	0.0004
Just before OT	7.5±0.37	7.5±0.54	7±0.67	0.0004
After 6 hr	8.3±0.47	8.03±0.66	8.03±0.80	0.1911
After 24 hr	8.6±0.62	8.66±0.71	8.33±0.99	0.2315

Table No.3 Shows Comparison of three groups with respect to Anxiety with Hospital Anxiety and Depression Scale, which was decrease in Group 1 and in Group 2 after 1 to 2 hours of drug administration, but markedly decrease in Group 3.This is found significant at 1 hr and just before OT.



DISSCUSION

Present study was aimed to analyze appropriateness of Alprazolam and Melatonin alone and in combination to be used as premedication for pre-operative anxiety.

DEMOGRAPHIC VARIABLES

All patients selected in the study belonged to age between 18 and 60 years of either sex and physical status of ASA grade 1 and ASA grade 2, and weight between 40-80 kg. A random allocation of the patients was done in three groups. Maximum patients were in between 18–50 years of age in all groups. Majority of patients were in between 51-70 kg weight in all groups. Out of 90 total patients, 61 were female and 29 were male. In all three groups majority of patients were female. **The three groups were comparable with respect to demographic profile including mean age, sex, weight, and ASA physical status.**

ANALYSIS OF DATA RELATED TO SEDATION:

Few studies showed that melatonin is less sedative compared to the benzodiazepines used especially midazolam. Few studies showed benzodiazepine midazolam affected sedative levels of patients hence not effective in day care surgeries.

1) In a study done by Naguib et al [7, 8] Midazolam group showed significant higher levels of sedation than the melatonin group at 30 and 60 min after premedication.
2) In a study done by Acil et al [9] Melatonin group exhibited increased levels of sedation only at 90 min after premedication versus placebo (P <0.05). However, significantly decreased sedation levels were evident in the melatonin versus midazolam group at 10, 30, and 60 min after premedication (P <0.001).
3) In a study done by Ahmed RA et al [10] Midazolam group had significant increase in level of sedation before operation when compared with melatonin and control groups.

There was only one study compared melatonin and alprazolam sedative effects and found that melatonin is better sedative than alprazolam and combination of both didn't increase sedation levels and not better than drugs alone. Krishna Pokharel et al [11] concluded that combination of melatonin and alprazolam produced sedation and amnesia to a similar degree as alprazolam alone but melatonin was more sedative compared to alprazolam alone.

In our study, we used Modified Ramsay Sedation Scale to assess for degree of sedation. Comparison of three groups at baseline, after 1 hour, just before OT, after 6 hours, and after 24 hour of drug administration. Sedative effect was maximum in Group 3 after 1-2 hours (p value <.05), and Group 2 (p value<.05) has slightly better sedative effect as compare to Group 1, which has minimal sedative effect (p value<.05). Sedation was better in Melatonin than Alprazolam and it was further improved on adding Alprazolam and Melatonin.

ANALYSIS OF DATA RELATED TO ANXIETY:

Few studies showed that melatonin effects are comparable to the benzodiazepines used in their studies, found effective in daycare surgeries since it didn't affect patient sedation level and recovery of the patient was smooth.

1) Samarkandi et al [12] compared the effects of melatonin and midazolam with that of a placebo and found that anxiolysis in the melatonin group was comparable to that produced by midazolam group. These studies also showed good anxiolytic effect of melatonin pre-operatively when compared to placebo.
2) Acil et al [9] showed in a study that 5mg sublingual melatonin produced effective anxiolysis comparable to 15 mg sublingual midazolam in adults undergoing surgery under general anaesthesia.
3) Ahmed RA et al [10] conduct a studywhere Patients received premedication neithermidazolam or melatonin had significant reduction in anxiety levels compared with control group. Postoperatively, there was no significant difference among the groups for anxiety levels. They concluded that melatonin can be used effectively for premedication for adult patients without hangover effects compared to midazolam.

4) Tushar patel, et al [13] study concluded that Oral melatonin 0.4 mg/kg provides adequate anxiolysis comparable to that of oral midazolam.
5) Few studies showed melatonin is better anxiolytic compared to the benzodiazepines used in their studies or the placebo which proved that melatonin is better anxiolytic compared to the drugs used since before.
6) A study was done by Caumo et al [14] concluded that preoperative melatonin produced clinically relevant anxiolytic and analgesic effects, especially in the first 24 postoperative hours.
7) A study was done by Ionescu D et al [15] Melatonin can be successfully used as premedication for laparoscopic cholecystectomy, especially for day care surgery. Melatonin is better perioperative anxiolytic compared to midazolam and placebo.
8) Krishna Pokharel et al [11] In a prospective, double-blind placebo-controlled trial concluded that addition of melatonin 3 mg to alprazolam 0.5mg had superior anxiolysis compared with either drug alone or placebo.

In our study, we used Hospital Anxiety and Depression Scale to measuring anxiety. Comparison of three groups at baseline, after 1 hour, just before OT, after 6 hours, and after 24 hour of drug administration with respect to Anxiety, which was markedly decrease in Group 3 after 1 to 2 hours of drug administration, decrease in Group 2 and slightly decrease in Group 1 after 1 to 2 hours of drug administration.

Adding melatonin to alprazolam reduced anxiety levels more than either of the two drugs given alone that may be due to synergetic effects of melatonergic and GABAergic systems.

CONCLUSION

In this study, melatonin 3mg and alprazolam 0.5mg was used to determine if its anxiolytic and sedative properties are effective enough to be used to alleviate anxiety in patients undergoing general anaesthesia for elective surgery. The degree of sedation and anxiety were measured, as well as the quality of recovery from the general anesthetic. Based on the findings of this study, combination of alprazolam 0.5mg and melatonin 3mg significantly reduced the patient's level of anxiety with sedative effect, which helped in smoother induction of anaesthesia.

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