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# PREOPERATIVE ANXIETY RELIEF: ORAL MELATONIN VERSUS ORAL MIDAZOLAM

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**Introduction:**

Preoperative anxiety is a worrisome state before anesthesia and surgery. Preoperative anxiety if unallayed is associated with intraoperative haemodynamic changes as well as postoperative hemodynamic issues, psychological problems, delayed wound healing, higher chances of infection etc. Hence preanesthetic medications must be given to effectively decrease pre - operative anxiety. Almost all drugs currently used to decrease pre - operative anxiety; including midazolam which has been the gold standard all these years; have other effects on the central nervous system, such as changes in orientation, cause drowsiness and other adverse effects; though the magnitude of these effects varies from drug to drug, the dosage, and the route of administration. This study will look at drug "Melatonin" as an effective alternative to midazolam for preoperative anxiolysis.

**Aim of the study:**

To determine the anxiolytic modification of Melatonin compared with Midazolam, when administered as pre anaesthetic medication before surgery.

**Objectives of the study:**

Primary: Anxiolysis
Secondary: Adverse effects, Changes in vital parameters

**Materials and Methods:**
Institutional ethical committee approval was taken.
**Study plan:** This is a double blinded randomized controlled clinical trial.

**Study Population:**
Inclusion criteria: Adult Patients of ASA – PS classification I and II status, between 18 – 60 years of age undergoing any surgery requiring anesthesia.

Exclusion criteria: Unwilling patients, patients on anti-psychotic drugs, language or communication difficulties, sleep disorders, renal or hepatic derangement, lesser intelligence quotient

**Sample size:**
A sample size of 66 patients was predetermined from a prior assessment at our hospital, where preoperative anxiety was computed to be around 96%. The patients were randomized to 2 groups of 33 each. Group A – oral melatonin & Group B – oral midazolam.

**Description of the clinical intervention:**
Patient's anxiety, orientation and sedation scores were assessed using NRS by trained anesthesiologist who was blinded to the group that the patient belongs to. The NRS is 'numerical rating scale' with score from 0 to 10. Score 0 means no anxiety, 1,2,3……9 indicates increasing levels of anxiety and a score of 10 indicates highest & worst level of anxiety. Orientation and sedation are assessed as below
Orientation score 0 = none
1 = orientation to either space or time or person
2 = orientation to 2 of the 3 parameters space/time/person. 3 = orientation to space, time and person

Sedation is assessed by "The Observer's Assessment of Alertness/Sedation (OAA/S) Scale Score"

| | |
|---|---|
| 5 | Fully awake |
| 4 | Sluggish responses when name uttered in normal tone |
| 3 | Retaliate only when name is called loudly or repeatedly |
| 2 | Respond only after mild poking or shaking |
| 1 | Respond only after squeezing the trapezius |
| 0 | Does not respond after squeezing the trapezius |

The drug was then administered to the patient 90 min before proposed induction time. Melatonin or midazolam was given orally in the dose of 0.1mg/kg body weight, according to the group. Patient was asked to calm down subsequently after the intake of the drug and monitored throughout. After 60min, patient was assessed again and parameters noted before shifting to operating room for induction of anesthesia.

**Statistical analysis:** The parameters were subjected to Statistical analysis using statistical software STATA 11.0. The p value of <0.05 was determined as significant. Continuous variables were depicted as Mean (SD), and categorical variables were denoted as Frequency (percentage). Chi- square test or Fisher's exact tests were used to evaluate differences in categorical data. Wilcoxon sign rank test, Mann Whitney U test and Kruskal Wallis test were also used.

Table 1: Analysis of Demographics

| Analysis of Demographics | | | | |
|---|---|---|---|---|
| | | Group A | Group B | P value |
| Gender | Male | 21(22.11%) | 17(17.89%) | 0.604 |
| | Female | 12(17.14%) | 16(22.86%) | |
| Age | 18-40 years | 16(17.58%) | 20(21.98%) | 0.287 |
| | 41-60 years | 17(22.97%) | 13(17.57%) | |
| ASA grade | I | 14(16.28%) | 16(18.60%) | 0.129 |
| | II | 19(24.05%) | 17(21.52%) | |
| Anaesthesia | RA (SA+Nerve block) | 24(22.86%) | 21(20%) | 0.766 |
| | GA | 9(15%) | 12(20%) | |

Table 2: Analysis of parameters after drug administration

| Analysis of parameters after drug administration | | | |
|---|---|---|---|
| | Group A | Group B | P-value |
| Anxiety score | 3.66±0.88 (36%) | 3.72±1.32 (37%) | 0.7697 |

| | | | |
|---|---|---|---|
| Sedation<br><br>Score / degree of sedation in % | 4.81±0.39 (33.33%) | 3.54±0.50 (41%) | <**0.001*** |
| Orientation score /Decrease in Orientation in % | 3±0 (0%) | 2.81±3.96 (29.75%) | <**0.001*** |
| Adverse effects | | | |
| Nausea/ vomiting | 1(3.03%) | 0 | 0.314 |
| Blurred vision | 0 | 1(3.03%) | 0.314 |
| Inability to concentrate | 0 | 2(6.06%) | 0.151 |
| Bitter taste | 0 | 1(3.03%) | 0.314 |
| ECG rhythm changes | 0 | 0 | 0 |
| Vital Parameters | | | |
| Heart Rate | 81.33±4.26 | 75±3.88 | <**0.001*** |
| Blood Pressure (MAP) | 83.45±0.36 | 81.75±0.45 | <**0.001*** |
| SpO2 | 99.57±0.50 | 96.81±0.91 | <**0.001*** |
| Respiratory Rate | 13.45±0.61 | 12.42±1 | <**0.001*** |

Figure 1: Comparison between Group A and Group B after drug administration

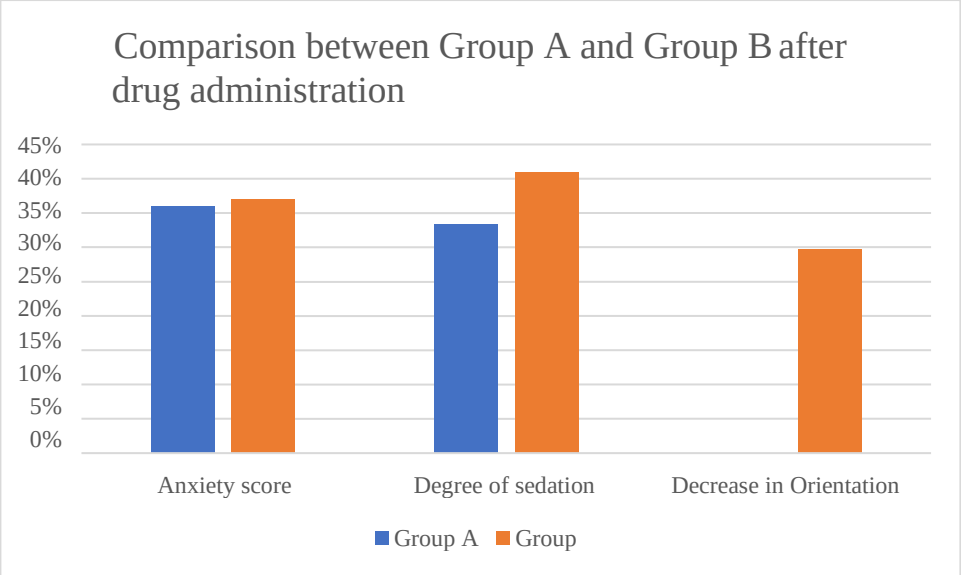



Figure 2: Comparison of adverse effects between Group A and Group B after drug administration

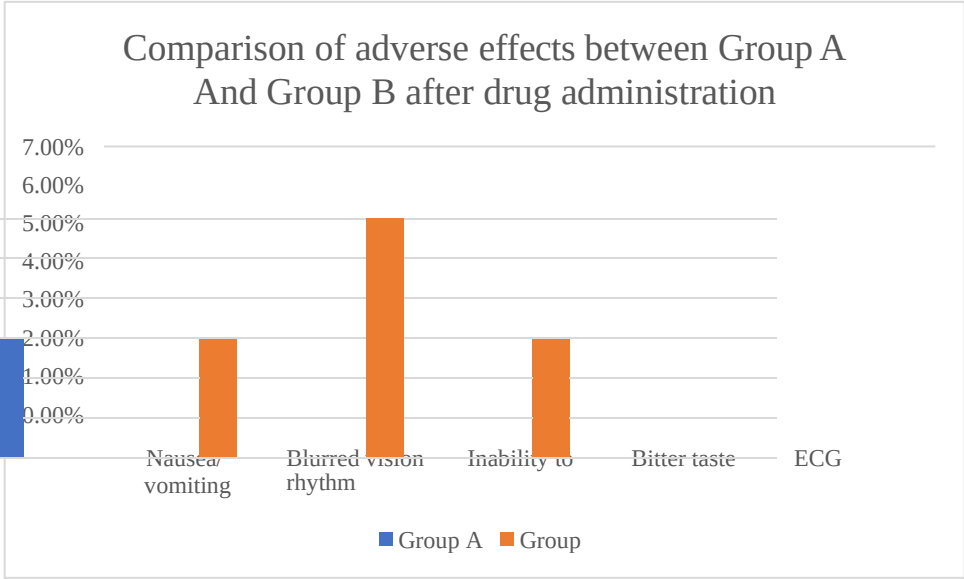
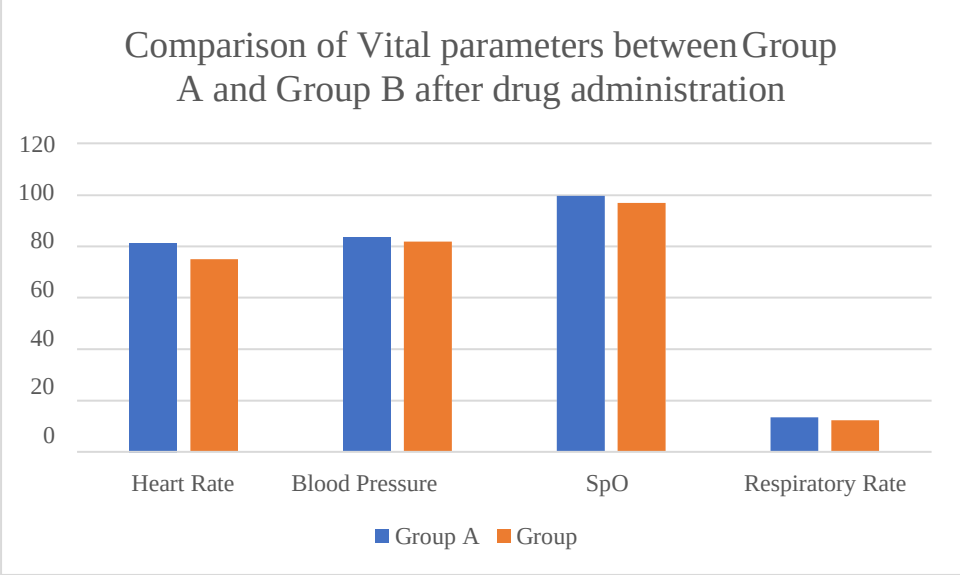


Figure 3: Comparison of vital status between Group A and Group B after drug administration




**Results:** Demographically among the groups, there was no statistical significant differences. The anxiety levels among the group before medication was not statistically significant. The degree of anxiolysis, post medication was comparable and not statistically significant between the groups. But on comparison of the adverse effects such as excessive sedation, changes in orientation, nausea, vomiting, visual disturbances, and inability to concentrate, there was a statistically significant difference; with group B midazolam patients having more adverse effects. Though changes in vital parameters were more pronounced in midazolam group, it was less than 30% from baseline and hence clinically insignificant.

Table 3: Summary of Results

| **Statistical analysis of…….** | **Result / Interpretation** |
|---|---|
| DEMOGRAPHICS | **NO DIFFERENCE between the groups** |
| ANXIETY RELIEF AFTER MEDICATION | |
| CLINICALLY SIGNIFICANT CHANGES IN VITAL PARAMETERS | |

| | |
|---|---|
| SEDATION | **MORE WITH MIDAZOLAM LESS WITH MELATONIN** |
| CHANGE IN ORIENTATION | **MORE WITH MIDAZOLAM NONE WITH MELATONIN** |
| VISUAL DISTURBANCES | |
| INABILITY TO CONCENTRATE | |
| NAUSEA/VOMITING | **NAUSEA WITH MELATONIN NONE WITH MIDAZOLAM** |

**Discussion:**

Midazolam is in clinical use for more than 20 years and has many clinical indications such as treatment of insomnia, epilepsy, anxiolysis and is used for sedation before diagnostic and therapeutic medical practice by several routes including oral, intravenous, intranasal, rectal and intramuscular. Several studies[1,2] have shown that Oral midazolam at a dose of 0.1 mg/kg, orally, exhibited sedative, anxiolytic with no adverse impact on hemodynamic stability.

Several clinical experiments have investigated the uses of melatonin in diverse fields of medicine, since the last 20 years. The efficacy of melatonin has been imposed in the treatment of cardiovascular diseases, diabetes, rheumatoid arthritis, myofascial pain syndromes, gastrointestinal tract diseases, neurological diseases etc. The usefulness of melatonin in anaesthetic procedures has also been proved.[3] A study[4] has established the very low toxicity of melatonin over an extensive set of doses. But, some studies[5,6] have shown that the Elderly population is resistant to the hypnotic and anxiolytic outcome of melatonin.

In our study the anxiolysis produced by melatonin was similar to midazolam, as in few other studies.[3,7,8] There was more than 20% difference in pre and post drug NRS scores in both the groups, this being clinically significant anxiolysis.

Also, more sedation was observed with midazolam, when compared to melatonin. Similar findings were observed in a study by Acil et al[9] who found that Midazolam promote elevated level of sedation when compared to melatonin and melatonin produced sedation which was enough to rest the patient and generate a natural sleep.

Another reason for higher depth of sedation with midazolam can be due to its mechanism of action. Midazolam is a benzodiazepine which produces its sedative effect by activating the brain's normal endogenous inhibitory neurotransmitter - Gamma Amino Butyric acid – GABA, by binding to numerous alpha subunits of the GABA

receptor complex (specifically GABAA) and potentiates opening of chloride channels; sometimes additional receptor sites also being concurrently activated by benzodiazepines.[10] The sleep-promoting and sleep/wake rhythm modulating effects of melatonin are ascribed to its action on MT (1) and MT (2) melatonin receptors positioned in the suprachiasmatic nucleus (SCN) of the hypothalamus.[11] Researchers[12] have found that drug channels that target added neurotransmitters, other than GABA are generally less effective for sedation when used single; thus, explaining the difference in the intensity of sedation between midazolam and melatonin drugs.

Regarding adverse effects such as change in orientation, visual disturbances and inability to concentrate was reported in the midazolam group and none in melatonin group in our study. This is similar to a study by Patel et al[13]. A study by Wang et al[14] indicated that midazolam-induced light sedation is correlated with decreased connectivity within the dorsal attention network (DAN) which regularly mediates external processing and attention-demanding cognitive function, thus explaining the cause for change in orientation and inability to concentrate. The excessive sedation with midazolam made the patient groggy, unable to concentrate on the pen paper tests and they also reported visual disturbances mainly blurring.

Melatonin caused nausea in 2 patients, but none in midazolam group as midazolam is said to have an antiemetic effect.[15] Splinter et al[16] reported less vomiting in children receiving midazolam after tonsillectomy. Though changes in the vital parameters were more pronounced in the midazolam group as compared to melatonin group; these changes were less than 30% from the baseline and hence clinically insignificant.

Thus, melatonin turns out to be a significant drug for anxiolysis with lesser secondary repsonses. Given the safety profile, melatonin can be used in Ambulatory or day care surgeries and in patients with psychiatric & neurological conditions. It can be safely advocated for use in centers with less facilities for perioperative monitoring.

**Conclusion:** Both Oral Melatonin and Oral midazolam at the dose of 0.1mg/kg body weight provided effective preoperative anxiolysis. But minimal adverse effects were observed in Oral Melatonin group in comparison with Oral midazolam group following premedication. Hence oral melatonin is a promising drug for effective preoperative anxiolysis, with minimal adverse effects.

**Limitation of the study:** This study was not conducted in pediatric and elderly population. Only one dose was studied.

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