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Comparing the Effect of Melatonin, Diazepam, and Placebo on Decreasing the Level of Anxiety Preoperatively

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Background

Surgery carries be a heavy mental burden for the patient and can result in anxiety [1]. Preoperative anxiety is typically managed with benzodiazepines which have unpleasant adverse effects and can lead to serious complications [2,3].

Melatonin is a naturally occurring hormone which has shown promising results as an anxiolytic in both experimental and clinical studies [4-7]. Melatonin has not been associated with any serious adverse effects [8], and the known adverse effects are dizziness, headache, nausea, and fatigue. Melatonin could potentially be an effective anxiolytic drug for treating perioperative anxiety [9].

Objective

To investigate the effect of oral melatonin as a preoperative anxiolytic.

Study design

This study is a prospective, randomized, triple-blinded, placebo-controlled clinical trial conducted at the Jordan University Hospital. Participants will be recruited from patients undergoing various elective surgeries at the Jordan University Hospital. Participants will be selected based on predefined inclusion and exclusion criteria.

Participants

Inclusion criteria:

- Patients with ASA grade 1 or 2
- Age between 18 to 60
- Posted for general anesthesia

Exclusion criteria:

- Patients with a known allergy to any of the drugs under study
- Pregnancy
- Illiteracy
- Patients with any mental illness
- Patients currently taking antipsychotics or antidepressants

Withdrawal and drop-out-criteria

1. If the participant wishes to withdraw from the trial at any timepoint.
2. If the participant suffers from any treatment complication the results in a reoperation or admission to an intensive care unit.

3. If circumstances not covered by criteria 1-2 occur and the investigator deems it necessary regarding the health of the participant.

Study course

Patients will be approached in the anesthesia clinic and provided with detailed information about the study. Contact information about the participants will be collected for future follow-up if needed. Patients are given written and verbal information about the purpose and conduct of the study and are required to give written and verbal consent to participate.
Participants will be contacted again in the holding clinic 120 minutes prior to their scheduled surgery. They will be asked to complete a questionnaire assessing their anxiety, sedation, and orientation.

Following the baseline assessment, participants will be administered oral 5 mg melatonin, 5 mg diazepam, or an identical placebo. The same variables (anxiety, sedation, and orientation) will be reassessed after 60 minutes. Any intraoperative or postoperative events will be recorded by the corresponding anesthesiologist.

Anxiety will be measured using both the Amsterdam Preoperative Anxiety and Information Scale (APAIS) [10] and visual analogue scales (VAS). Sedation will be measured using Ramsay sedation scale [11], and orientation to time and place was assessed.

Randomization

Medications were packaged in identical containers and labeled by an independent investigator. Randomization was conducted using Microsoft Excel (Microsoft Corporation, 2021) VBA scripting, which assigned treatments and patient codes independently. The script ensured equitable distribution of treatments across genders.
Furthermore, the patients' identity was safeguarded through the utilization of unique fake IDs. Participants are randomized at a ratio of 1:1:1. The investigators and data analysts are not aware of the content of the containers. An identification key is stored in sealed envelopes.

OUTCOMES

Primary outcome 1:

Title: Change in the anxiety score based on VAS
Time frame: Before pre-medication, and after 1 hour from the administration of the premedication.
Description:
VAS (Visual Analogue Score) Anxiety Scale is a 100 mm long scale. The scale is marked in millimeters from 0 to 100, where 0 correlates with no anxiety at all, and 100 correlates to anxiety as bad as possible. The maximum score is 100 and minimum 0. The patient is asked to point on the scale according to his anxiety level. The more the reduction in anxiety from baseline, the better the outcome.

Primary outcome 2:
Title: Change in anxiety score based on The Amsterdam Preoperative Anxiety and Information Scale (APAIS)
Time frame: Before administration of pre-medication, and after 1 hour from the administration of premedication.
Description:
The Amsterdam Preoperative Anxiety and Information Scale (APAIS) is a self-reported questionnaire. The scale consists of six items, four of which assess the patient's anxiety, while the last two assess the patients' need-for-information and the patient must choose how much he agrees with each item on a scale of 1 (not at all) to 5 (very much). The more the reduction in the anxiety score from baseline the better the outcome.

Secondary outcome 1:
Title: Change in sedation
Time frame: Before pre-medication, and after 1 hour from the administration of the premedication.
Description:
Sedation will be assessed with Ramsay sedation scale (RSS) as follows:
1 – Patient is anxious and agitated or restless, or both
2 – Patient is cooperative, oriented, and tranquil
3 – Patient responds to commands only
4 – Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5 – Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus

6 – Patient exhibits no response.

Secondary outcome 2:

Title: Change in orientation

Time frame: Before pre-medication, and after 1 hour from the administration of the premedication.

Description:

Orientation will be assessed with a three-point scale as follows:

0 – None

1 – Orientation in either time or place

2 – Orientation in both

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