Comparing Melatonin to Diazepam as a Premedication: a Triple-blind, Randomized, Placebo Controlled Clinical Trial

NCT06103188

30/10/2024

Statistical Analysis Plan (SAP)

Benzodiazepines vs Melatonin for Preoperative Anxiety: A randomized controlled trial

Principal Investigator	Omar Ismail Student University of Jordan, Amman, Jordan
Sponsor:	Jordan University Hospital

Authors	Karam Albdour Student University of Jordan, Amman, Jordan
	Kamel Jaber Student University of Jordan, Amman, Jordan

Version	Draft 1.0

SIGNATURE PAGE

Principal Investigator 

Omar Ismail (15/09/2023)

Authors 

Karam Albdour (15/09/2023)

Kamel Jaber (15/09/2023)

Abbreviations

VAAS: Visual Analogue Anxiety Scale

ASA: American Society of Anesthesiologists

APAIS: Amsterdam Preoperative Anxiety and Information Scale

RSS: Ramsay Sedation Scale

DSST: Digital symbol substitution test

CI: Confidence Interval

IQR: Interquartile range

SD: Standard Deviation

ANOVA: Analysis of Variance

1. Study Overview

The primary objective of this triple-blind, randomized clinical study, is to conduct a comparative analysis of the impact of melatonin, diazepam, and placebo on anxiety levels in patients undergoing surgical procedures. This study aims to address the research question:

Does melatonin demonstrate efficacy in reducing anxiety among patients undergoing surgery?

Participants will be asked to complete a questionnaire, after which they will be administered melatonin, diazepam, or placebo. One hour later, they will be asked to complete the same questionnaire again. Researchers will compare melatonin, diazepam, and placebo to determine if melatonin is as effective as diazepam in reducing the level of anxiety in patients undergoing surgery

2. 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 as follows:

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

Patients will be approached in the anesthesia clinic and provided with detailed information about the study. Those who are willing to participate will provide written informed consent. Contact information of the participants will be collected for future follow up if needed. Patients will be contacted 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, the assigned medication will be administered to each patient. 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.

2.1 Randomization and blinding

To ensure robustness in participant assignment and minimize potential biases, a triple-blind design was adopted. This involved concealing the treatment assignments not only from the participants and researchers but also from those responsible for administering the treatments and collecting the responses. The study's sample comprised 87 participants, evenly distributed across three groups of 29 each.

Randomization was conducted using Excel 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.

2.2 Sample size calculation

In order to achieve an alpha error probability of 0.05, and power of 0.9, power analysis was conducted using G*Power 3.1.9.7. The literature reports the smallest effect size as f = 1, with a convention that considers effect sizes greater than 0.4 as strong. To detect even more subtle effects (f = 0.5) with an alpha-error of 0.01 and a power of 0.9, a sample size of 75, divided into 3 groups, was required, and to account for possible dropouts we decided on 87 as the total sample size with 29 participants in each arm.

3. General Analysis Considerations

3.1 Timing of Analysis

The primary analysis will be conducted after the completion of data collection, which is anticipated to be in August 2023. No interim analysis is applicable

3.2 Analysis Populations

3.2.1 Full Analysis Population

The Full Analysis Population, also known as the Intention to Treat population, will include all randomized participants who received their assigned medication, and completed both pre- and post-administration assessments. Missing data will be handled as described in section 3.4

3.2.2 Per Protocol Population

The per-protocol population will include all participants who received the assigned medication and completed both pre- and post-administration assessments. Any subjects with missing data will be excluded from this population.

3.2.3 Safety Population

The Safety Population will comprise all participants who received at least one dose of the study medication (Full analysis population). Safety outcomes and adverse events will be analyzed in this population.

3.3 Multi-center studies

N/A

3.4 Missing Data

The statistical analysis plan will employ a complete case analysis approach, whereby cases with missing data will be excluded from the primary analysis. To ensure the validity of the findings, efforts will be made to minimize missing data during the study, and any instances of missing data will be thoroughly documented. Anticipated missing data is expected to be minimal. However, if the proportion of missing data exceeds 20%, sensitivity analyses will be conducted to assess the potential impact on the study outcomes. Given the expectation of minimal missing data, the use of additional methods such as multiple imputation is considered unnecessary.

3.5 Interim Analysis

N/A

3.6 Multiple testing

If significant differences are found among the study arms, post hoc analysis will be utilized to reveal which groups actually differ from one another. This multiple comparison testing will increase the type 1 error, and thus, correction of alpha using the Tukey's test will be employed to reduce the rate of false positives. This would reduce the power of analysis and increase the type 2 error, but as a conservative safety approach, it’s considered superior.

4 Summary of Study Data

The summary of the data will be presented according to the nature and distribution of the variables. Normally distributed continuous data will be reported using the following statistics: number of observations, mean, standard deviation (SD), minimum, and maximum. Non-normally distributed continuous data will include: number of observations, median, and IQR unless specified otherwise. Categorical data will be summarized by providing the count and percentage of patients in each category.

Summary statistics will be reported with an appropriate level of precision. Mean, SD, median, and IQR will be reported with an additional decimal place compared to the original data. The 95% confidence interval (CI) will be reported to two decimal places. Minimum and maximum values will be reported with the same number of significant figures as the original data. In frequency tables, percentages will be presented with one decimal place, which p-values will be reported up to 3 decimal places or displayed as <0.001.

In all summary tables, the structure will be organized to include a column for each treatment arm. Each table will be appropriately annotated to indicate the total population size relevant to that specific table and treatment, taking into account any missing observations.

4.1 Derived variables

N/A

4.2 Protocol Deviations

Major deviations: Participants who undergo the baseline assessment, receive their assigned medication but subsequently decline to complete the post-medication assessment. In the full analysis population, these participants will be included; however, they will be excluded from the per-protocol analysis.

4.3 Demographic and Baseline Variables

Demographic variables include: Participants' age and gender.

Baseline variables include: Visual analogue score (VAS) Anxiety scale, The Amsterdam Preoperative Anxiety and Information Scale (APAIS), the Ramsay Sedation scale (RSS), and orientation. The summary statistics will be produced in accordance with Section 3.

4.4 Treatment Compliance

N/A

5 Efficacy Analysis

The summary statistics will be produced in accordance with Section 3. Differences in baseline variables among treatment arms will be assessed using one-way ANOVA or the corresponding non-parametric test. All efficacy analyses will be based on the full analysis population as this approach is considered more conservative and prevents overestimation of the effects. However, Per protocol analysis will be used for sensitivity analysis as needed.

5.1 Primary Efficacy Analyses

Continuous primary outcomes, such as the changes in the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and the Visual Analogue Anxiety Scale (VAAS), will be reported as the mean difference. The statistical analysis will involve computing p-values to compare the mean difference among the three treatment arms. This comparison will be conducted using either one-way analysis of variance (ANOVA) or the corresponding non-parametric test (e.g.Kruskal Wallis test), as appropriate.

5.2 Secondary Efficacy Analyses

Continuous primary outcomes, such as the changes in sedation level will be reported as the mean difference. The statistical analysis will involve computing p-values to compare the mean difference among the three treatment arms. This comparison will be conducted using either one-way analysis of variance (ANOVA) or the corresponding non-parametric test (e.g.Kruskal Wallis test) as appropriate.

Categorical secondary outcomes, such as changes in orientation, will be evaluated using statistical tests to determine if there are significant differences among the three treatment arms. The chi-square test of independence or Fisher's exact test will be employed to assess these differences and identify any statistically significant results.

5.3 Post Hoc Analysis

In the case of statistically significant findings, post-hoc testing will be conducted using Tukey-Kramer Test. This additional analysis aims to further explore and characterize the specific group differences observed.

5.4 Subgroup Analysis

To assess for any differences in the response between both genders, subgroup analysis using the participants' genders will be conducted using independent samples t-test for each study arm if the one-way ANOVA proved significant, or for the whole sample if no significant differences were found between the study arms.

5.5 Sensitivity Analysis

Not applicable

6 Statistical Analysis Software

All statistical analysis and summaries will be carried out on IBM SPSS statistics V29. Software R 4.2.2 will be used for drawing plots where applicable