Title page

Study Title: Anxiolytic and Analgesic Effects of Melatonin

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Background

Surgery can be a serious mental strain for the patient and can result in anxiety [1]. Anxiety is usually treated with benzodiazepines which have unpleasant adverse effects and can lead to serious complications [2,3].

Melatonin is a naturally occurring hormone which has documented anxiolytic effects in both experimental and clinical studies [4-7]. Melatonin does not have any known 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 on perioperative anxiety.

Study design

Randomized, double-blinded, placebo-controlled trial involving patients undergoing elective inguinal/umbilical hernia repair. Outcomes of interest are anxiety, well-being, and sleep quality. Participants will be allocated to either melatonin or placebo in a 1:1 ratio and will be randomized in blocks of 4.

Participants

Inclusion criteria:

- Male patients undergoing elective inguinal or umbilical repair.

Exclusion criteria:

- Patients with regular consumption of opioids, benzodiazepines, or melatonin.
- Patients with psychiatrics comorbidity (ongoing treatment) or patients classified as ASA 3 or 4
- Patients with an ongoing abuse of alcohol or recreational drugs´
- Patients suffering from liver disease (ongoing treatment)´
- Patient diagnosed with a sleeping disorder
- Allergy towards melatonin
- Patients incapable of participating in accordance with the study protocol

Withdrawal and drop-out-criteria

1. If the participants 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 in regard to the health of the participant

Study course

Participants will be recruited according to the above criteria by study personnel after their preoperative consultation with the surgeon. 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. Baseline data are collected.

Participants will be administered oral 10 mg melatonin at four different timepoints: at 9 pm the evening before surgery, 120 minutes before surgery, immediately after surgery, and at 9 pm the evening on the day of surgery.

Anxiety will be measured at different timepoint using both the State-Trait Anxiety Inventory (STAI) [10] and visual analogue scales (VAS). All data will be collected electronically using the platform Research Electronic Data Capture (REDCap).

Pharmacology

Pharmaceuticals are produced and packaged according to Good Manufacturing Practice guidelines by and authorized manufacturer. The applied drugs are tablets containing 10 mg melatonin or placebo. Tablet are identical in size, shape, color, and flavor. Labelling is performed by the manufacturer in accordance with Good Manufacturing Practice guidelines.

Randomization

Randomization, blinding, and labelling is performed by the authorized manufacturer. Randomization is performed trough Randomization.com using the first generator functionality. Participants are randomized in blocks of 4 and in a ratio of 1:1. The investigator are not aware of the content of the tablets. An identification key is stored in sealed envelopes.

OUTCOMES

Primary outcomes

- Preoperative anxiety 1 hour before surgery using STAI [10]

Secondary outcomes

- Postoperative anxiety using STAI [10]
- Pre- and postoperative anxiety using VAS
- Length of stay
- Quality of sleep the night before and after surgery
- Intraoperative use of remifentanil
- Intraoperative use of propofol
- Use of rescue-opioid (0-6 hours postoperatively)

- Use of rescue-opioid (0-24 hours postoperatively)
- General well-being
- Fatigue

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Perioperative anxiety

Perioperative anxiety is measured using both STAI and VAS at recruitment, 60 minutes before surgery, and 4 hours after surgery.

Sleep quality

Quality of sleep is measured using a VAS where higher score equals better quality of sleep. Data on length of sleep and number of awakenings will also be collected.

Karolinska sleepiness scale

This is a 9-point interval scale (1 = very awake; 9 = very sleepy) used to measure the degree of sleepiness. Will be administered on the morning before and after surgery.

Fatigue and well-being

Subjective fatigue will be measures on a 10-point scale (higher score indicates more fatigue). Well-being will be measured using as VAS (higher score indicates less well-being). Will be administered on the morning before and after surgery.

Power and sample size

The primary outcome is preoperative anxiety measured using STAI. A previous study investigated anxiety in relation to inguinal hernia surgery and found a mean preoperative STAI of 35.4 (SD 10.0) [11]. The are no generally agreed recommendation for what constitutes a clinically significant change on the STAI, but a change of one SD has been proposed [12]. In the current study, this equals a minimal relevant difference (MIREDIF) of 10 point in the STAI or 28%. Necessary power is set at 0.80 and level of significance at 5%. This results in a necessary sample size of 16 participants in each group.

Statistics

Level of anxiety will be compared using Mann-Whitney's test or unpaired T test depending on the distribution of data. Data will be analyzed using Graphpad Prism (Graphpad Software, La Jolla, CA) and/or SPSS (IBM SPSS, Statistics for Windows, Version 20.0, Armonk, NY, IBM Corp). A p value of 0.05 will be considered significant. Data will be reported as mean (SD) or median (IQR) depending on distribution.

Ethical considerations

This trial will be conducted in accordance with the Helsinki Declaration and with the permission of the Medical Ethics Committee of the Capital Region of Denmark. The study will contribute to the understanding of melatonin's anxiolytic

benefits and will be conducted using a randomized double-blinded design. The safety of oral administration of melatonin is well-established [13-27]. All participants will give written and verbal informed consent to participate. Participants can withdraw from the trial at any timepoint.

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The trial will be conducted in accordance with the current protocol, ICH-GCP guidelines, and applicable legislation. The sponsor will allow direct access to the collected data throughout the monitoring of the trial by the applicable authorities. Permissions will be obtained from the Danish Data Protection Agency, the Danish Medicines Agency, and the Medical Ethics Committee of the Capital Region of Denmark.

This document is an abbreviated and translated version of the original protocol approved by the Danish authorities. The translation was performed on 5 August 2021 at the request of ClinicalTrials.gov.