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MELATONIN USE AFTER PRIMARY TOTAL JOINT ARTHROPLASTY: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

A Phase 1, randomized control trial, single-center study of the effect of melatonin supplementation on early postoperative outcomes and sleep quality

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Study Product:	*Melatonin*
Study Product Provider:	*n/a*
ClinicalTrials.gov Number	*n/a*

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Protocol Summary

Title	MELATONIN USE AFTER PRIMARY TOTAL JOINT ARTHROPLASTY: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL
Brief Summary	The purpose of this study is to determine the effect of melatonin supplementation on patient sleep quality, length of stay, and opioid consumption following primary, unilateral, elective total hip or knee arthroplasty.
Phase	N/A
Objectives	The primary objective is improved sleep quality postoperatively
Methodology	Single Center, randomized, double-blind, placebo-controlled clinical trial
Endpoint	The primary endpoint will be enrollment and completion of the study of 256 patients as pre-determined by statistical analysis.
Study Duration	Approximately 12 months (post IRB approvals)
Participant Duration	We estimate each patient will need to participate for roughly 60 days
Duration of IP administration	Patients will take the melatonin or placebo for 14 days
Population	Sample size will be 252 patients, both male and female patients will be included, all adult patients undergoing primary elective TKA or THA will be included. No vulnerable populations will be enrolled
Study Sites	Langone Orthopedic Hospital, New York, NY NYU Brooklyn Hospital, Brooklyn, NY
Number of participants	256 participants
Description of Study Agent/Procedure	Melatonin is an over-the-counter sleep aid
Reference Therapy	None
Key Procedures	Pre- and postoperative sleep survey, survey on quality of sleep, patient reported outcome questionnaires, narcotic consumption and pain daily for 14 days postoperatively
Statistical Analysis	Descriptive statistics will be used to report baseline characteristics and primary study objectives

1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

Utilization of total hip and knee arthroplasty (THA and TKA, respectively) has increased over the last decade and is expected to continue to rise as the population of the United States ages. By 2030, over 2 million total joint arthroplasty (TJA) procedures are anticipated to be performed annually[1]. With increasing numbers and to maintain excellent patient outcomes after total joint arthroplasty, it has become important to optimize every aspect of patient recovery. Sleep disturbance is a routinely encountered problem during the perioperative period in adults undergoing elective surgery[2]. Sleep in postoperative patients is negatively influenced by exposure to anesthesia[3, 4] and the presence of postoperative pain[5]. Reciprocally, poor sleep also portends poor coping and exacerbation of post-operative pain[6, 7]. Nighttime awakenings may be frequent, and require the use of additional pain medication to go back to sleep.

1.2 Name and Description of the Investigational Agent

1.2.1 Preclinical Data

Melatonin or 5 methoxy-N-acetyltryptamine was discovered and isolated from bovine pineal gland in 1957[8]. A naturally occurring hormone, melatonin is synthesized by pinealocytes from tryptophan and once synthesized released into the systemic circulation to reach several central and peripheral target tissues[9]. Melatonin works through activation of ML1 and ML2 receptors in target cells through a G-protein coupled receptor – adenyl cyclase pathways[8, 10]. The molecule is important in regulation of human circadian rhythms such as the sleep-wake rhythm, neuroendocrine rhythms or body temperature cycles through its action on various target cells throughout the body[11]. Consumption of melatonin, either orally or intravenously, induces fatigue, sleepiness and a diminution of sleep latency in humans[12]. Given its physiologic effects, melatonin is an agent of great interest in perioperative patients experiencing sleep disturbance.

1.2.2 Clinical Data to Date

Decreased levels of melatonin production have been observed in postoperative patients undergoing minor orthopedic procedures whether under general or regional anesthesia[13]. Perioperative melatonin has been studied in other fields of surgery. Caumo et al have demonstrated preoperative administration of melatonin has been associated anxiolytic and analgesic effects in addition to increased potency of sleep/wake circadian rhythms in patients undergoing gynecologic procedures[14, 15]. Borazan et al demonstrated improved subjective sleep quality after prostate surgery after perioperative administration of melatonin[16]. A systematic review of randomized trials with melatonin has demonstrated efficacy in reducing perioperative anxiety and some positive effects on perioperative pain[17].

1.3 Rationale

Sleep disruption following elective, primary total joint arthroplasty is very common. The cause is likely multifactorial, resulting from anxiety, anesthesia, the patient's recovery environment, and pain. Overall tiredness can lead to decreased energy, restlessness, less ambulation, and slow progress with physical therapy and recovery. Melatonin is an inexpensive, over the counter dietary supplement with an established safety profile that has been used to help create a more restful sleep cycle. There is no consensus as to the utility, dose, duration, or timing of melatonin administration in the period before and after elective hip and knee arthroplasty to improve sleep quality. This study design is supported by sleep disturbance usually occurs within the first 2 weeks of surgery due to a disrupted sleep wake cycle and pain. 5mg is a safe and effective starting dose for any sleep disturbance.[20] Further, inconsistent methods of assessing patients' sleep and pain postoperatively has made the study of sleep quality difficult.

1.4 Potential Risks & Benefits

1.4.1 Known Potential Risks

Short term use of melatonin is safe, even in extreme doses with only mild adverse effects which can include dizziness, headache, nausea and sleepiness[18]. Randomized clinical studies have indicated that even long-term exogenous melatonin only mild adverse effects such as dizziness and headaches comparable to placebo[17].

1.4.2 Known Potential Benefits

In addition to its importance in in regulation of human circadian rhythms such as the sleep-wake rhythm, neuroendocrine rhythms or body temperature cycles; perioperative melatonin is also known to reduce the incidence of delirium in older patients[19].

2 Objectives and Purpose

2.1 Primary Objective

The primary objective is the Epworth Sleep Score used to evaluate the impact of melatonin use on the quality of sleep, including total hours of sleep and nighttime awakenings in patients undergoing elective primary total hip and knee arthroplasty.

Secondary Objectives are to monitor and investigate hospital length of stay, and narcotic consumption patterns, scores in patients who take melatonin as a sleep aid for 14 days after surgery.

3 Study Design and Endpoints

3.1 Description of Study Design

This will be a single-center randomized double blind placebo control clinical trial. In the cohort of patients undergoing primary elective total hip and the cohort of patients undergoing primary elective knee arthroplasty, participants are recruited from those who are willing to consent and participate in the study, and will be randomly 1:1 divided into intervention group and placebo group.
Knee cohort:

- Intervention group will receive a 5mg Melatonin prescription for 14 days
- Control group will receive a placebo pill for 14 days

Hip cohort:

- Intervention group will receive a 5mg Melatonin prescription for 14 days
- Control group will receive a placebo pill for 14 days

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint will be the Epworth Sleep Score for patients indicating the impact of melatonin on quality of sleep, including total hours of sleep and nighttime awakening. The ESS will be evaluated post-operatively from days 1-14.

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Patient are current candidates for elective primary total hip or total knee arthroplasty
2. Patients ≥18 years of age but ≤ 95
3. Patients have been medically cleared and scheduled for surgery

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Non-elective conversion arthroplasty
- Consistent melatonin use within 1 month of surgery
- Bilateral total joint arthroplasty
- Contraindications to use of melatonin (diabetes, calcium channel blocker use, depression)
- Conditions and medications likely to confound results due to impact on subjective and/or objective sleep quality (insomnia, drug/alcohol abuse, and use of benzodiazepines, and prescription sleep aids)
- Conditions likely to impair capacity to adhere to protocol (mental impairment, psychiatric disorders other than anxiety/depression)

4.3 *Vulnerable Subjects*

No Vulnerable subjects will be enrolled in this study

4.4 Duration of Study Participation

Participants will be enrolled for approximately 2months after surgery.

4.5 Total Number of Participants and Sites

252 patients will be recruited at NYU Langone Orthopedic Hospital and NYU Brooklyn Hospital.

4.6 Participant Withdrawal or Termination

4.6.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

4.6.2 Handling of Participant Withdrawals or Termination

Any patient that wishes to withdraw or in whom a clinical adverse effect is noticed, will be allowed to do so without recourse. They will still be given appropriate standard of care follow-up as would be given any pre- or post-operative TJA patient. If a patient is presumed lost to follow-up they will be contacted via phone-calls and certified letters, which will be tracked. There is no safety risk predicted from abrupt termination. Any patients who withdraw or discontinue early will be replaced via recruitment of new patients. As LOH is a high-volume arthroplasty center performing thousands of primary TJA procedures there is not expected to be an issue in recruiting new subjects as approximately 10-50% of patients are projected to be affected by malnutrition (previously cited data).

4.7 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided

by the suspending or terminating party to the IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

5 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

5.1 Study Agent(s) and Control Description

Melatonin, as previously described, is a widely available over the counter sleep aid.

5.1.1 Acquisition

Melatonin will be ordered in bulk from a generic retail option that can be found. Once ordered it will be shipped via standard US mail. It will be distributed to the patient during the pre-operative booking appointment. Placebo pills will also be ordered in similar fashion. Melatonin and placebo pills will be re-packaged in the new blank pill bottles with a generic label with dosage instructions by the research coordinator. Only the unblinded research coordinator, will know which bottles correspond to the treatment group.

5.1.2 Formulation, Appearance, Packaging, and Labeling

Melatonin is a widely sold synthetic molecule in various forms including tablets, gummies and liquid. In the present study, the tablet version of the medication will be used at a dose of 5mg. It will be distributed to patients in a standard pill pack labelled as “Study Drug.” Patients will be informed that they will either be taking melatonin or a placebo pill with no chemical activity. Only the research staff involved in the randomization process will know if the patient is in the melatonin arm or the placebo arm. The placebo ingredients are Microcrystalline Cellulose, Silica, Gelatin, Titanium Dioxide, Red #3, and Blue #1.

5.1.3 Product Storage and Stability

The melatonin and placebo tablets will be stored in the Department of Orthopedic Surgery research offices at 380 2nd Avenue, 6th Floor, New York, NY, in a climate controlled office. As the product does not need to be refrigerated prior to being open there is no need for refrigeration storage. The average expiration date for a bottle of melatonin tablets is more than 1 year from purchase.

5.1.4 Preparation

There is no special preparation necessary for this product.

5.1.5 Dosing and Administration

There will be no special administration instructions given to patients, only that they should take one pill in the evening with water within 1 hour of bedtime each night for 14 days.

5.1.6 Route of Administration

Oral

5.1.7 Duration of Therapy

Patients will consume melatonin for 2 weeks.

5.1.8 Tracking of Dose

Patients will be encouraged to return the empty bottle at the 2 week postoperative visit.

5.2 Study Agent Accountability Procedures

The study agent, melatonin, and placebo will be stored at the Department of Orthopedic Surgery research office. When the patients are randomized to either arm of the study, the designated agent will be given to the patient at the preoperative visit. At the termination of the project any unused study agent will be destroyed on site in the trash. Any tablets or capsules will be mixed them all together with normal trash and placed in a sealed bag, then placed in a trash bin.

6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

- Medical history- a patient's medical history will be elicited during their pre-operative indication for surgery by their operative surgeon. This information will be then accessed via the EMR
- Medication history- current medications will be elicited during the patient's pre-operative indication for surgery by their operative surgery. This information will then be accessed via the EMR
- Physical examination- the patient's height and weight at each visit will be recorded, as well as a targeted physical musculoskeletal examination of the affected joint (ie hip for THA and knee for TKA). This information will then be accessed via the EMR
- Pre- and postoperative sleep survey,
- Survey on quality of sleep,
- Sleep diary
    - To be kept every day for the first 2 weeks
- VAS
- Opioid consumption will be measured based on in-patient pain medications given following surgery. This data will be pulled from Epic following discharge.

6.1.2 Standard of Care Study Procedures

The following procedures will be provided as standard of care:

1. Preoperative interview and evaluation of patients for indication for primary THA or TKA
2. Preoperative health assessment and medical clearance
3. THA or TKA
4. Inpatient stay following procedure
5. Post-operative follow-up appointments

6.2 Study Schedule

Procedure	Screening/Visit 1 (SOC visit within -3 months of surgery)	Surgery	Visit 2 (SOC visit within +2 months of surgery)

Screening	X (Research only)		
Consent	X (Research Only)		
Medical History	X (SOC)		
Surgical History	X (SOC)		
Demographics	X (SOC)		
Distribute medication		X (Research Only)	
Collect pill bottle			X (Research Only)
Collect Adverse Events			X (Research Only)
Collect Questionnaires and peri-operative data (in-patient opioid consumption, Epworth and Stanford sleepiness scale, VAS Pain Scale)	X (Research Only)		X (Research Only)
Collect Sleep Diary			X (Research Only)

6.2.1 Screening

Study subjects will be identified/recruited by all study investigators. Investigators will recruit subjects among their own patients who have been recommended to have a Total Hip or Knee Arthroplasty. Eligibility will be confirmed through a review of subject medical records. Investigators will reinforce with their patients that participation is voluntary, that they do not have to participate, and that their decision to not participate will not affect their care, now or in the future. During the course of the recruitment process, subjects will interact with all study personnel.

With access granted by MCIT, Study team will access data/records in EPIC for patients identified by study investigators as meeting the study criteria.

6.2.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1)

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Obtain and record vital signs, results of examinations, demographic information, medical history, medication history, alcohol and tobacco use history, and other assessments from the medical records.
- Record PROMIS – Sleep Disturbance

6.2.3 Intermediate Visits

TKA or THA Surgery

- Give patients the pill bottle with the study drug or placebo pill.

Visit 2 (standard of care post-operatively visit within 2 months of surgery)

- Observe patient's recovery from TJA surgery as per standard of care
- Record participant's adherence to treatment program.
- Record patient standard sleepiness scale, PROMIS – Sleep Disturbance, VAS pain scores, collect sleep diary and opioid consumption.

6.2.4 Withdrawal/Early Termination Visit

If a patient wishes to terminate early no further procedures or interventions will be performed and the patient will be allowed to continue their pre- or post-operative care as per standard of care

6.2.5 Unscheduled Visit

Any unscheduled visits or contact from patients will be recorded in the EMR, which will be checked regularly by members of the research team for all study participants

6.2.6 Precautionary Medications, Treatments, and Procedures

There is no precautionary medications, treatments, and or procedures associated with the use of Melatonin

6.3 Participant Access to Study Agent at Study Closure

If a patient wishes to continue usage of melatonin after closure of the study they will be informed that it is a commercially available product they can obtain from any major retailer.

7 Assessment of Safety

7.1 Specification of Safety Parameters

All safety parameters including patients vital signs and clinical examination as per standard of care will be recorded in their EMR.

7.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must

have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

7.2.3 Expectedness

The principal investigator, Joshua Rozell, MD will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

7.3.1 Adverse Event Reporting

Any AE's encountered during the study will be identified by research personnel and brought to the attention of the PI. After investigation by the PI of the surrounding circumstances they will then be reported as quickly as possible, within 1 week, to the IRB, as indicated

7.3.2 Serious Adverse Event Reporting

Any SAE's encountered during the study will be identified by research personnel and brought to the immediate attention of the PI. They will then be reported as quickly as possible, within 3 days, to the IRB

7.3.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to Dr. Rozell/lead PI within 1 week of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to Dr. Rozell/lead PI within 1 week of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 1 week of the IR's receipt of the report of the problem from the investigator.

7.3.4 Reporting of Pregnancy

No pregnant patients will be included in the study. Any patient who becomes pregnant during the study will be removed from the study group.

7.4 Reporting Procedures – Notifying Dr. Rozell

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to Dr. Rozell within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to Dr. Rozell within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by Dr. Rozell and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event.

7.5 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events. PI will oversee data on an annual basis by creating reports from data entered into RedCap.

8 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the PI.
- Monitoring will be on sight with frequent random checks of data. At conclusion of the study another independent member of the LOH arthroplasty research team not affiliated with the study will check all available data to ensure its validity

Statistical Considerations

8.1 Statistical Hypotheses

- Primary endpoint: The null hypothesis is that there is no difference between the melatonin and placebo group in the mean ESS score from days 1-14 postoperatively. The alternative hypothesis is that there is a difference between the melatonin and placebo group in the mean ESS score during any of these time points

- Secondary endpoints:
  - Hours of sleeping measured each day from days 1-14 for overnight sleep: The null hypothesis is that there is no difference between the melatonin and placebo group in the mean hours of sleeping at these time points. The alternative hypothesis is that there is a difference between the melatonin and placebo group in the mean hours of sleeping at these time points. Nighttime awakenings are those that require an additional dose of pain medication to go back to sleep.
  - Other secondary endpoints to be listed

8.2 Sample Size and Power

The overall study sample size is based on the primary endpoint of ESS measured at days 1-14. The MCID of the ESS is 2.65 and the SD is 5.3 based on previous literature[21]. We assume the MCID and ESS values are the same for both THA and TKA cohorts. 64 patients are needed in the control and intervention groups separately for a two-sided alpha = 0.05, 80% powered study based on an ANOVA for the comparison of the ESS at days 1-14 between the control and intervention group, which provides us a total of 128 patients for THA cohort and TKA cohort separately.

8.3 Analysis Datasets

All patients will be included in the efficacy analyses as randomized (intent-to-treat population). THA cohort and TKA cohort will be analyzed separately throughout.

8.4 Description of Statistical Methods

8.4.1 Analysis of the Primary Efficacy Endpoint

The primary outcome, the ESS score measured at days 1-14 postoperatively for each group, will be summarized using means, standard deviation, median and inter quartile ranges. In the main analysis, the ESS score of the control and intervention group in either THA or TKA cohort will be compared using repeated measures ANOVA. Significant tests will be two-sided at significant level at 0.05.
The normality assumption of the primary efficacy outcome will be checked and strategies to transform the outcome variable will be considered. As a sensitivity analysis, the ANOVA will be replaced with the Wilcoxon rank sum test to ensure the robustness of the results.

8.4.2 Analysis of the Secondary Efficacy Endpoints

The secondary endpoints include number of total hours of sleep, number of nighttime awakenings, and narcotic consumption.

8.4.3 Safety Analyses

AE's will be recorded according to the Medical Dictionary for Regulatory Activities, counted once per individual occurrence, presented in terms of its severity and relationship to AE, and its start date, stop date, severity, relationship, outcome and duration will be reported. All AE's will be ascertained via PI report.

8.4.4 Adherence and Retention Analyses

Adherence to the study will be analyzed by collecting the pill bottles at the first postoperative visit.

8.4.5 Baseline Descriptive Statistics

Baseline characteristics including age, sex, ASA class, BMI, past medical and surgical history will be recorded be summarized by melatonin and placebo group for THA and TKA cohort separately. Summary statistics will be used, where means and standard deviations will be reported for continuous variables, and count and proportion will be calculated for categorical variables. Inferential tests to assess differences in baseline characteristics of the groups will be performed using ANOVA or the Wilcoxon rank sum test if the normality assumption does not hold for continuous variables, and the Chi-square test for categorical variables. All tests will be two-sided with a significance level at 0.05.

8.4.5.1 Efficacy Review

Planned interim analyses of the primary endpoint will not be performed.

8.4.6 Additional Sub-Group Analyses

Subgroup analyses of the primary and secondary endpoints will be done on the subgroups of THA vs TKA with ANOVA, and all other categorical variables will be analyzed using Fisher's Exact Test. All tests will be two-sided with a significance level of 0.05.

8.4.7 Multiple Comparison/Multiplicity

Not applicable

8.4.8 Tabulation of Individual Response Data

Individual participant data will be listed by measure and time

8.5 Measures to Minimize Bias

8.5.1 Enrollment/Randomization/Masking Procedures

Research assistants not involved in the study protocol will be responsible for maintaining the patient database and randomization algorithm. Treatment will begin on postoperative day zero. The control groups will receive 14 placebo pills. The treatment group will receive 14 pills of 5mg melatonin. Patients will begin taking a daily pill for 14 days postoperatively. They will continue to receive their selected treatment during their inpatient hospital stay.

Block randomization will be done through RedCap to ensure equal distribution of intervention vs control subjects. The block size will be undisclosed. There will be no stratification based on age, gender, or surgery type.

8.5.2 Evaluation of Success of Blinding

Not applicable

9 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11 Ethics/Protection of Human Subjects

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

11.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 Informed Consent Process

11.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: informed consent for participation

11.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document.
The informed consent process will take place at a pre-surgery clinic visit prior to the day of surgery or in the holding area on the day of surgery. If consenting occurs on the day of surgery, the study team will ensure that efforts are made so patients have enough time to make an informed decision to enroll in the study. A study coordinator, not associated with the surgery, will be the one to introduce the study to the patient in the holding area and patients will be given the opportunity to enroll in the study after the surgery is complete.

The Informed Consent Form (ICF) will be thoroughly explained in a private room with any and all questions addressed prior to signing the ICF. In the event additional time to make an inform decision is required, patient(s)/subject(s) will be able to take a copy of the ICF home for further review and discussion with their friends and family. During the course of the consenting process, subjects will interact with all study personnel. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

11.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified

by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

12 Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a RedCap database, a encrypted, HIPAA-compliant data capture system managed by MCIT. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Each site will have access to its identifiable data. Only de-identified data will be passed between institutions.

12.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication.

12.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to the IRB and Lead PI

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

12.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

13 Study Finances

13.1 Funding Source

This study is funded by the NYU Department of Orthopedic surgery specifically via the established William Jaffe grant for resident research.

13.2 Costs to the Participant

The participant will incur no costs for participation in the study

13.3 Participant Reimbursements or Payments

Participants will not be given any reimbursements or payments for participation in the study

14 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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