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Effect of melatonin versus placebo for prevention of delirium among medically hospitalised patients: study protocol for a single-centre, double-blinded, randomised controlled trial (project RESTORE)

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ABSTRACT

Introduction Delirium, a common neuropsychiatric condition in hospitalised older adults, is associated with increased mortality, longer hospital stays and cognitive decline. The potential of melatonin to prevent delirium by improving sleep patterns and regulating circadian rhythms is promising, though existing evidence is mixed. This study aims to evaluate the efficacy of melatonin in preventing delirium in medically hospitalised patients aged 65 years and older.

Methods and analysis This randomised, double-blind, placebo-controlled trial will enrol 240 patients aged 65 or older admitted to general medical wards at Sultan Qaboos University Hospital starting from September 2024. Participants will be randomly assigned to receive either 5 mg or 8 mg of melatonin or a placebo nightly for up to 5 days. The primary outcome is the incidence of delirium, assessed using the 3 min Diagnostic Confusion Assessment Method during the first 5 days. Secondary outcomes include the duration of delirium, sleep patterns and other clinical measures, such as hospital length of stay and 28-day readmission.

Ethics and dissemination The study protocol has received ethical approval from the Medical Research Ethics Committee at Sultan Qaboos University (REF. NO. SQU-EC/024\2024, MREC #3240). All participants or their legal proxies will provide informed consent prior to enrolment. Results will be disseminated through peer-reviewed publications and conference presentations, contributing to the global evidence base on delirium prevention strategies in hospitalised older adults.

Trial registration number ClinicalTrials.gov under the identifier NCT06509191.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study uses a robust double-blind, placebo-controlled design, minimising bias and enhancing the reliability of the results.
⇒ Utilisation of the 3-Minute Diagnostic Confusion Assessment Method, a validated tool, ensures accurate and sensitive delirium detection.
⇒ The sample size is sufficiently powered to detect clinically significant differences in delirium incidence, addressing prior studies' limitations of small sample sizes.
⇒ The study focuses on general medical wards, where limited previous research has explored melatonin's effect, filling an important research gap.
⇒ The short follow-up duration may limit the assessment of long-term outcomes and delirium recurrence after discharge.

INTRODUCTION

Background and rationale

Delirium, a neuropsychiatric syndrome, manifests acutely with altered consciousness, cognitive impairment and inattention, showing a fluctuating course.[1] Delirium can present as hyperactive, hypoactive or mixed, posing challenges for identification, especially in the elderly.[1] Recent systematic reviews reveal its presence in approximately 50% of hospitalised individuals aged 65 or older, with 15%–25% developing delirium postmajor elective surgeries, and up to 80% in intensive care units (ICUs) requiring mechanical ventilatory support.[2 3] Various modifiable and non-modifiable risk factors contribute to delirium, emphasising the need for appropriate interventions to reduce risk.[2 3]

The presence of delirium in the elderly has been associated with poor health outcomes. A meta-analysis demonstrated a significant association with increased mortality risk at a 22-month follow-up (HR of 1.95).[4] Unlike several other medical conditions,

delirium-associated mortality has not declined over the past three decades.[5]

Delirium is linked to higher mortality rates both during and after hospital admission, especially in critically ill patients with severe symptoms.[6] It often results in prolonged hospital stays, including prolonged stay in the ICU, due to the condition's complexity and severity.[7] Delirium is significantly associated with long-term cognitive impairment and an increased risk of dementia, with cognitive decline persisting beyond the hospital stay.[7 8] It can also lead to poor functional recovery, affecting patients' ability to return to their previous level of independence and quality of life.[6] The condition is associated with higher healthcare costs due to longer stays, increased need for specialised care and potential readmissions. Additionally, patients experiencing delirium are more likely to be discharged to long-term care facilities rather than returning home, reflecting the impact on their functional and cognitive abilities.[9]

Non-pharmacological interventions are vital for preventing delirium in hospitalised patients, as treatment options for established delirium are limited.[10] These interventions focus on altering environmental and care practices to reduce delirium incidence. Multicomponent strategies, which include cognitive stimulation, sleep hygiene, reorientation with familiar objects and nutritional attention, significantly reduce delirium compared with standard care. Involving family members in patient care fosters patient-centred care and lowers delirium rates.[11] Environmental modifications, such as reducing sensory deprivation and ensuring proper lighting, create a more familiar environment to prevent delirium.[10] Cognitive and sensory stimulation help maintain orientation and cognitive function. Sleep hygiene and exercise programmes support restful sleep and physical activity, respectively, aiding in delirium prevention.[11]

Despite extensive pharmacological interventions, no definitive advantages have emerged. Haloperidol, a prototypical first-generation antipsychotic, has been thoroughly studied for delirium treatment, yet the evidence supporting its efficacy remains limited.[12] Its administration failed to demonstrate significant advantages concerning delirium incidence, mortality or length of hospital stay (LOS) compared with a placebo.[12] While olanzapine and quetiapine are potential pharmacological alternatives, their association with adverse events, including metabolic abnormalities and corrected QT interval prolongation, raises concerns. Both drugs share similar risks for diabetes and cardiovascular events, but quetiapine may pose a higher risk for hyperlipidaemia and ischaemic stroke in certain populations.[13] Olanzapine is more associated with weight gain.[13] Due to this risk profile and a lack of substantial evidence supporting their effectiveness in preventing or treating delirium, these second-generation antipsychotics have not gained widespread clinical adoption.[14]

Although an altered sleep–wake cycle is not a diagnostic criterion for delirium, sleep deprivation and delirium share many epidemiologic, biochemical and anatomic similarities.[15] Nearly 75% of patients with delirium have sleep disorders, and the quality of sleep is an integral part of certain delirium screening tools.[16] The diagnostic criteria for delirium, proposed by Trzepacz, Meagher, and Franco Research Diagnostic Criteria, emphasise core domains including cognition, higher level thinking and circadian rhythm. These are evidenced by impaired attention (criterion B), deficits in cognitive domains and disorganised thinking (criterion C) and circadian disruptions such as sleep–wake cycle disturbances or motor activity changes (criterion D). This framework provides a comprehensive basis for understanding delirium and its associations with sleep–wake cycle disruptions.[17] Hence, the hypothesis emerges that preventing or treating sleep abnormalities could impact delirium. Melatonin, a neurohormone principally produced by the pineal gland at night, improves the quality of sleep and has hypnotic effects when administered exogenously. Studies have shown that melatonin circadian rhythm is disturbed in patients with delirium.[16]

Melatonin improves sleep quality at doses ranging from 0.3 mg to 5 mg, with the optimal dose varying based on individual factors like age and health status.[18] Higher doses may be beneficial for older adults and specific conditions such as postoperative recovery. Doses above 0.5 mg/day help in resetting the sleep–wake cycle.[19 20] Melatonin also acts as an antioxidant, similar to glutathione and tocopherol, by scavenging hydroxyl and neutralising peroxyl radicals, reducing cellular damage.[21] Due to its antioxidant properties, melatonin may offer neuroprotective effects and potentially diminish the risk of neurodegenerative diseases.[21] Utilising melatonin in delirium treatment could thus address circadian rhythm disturbances and impact various hypothesised pathways in delirium development.

A systematic review and meta-analysis assessed the prophylactic effect of melatonin receptor agonists (MMRAs) on postoperative delirium (POD) in elderly patients.[22] Analysing 11 randomised controlled trials (RCT) with a total of 1558 patients, the results revealed that the MMRA group had a significantly lower occurrence of POD compared with the placebo group (risk ratio=0.70, 95% CI 0.51 to 0.97, p<0.05, I^2=59%). Due to high heterogeneity, a subgroup analysis was performed, which indicated that melatonin significantly reduced POD occurrence, supported by moderate-quality evidence, whereas ramelteon and tryptophan showed no significant impact.[22] Another systematic review and meta-analysis was done to determine the preventive effect of melatonin on delirium in the ICU, including six RCTs (n=2374).[23]

A meta-analysis of six studies involving 2374 patients examined the effects of melatonin on delirium in intensive care settings.[23] Overall, melatonin did not significantly reduce the incidence of delirium in ICU patients (OR (OR): 0.71; 95% CI (CI): 0.46 to 1.12; p=0.14), with notable heterogeneity among studies (I^2 = 74%). However, subgroup analysis revealed that melatonin

significantly reduced delirium incidence in cardiovascular care unit (CCU) patients (OR: 0.52; 95% CI 0.37 to 0.73; p=0.0001), but not in general ICU (GICU) patients (OR: 1.14; 95% CI 0.86 to 1.50; p=0.35). Secondary outcomes showed no significant differences in all-cause mortality (OR: 0.85; 95% CI 0.66 to 1.09; p=0.20), length of ICU stay (mean difference (MD): 0.33; 95% CI −0.53 to 1.18; p=0.45), or LOS (MD: 0.51; 95% CI −1.17 to 2.19; p=0.55) between the melatonin and placebo groups.[23]

A recent systematic review and meta-analysis included three RCTs and six observational studies (n=1211). All three RCTs compared melatonin to placebo, while most observational studies compared melatonin or ramelteon to antipsychotics.[24] Two RCTs reported the duration of delirium, showing a statistically significant reduction with melatonin compared with placebo (−1.72 days, 95% CI −2.66 to −0.77, p=0.0004). Five observational studies examined the duration of delirium, but only one showed a significant reduction with ramelteon combined with antipsychotics compared with antipsychotics alone (6.6±1 vs 9.9±1.3 days, p=0.048). Delirium severity showed mixed results; melatonin improved the BPRS score in one RCT, while other studies found no benefit.[24]

In an RCT comprising 497 patients admitted with acute decompensated heart failure (HF), the administration of melatonin at a dosage of 3 mg/day for a duration of 7 days demonstrated a significant reduction in the incidence of delirium within the melatonin group compared with the placebo group (27.0% vs 36.9%, p=0.021). Safety assessments revealed comparable occurrences of rhabdomyolysis and abnormal hepatic function in both groups.[25]

Most trials assessing the role of melatonin in preventing delirium were conducted in intensive care settings or surgical wards. There are very few trials involving hospitalised patients in medical wards.[26 27]

There was randomised, double-blinded, placebo-controlled study conducted in a London, Ontario tertiary care centre involved 145 individuals aged 65 or older admitted through the emergency department to medical wards. Participants were randomised to receive 0.5 mg of melatonin or placebo nightly for 14 days or until discharge. The study showed lower risk of delirium in the intervention group (12.0% vs 31.0%, p=0.014).[28] Another randomised clinical trial involving hospitalised individuals aged 65 or older (n=36 received melatonin, n=33 received placebo) administered 3 mg of melatonin. The study concluded that the nightly use of 3 mg melatonin did not reduce the incidence of delirium.[29] Overall, the trial conducted on hospitalised patients in medical wards had limitations, including small sample sizes, variations in medication doses and a lack of assessment of healthcare outcomes such as mortality, LOS and hospital readmission associated with delirium.[29]

The high prevalence of delirium in hospitalised older adults, with significant associated morbidity and mortality, highlights the need for effective prevention strategies. Despite extensive exploration of pharmacological interventions, current evidence lacks definitive advantages, and widely used antipsychotics present concerns. Recognising the link between sleep disturbances and delirium, melatonin, a neurohormone regulating the sleep–wake cycle, emerges as a promising medication. Previous studies demonstrated mixed results, with some indicating a prophylactic effect on postoperative delirium, while others show no significant impact on delirium incidence in ICUs. Importantly, limited trials have explored melatonin's potential in preventing delirium among patients admitted to general medical wards. Previous trials faced limitations such as small sample sizes and the use of very small doses of melatonin.

Objectives

This study aims to investigate the efficacy of melatonin, a neurohormone regulating the sleep–wake cycle, in preventing delirium among medically hospitalised patients aged 65 years or older. Given the high prevalence of delirium in this population and its association with adverse outcomes, the study seeks to contribute valuable insights into an effective preventive strategy. The planned trial will be novel in focusing on patients admitted to general medical wards where evidence is scarce. It will use two doses of melatonin versus placebo and include a larger sample size to ensure good statistical power. This study's robust, double-blinded, placebo-controlled design will address the existing gaps and limitations, offering new insights into melatonin's preventive role against delirium.

METHODS AND ANALYSIS

Trial design

The study is described as a randomised, double-blind, parallel-arm, placebo-controlled trial with an allocation ratio of 1:1:1. The framework of the study is superiority, aiming to test whether melatonin is more effective than placebo in preventing delirium among hospitalised older adults.

Methods: participants, interventions and outcomes

Study setting

Sultan Qaboos University Hospital is a 500-bed multispecialty tertiary referral hospital with unique services and specialised medical facilities and two main medical wards with a total bed capacity of 45, along with high dependency unit (HDU) featuring 10 beds. The General Internal Medicine Unit, receiving 70%–80% of medical patients from the emergency department, manages a spectrum of illnesses from single organ system diseases to complex and undifferentiated cases.[30]

All patients aged 65 years and above admitted to the general medicine unit will be screened for eligibility. Exclusion criteria are outlined in table 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria (should be assessed on admission)
► Patient aged 65 years and above acutely admitted under the care of General Internal Medicine Unit.	► Patients admitted to the ward, however meeting requirement for vasopressors or non-invasive ventilation. ► Patient admitted through emergency to intensive care unit (ICU) or high dependency unit (HDU). ► Aphasic patients. ► Patients with language barriers. ► Already taking melatonin or ramelteon at the time of randomisation. ► Presence of delirium at the time of randomisation. ► If enteral medications are contraindicated due to gastrointestinal conditions. ► If enteral medications are not allowed due to unavailability of nasogastric tube. ► Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (liver function tests) > 3 times the upper limit of normal. ► Patient on strong cytochrome P450 1A2 (CYP1A2) inhibitors (namely: fluvoxamine and viloxazine).[39 42] ► Patient with active alcohol drinking or admitted with alcohol withdrawal syndrome.[39] ► Subject or proxy unable to provide informed consent within 24 hours of admission. ► Patients with the following autoimmune diseases (rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus).[43 44] ► Allergy to melatonin.

Eligibility criteria

Interventions

Melatonin syrup and placebo syrup

Melatonin and placebo syrups are identical in smell, colour and shape. They are sealed with the same label ('10 mg melatonin') and have an expiry date of 1 month from the manufacturing date. The syrups are prepared by a specialised pharmacist in the pharmacy department. The study drug will be administered between 20:00 and 22:00 daily, starting on the day of enrolment until discharge, death or up to 5 days, as most medically hospitalised patients are at great risk of delirium in the first few days of admission. The medication will be given by mouth or, if needed, via a feeding tube, followed by a 20 mL water flush.

Unmasking and withdrawal of participants

This study will employ a double-blind design to ensure that both the participants and the study team members involved in data collection and analysis remain blinded to the treatment allocation. The study drugs (active treatments and placebo) will be identical in appearance, taste and packaging and will be labelled with unique codes by the pharmacy team, who will not be involved in patient care or data collection.

In the event of a medical emergency (eg, severe hepatic failure) where knowledge of the treatment allocation is deemed critical for patient safety, unmasking may be requested by two independent senior experts. Unmasking will be conducted in a controlled manner by the pharmacy team, and the reasons for unmasking will be documented. Participants whose treatment allocation is unmasked will be considered withdrawn from the intervention but will remain in the study under the intention-to-treat (ITT) principle. If a participant withdraws before completing the 5-day treatment period, follow-up data may still be collected with the participant's consent. A separate consent form will be used for this purpose, adhering to the Food and Drug Administration (FDA) regulations on data handling.[31] All participants, regardless of whether they complete the treatment period or are unmasked due to emergencies, will be included in the final analysis under the ITT framework.[32]

Outcomes

Primary outcome measures

Incidence of delirium during hospitalisation using the 3-Minute Diagnostic Confusion Assessment Method (3D-CAM).

Secondary outcome measures

1. Onset time of delirium: the time from hospital admission to the first diagnosis of delirium is measured in hours or days from admission and is assessed daily during the first 5 days of hospitalisation. The development of delirium will be ascertain assessed daily by trained research assessors, using the 3D-CAM tool.
2. Duration of delirium during hospitalisation: the total time a patient remains in a state of delirium during the hospital stay is recorded in hours or days using the 3D-CAM. This duration is assessed daily during the first 5 days of hospitalisation.
3. Sleep pattern and night awakenings: the quality of sleep, including the number of awakenings and disruptions during the night, is assessed using patient self-reports, nursing records or information from attendants. Night awakenings are quantified by the number of instances per night and are evaluated nightly during the first 5 days of hospitalisation by trained research assistant.

4. Days utilising physical restraints: the number of days physical restraints were used during hospitalisation is recorded in days based on hospital records and staff documentation and is assessed for first 5 days.
5. Number of rescue medications and doses used for delirium management: the number of doses and types of rescue medications, such as antipsychotics, administered for managing delirium symptoms is recorded as a count of doses and includes specific drug names with doses in milligrams from hospital records. This is assessed during the first 5 days of hospitalisation.
6. LOS: the total duration of hospitalisation, from admission to discharge, is recorded in days and assessed at the end of the hospitalisation.
7. Requirement to transfer to HDU or ICU: whether the patient required transfer to HDU or ICU during hospitalisation is recorded as a binary variable (yes/no), with reasons for transfer documented. This is assessed continuously during the hospitalisation.
8. Inpatient all-cause mortality: mortality occurring during the hospital stay, regardless of cause, is recorded as a binary variable (yes/no) from hospital records and is assessed for the entire hospitalisation period.
9. 28-day all-cause mortality: mortality occurring within 28 days of hospital admission, regardless of cause, is recorded as a binary variable (yes/no) from follow-up records and is assessed within 28 days postdischarge
10. 28-day hospital readmission: whether the patient was readmitted to the hospital within 28 days of discharge is recorded as a binary variable (yes/no) based on follow-up records and is assessed within 28 days postdischarge.

Participant timeline

The anticipated timeline for running the study is outlined in table 2.

Sample size calculation

The incidence of delirium in medically hospitalised patients is estimated to be 55% in our setting.[33] Additionally, we anticipate a 20% reduction in delirium incidence through melatonin administration.[29] With a significance level (alpha) set at 0.05 and a power of 80%, the calculated sample size is 240 participants, accounting for a 12% dropout rate.

Recruitment

The study will take place at Sultan Qaboos University Hospital, Muscat, Oman. Each year, the General Medicine Unit admits around 3000 patients, with approximately 1000 patients aged 65 years and above. We expect to recruit all participants within 6 months from the start. The anticipated recruitment start date is 1 June 2024, with completion by 28 February 2025.

Assignment of interventions

Randomisation

Simple randomisation will be performed using the Stata V.18 software to generate a computer-based allocation sequence. The sequence will assign participants to one of three groups (intervention group 1, intervention group 2 and control group) in a 0.5:0.5:1 ratio to ensure equal distribution across the groups. The allocation sequence will be concealed using sequentially numbered, opaque, sealed envelopes, which will be stored securely at the study site. The envelopes will only be opened after obtaining written informed consent and patient contact details to ensure blinding. Both study participants and investigators involved in administering the interventions will remain blinded to group allocations throughout the study period. This approach follows best practices for maintaining allocation concealment and blinding in RCTs.[20]

Allocation and intervention

All included patients will be randomly assigned to receive either 5 mg/day or 8 mg/day of melatonin or placebos within 24 hours of admission and up to 5 days, death or hospital discharge. A research assistant, who is a member of the nursing staff, will administer the study drugs according to the randomisation sequence. Both the study team members and patients will be blinded to the study drug allocation. Melatonin will be stored, prepared, labelled and dispensed in the pharmacy department. Each patient will have his/her own bottle of melatonin labelled according to the codes created for allocation (table 3).

Table 2 Time schedule for running the study

Timeline	Tasks
January 2024–March 2024	► Project initiation, team setup and ethical approvals. ► Trial registration.
April 2024–May 2024	Training sessions, system setup and procurement.
October 2024–October 2025	► Commence patient recruitment and screening. ► Baseline data collection and initiation of melatonin/placebo administration.
November 2025–December 2025	Preliminary data analysis and statistical assessment.
January 2026–February 2026	Report writing and internal review.
March 2026–May 2026	Peer review, journal submission and conference preparation.
June 2026–December 2026	Knowledge dissemination through presentations and publications. Project conclusion, summary and identification of future directions.

Table 3 Melatonin and placebo preparations for study interventions

Preparation type	Composition	Group	Dosage
Active 1	5 mg melatonin mixed with 5 mL of Oral Mix SF (sugar-free flavoured suspending vehicle) (0.5 mg/mL concentration, final volume: 10 mL)	Intervention group 1	Melatonin 5 mg/day
Active 2	8 mg melatonin mixed with 2 mL of Oral Mix SF (0.8 mg/mL concentration, final volume: 10 mL)	Intervention group 2	Melatonin 8 mg/day
Placebo	0 mg melatonin in 10 mL of Oral Mix SF (0 mg/mL concentration, final volume: 10 mL)	Control group	Placebo

Data collection methods

Efficacy/outcome assessment and data collection

The following relevant patient data will be collected, demographic data (age, sex, body mass index), data on comorbidities (hypertension, HF, cardiovascular diseases (CVD) and chronic kidney disease) and history of medications, drug abuse, smoking and alcoholism. Data on reason for admission classified according to ICD-10 (the 10th revision of the International Classification of Diseases) class, and the anticipated date of discharge.

All clinical and outcome data will be assessed by a blinded independent assessment committee to maintain the integrity of the study. This committee will consist of an independent expert who are not involved in the clinical care of patients or the administration of the study intervention. These assessors will remain blinded to the treatment allocation throughout the study to avoid bias in data collection and outcome assessment.

The primary endpoint, the incidence of delirium, will be assessed using the 3D-CAM. Delirium will first be evaluated approximately 24 hours after acute admission and subsequently assessed daily each morning during the first 5 days of hospitalisation.

In addition, data will be collected to assess secondary endpoints, including patient demographics, relevant clinical information, laboratory results obtained through routine standard care and follow-up data.

All patients will be screened for delirium using the 3D-CAM. This validated bedside measurement tool, known for its 94% sensitivity and 89% specificity, uses objective measurements and clinical observation to identify the presence of delirium.[34] The 3D-CAM evaluates four key characteristics of delirium: acute onset or fluctuating course (feature 1), inattention (feature 2), disorganised thinking (feature 3) and altered level of consciousness (feature 4).[35] Diagnosis requires the presence of features 1 and 2, along with either 3 or 4. The study will use a previously validated Arabic version of 3D-CAM in a similar healthcare setting.[36]

For all patients who develop delirium during hospitalisation, additional data will be collected, including the date of onset of delirium, type of delirium (hyperactive, hypoactive or mixed) and the in-hospital course of delirium categorised as transient (recovered within 24 hours), recovered (resolved by discharge) or persistent (present at discharge). The cause of delirium, as determined by the treating team, will also be recorded. Agitation will be measured through clinical observations documented by the treating team or bedside nursing staff, adhering to standard hospital protocols. Medications administered to manage delirium-related agitation, including antipsychotics (eg, haloperidol, quetiapine), benzodiazepines and other sedative agents, will be documented with details such as drug names, dosages and frequencies. Additionally, the recognition of delirium will be noted, including whether it was documented by the treating team in the medical record or identified through the study's independent assessment.

Screening for a pre-existing cognitive impairment and potential dementia will be done using the Informant Questionnaire on Cognitive Decline in the Elderly Short Form. This is a validated screening tool, involving 16 items answered by the patient's relative, retrospectively assesses changes in cognitive and functional performance over a 10-year period. Each item is rated on a scale from 1 to 5, with higher scores indicating a more significant cognitive decline. The average final score ranged from 1.0 to 5.0. Previous studies have established cut-off scores suggestive of dementia, ranging from 3.3 to 3.6.[37]

Compensation to participants

Not applicable

Protocol/schedule for assessment

Outcome measurement will be done by trained research assistant with close supervision of research team members (table 4).

Laboratory measurements

No extra laboratory measurements are required apart from the routine investigations collected for any admitted patient as per the usual practice of care.

Statistical analysis

Descriptive statistics will be used to summarise baseline characteristics of participants in both the melatonin and control groups. Continuous variables will be presented as means with SD or medians with IQRs, depending on their distribution, while categorical variables will be summarised using frequencies and percentages. To evaluate the primary outcome, which is the incidence of delirium, we will use a χ^2 test or Fisher's exact test

Table 4 Schedule of outcome measurement

Outcome	Time of measurement	Details
Eligibility criteria	At zero time (Q0)	To look for eligibility, inclusion, and exclusion criteria for admitted patients under the general medicine unit.
Incidence of delirium	► At zero time (Q0): Within 24 hours after acute admission. ► Daily: After 24 hours (Q1), 48 hours (Q2), 72 hours (Q3) and 96 hours (Q4) of admission using the 3D-CAM tool.	Assessed daily for the first 5 days using the 3D-CAM score.
Demographics and clinical data	At zero time (Q0)	Document patient demographics, pre-existing cognitive impairment, laboratory data and other relevant clinical information.
Onset time of delirium	Daily during the first 5 days of hospitalisation.	Time from hospital admission to the first diagnosis of delirium, measured in hours or days using the 3D-CAM tool.
Duration of delirium	Daily during the first 5 days of hospitalisation.	Total time a patient remains in delirium during the hospital stay, recorded in hours or days using the 3D-CAM tool.
Sleep pattern and night awakenings	Nightly during the first 5 days of hospitalisation.	Assessed using patient self-reports, nursing records, or attendants' information. Number of awakenings/disruptions quantified nightly by trained research assistants.
Days utilising physical restraints	During the first 5 days of hospitalisation.	Number of days physical restraints were used, recorded from hospital records and staff documentation.
Rescue medications for delirium	During the first 5 days of hospitalisation.	Number and type of medications (eg, antipsychotics) used to manage delirium symptoms, with dosages and frequencies recorded.
Length of hospital stay (LOS)	At the end of hospitalisation.	Total duration of hospitalisation, from admission to discharge, recorded in days.
HDU or ICU transfer requirement	Continuously throughout hospitalisation.	Documented as a binary variable (yes/no), with reasons for transfer.
Inpatient all-cause mortality	Entire hospitalisation period.	Mortality occurring during hospitalisation, recorded as a binary variable (yes/no).
28-day all-cause mortality	Within 28 days postdischarge.	Mortality recorded as a binary variable (yes/no) from follow-up records.
28-day hospital readmission	Within 28 days postdischarge.	Documented as a binary variable (yes/no) from follow-up records.

3D-CAM, 3-Minute Diagnostic Confusion Assessment Method; HDU, high dependency unit; ICU, intensive care unit.

for categorical variables, comparing the proportion of patients with delirium between the melatonin and control groups.

For secondary outcomes, such as the duration and severity of delirium, continuous variables will be compared between the two groups using t-tests or non-parametric tests as appropriate. Time-to-event outcomes, like the onset of delirium, will be analysed using survival analysis techniques, such as Kaplan-Meier curves and the log-rank test. Subgroup analyses may be conducted based on relevant factors such as age, gender and baseline cognitive status. Both ITT and per-protocol analysis will be performed.[32] All statistical tests will be two-sided, and p values less than 0.05 will be considered statistically significant. The analysis will be performed using Stata V.18, and results will be reported with corresponding CIs.

Monitoring

Human subject protection

This study will not interfere with the patient's usual practice of care and, therefore, will not be associated with any major risk/harm to patients. This study will not interfere with the patient's usual standard care practices.

Standard care in the General Internal Medicine Unit involves routine medical management, including comprehensive clinical assessments, regular monitoring of vital signs and necessary laboratory tests. It includes treatment of underlying conditions per clinical guidelines, with medications and supportive care, along with standard nursing care to address hydration, nutrition and individual needs.

Graduated nurses with clinical experience will conduct assessments using the 3D-CAM. These research assistants

will receive comprehensive training on the study protocol, which includes workshops on delirium assessment, hands-on sessions with the 3D-CAM and mock assessments supervised by senior clinicians. Training will be thoroughly documented, and periodic refresher sessions will be held to ensure consistency and reliability in data collection throughout the study.

The assessment will be done by experts, and it will involve clinical assessment and questionnaire form, there are no extra blood investigations that are needed and no other invasive procedures.

Melatonin is a proven safe and remarkably well-tolerated supplement, with no evidence of major toxicities even at high doses.[38] For some of the intervention group, however, as shown from previous studies, they may experience minor adverse reactions including headache, transient depression, enuresis, dizziness, nausea, stomach cramps, irritability, insomnia, nightmares, hypothermia and excessive daytime somnolence.[39–41] Drowsiness may be experienced within 30 min after taking melatonin and may persist for approximately 1 hour.

Nevertheless, participants will be protected through proper counselling and monitoring closely during the trial time for any major side effects, if any.

Proper counselling ensures participants understand the study's purpose, potential risks and safety measures. It includes clear communication, addressing concerns and guidance on adverse effects. In cases of issues, the team involved two internal medicine senior consultants that are on-call during the study recruitment time to ensure patient safety.

Quality control and assurance

The study team includes researchers and assistant researchers to ensure optimal work quality. Eligible participants for the trial will be assessed by research assistants and confirmed by the researcher on-call, as per the on-call roster provided monthly by the principal investigator. The intervention (study drug or placebo) will be administered by blinded research assistant (nursing background) who are not part of the clinical care team. At each stage of data collection and entry, two independent researchers will validate the data and report any discrepancies to the research assistants for corrections and improvements.

Criteria for terminating the study

The study will be terminated if interim analysis reveals that the intervention represents significant risks to participants, such as severe adverse effects or unexpected harm, that outweigh the potential benefits, as determined by the independent data monitoring committee based on predefined safety criteria. Additionally, the study will be terminated if the target number of participants is not achieved within 1 year after the expected completion date due to low recruitment rates or other logistical challenges.

Patient and public involvement statement

None.

Ethics and dissemination

Ethical consideration/confidentiality

Written informed consent (online supplemental appendix 1) from all eligible patients for randomisation will be obtained either directly from the patient or, if their capacity is impaired, from their next of kin. All trial participants will receive a comprehensive trial information sheet along with a contact number for further inquiries. All collected data will be securely stored in a password-protected electronic database specifically designed for this study, ensuring confidentiality by excluding any identifiable details.

Benefits to participants

The favored outcome of the study is to prevent delirium incidence in comparison to placebo, participant will have a better sleeping pattern during the hospital stay and a closer monitoring plan as well.

Dissemination plan

The findings of this study will be published in peer-reviewed journals and presented at relevant national and international conferences.

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