


BMJ Open Melatonin for prevention of postoperative delirium after lower limb fracture surgery in elderly patients (DELIRLESS): study protocol for a multicentre randomised controlled trial

Stéphanie Sigaut ^{1,2}, Camille Couffignal,³ Marina Esposito-Farèse,³ Vincent Degos,^{4,5} Serge Molliex,⁶ Jacques Boddaert,^{5,7} Agathe Raynaud-Simon,^{8,9} Isabelle Durand-Zaleski,¹⁰ Estelle Marcault,³ Madalina Jacota,¹¹ Souhayl Dahmani,^{9,12} Catherine Paugam-Burtz,⁹ Emmanuel Weiss^{1,9}

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For numbered affiliations see end of article.

Correspondence to

Dr Stéphanie Sigaut;
stephanie.sigaut@aphp.fr

ABSTRACT

Introduction Postoperative delirium (POD) is one of the most frequent complication after surgery in elderly patients, and is associated with increased morbidity and mortality, prolonged length of stay, cognitive and functional decline leading to loss of autonomy, and important additional healthcare costs. Perioperative inflammatory stress is a key element in POD genesis. Melatonin exhibits antioxidative and immune-modulatory properties that are promising concerning delirium prevention, but in perioperative context literature are scarce and conflicting. We hypothesise that perioperative melatonin can reduce the incidence of POD.

Methods and analysis The DELIRLESS trial is a prospective, national multicentric, phase III, superiority, comparative randomised (1:1) double-blind clinical trial. Among patients aged 70 or older, hospitalised and scheduled for surgery of a severe fracture of a lower limb, 718 will be randomly allocated to receive either melatonin 4 mg per os or placebo, every night from anaesthesiologist preoperative consultation and up to 5 days after surgery. The primary outcome is POD incidence measured by either the French validated translation of the Confusion Assessment Method (CAM) score for patients hospitalised in surgery, or CAM-ICU score for patients hospitalised in ICU (Intensive Care Unit). Daily delirium assessment will take place during 10 days after surgery, or until the end of hospital stay if it is shorter. POD cumulative incidence function will be compared at day 10 between the two randomised arms in a competing risks framework, using the Fine and Grey model with death as a competing risk of delirium.

Ethics and dissemination The DELIRLESS trial has been approved by an independent ethics committee the Comité de Protection des Personnes (CPP) Sud-Est (ref CPP2020-18-99 2019-003210-14) for all study centres. Participant recruitment begins in December 2020. Results will be published in international peer-reviewed medical journals.
Trial registration number NCT04335968, first posted 7 April 2020.

Protocol version identifier N°3-0, 3 May 2021.

Strengths and limitations of this study

- High-quality methodology using randomised clinical trial design that will provide a high level of evidence on the efficacy and safety of melatonin for prevention of postoperative delirium.
- Anaesthesia management not imposed by the protocol, to maximise the external validity of the results.
- Specific training of the investigators for delirium assessment with a validated tool, to ensure good specificity and sensibility.
- Risk of early discharge from hospital which will reduce the period of melatonin intake and of evaluation of the postoperative delirium.
- Risk of Hawthorne effect as daily delirium assessment may improve postoperative care in both groups.

INTRODUCTION

Background and rationale

Delirium is a clinical syndrome characterised by the acute onset of a cognitive disorder with inattention. It is a frequent condition in perioperative context: a global incidence around 20% has been described,¹ which can go up to 35%–55% after high-risk procedures such as hip fracture repair² and cardiac surgery.³ Thus, it is the most common surgical complication among older adults. Despite its frequency, delirium is often not recognised, poorly assessed and inappropriately managed. In fact, studies comparing clinical documentation with research assessment suggest that only 12%–35% of delirium cases are recognised.⁴

Delirium is associated with increased postoperative morbidity and mortality. With respect to long-term outcomes, it is associated



with cognitive decline,⁵ onset of dementia, reduced functional ability and admission to long-term care.^{6 7} It is consequently associated with US\$60 000 of incremental costs over the following year in the USA.⁸ Therefore, it has huge consequences for patients, families and for society. In addition, with the ageing of the population and increasing life expectancy, the number of elderly patients undergoing surgery rises, which makes of postoperative delirium a major public health problem.

It is documented that multicomponent intervention and non-pharmacological preventive measures can reduce the incidence of postoperative delirium.^{9 10} However, when these measures fail or are not available (given the lack of human resources in hospitals for example), the idea that a medication could reduce the incidence of postoperative delirium incidence is interesting and potentially timesaving. Nevertheless, the effectiveness of pharmacological approaches for postoperative delirium incidence prevention remains unclear.¹¹

The particular sensitivity of elderly in perioperative context finds a logical explanation in the pathophysiology of postoperative delirium incidence. This pathology can be thought as an acute brain failure that is the final pathway of multiples mechanisms, with neurotransmitters imbalance and neuroinflammation playing a critical role. Indeed, perioperative inflammatory stress is one of the key elements in delirium genesis,¹² and with ageing an increase in initial neuroinflammatory response and a decrease in subsequent resolution phase are observed,¹³ making postoperative delirium incidence all the more possible in this population.

Melatonin is a neurohormone regulating circadian rhythm in mammals. It also exhibits antioxidant and free radical scavenger properties, and regulates energy metabolism and immune function.¹⁴ Melatonin receptors have been found on most of immune cells, allowing melatonin to play an immunomodulating role on immune cell proliferation and cytokine secretion. It neutralises exacerbated proinflammatory mediator production in various in vivo models of inflammation.¹⁴ It has also demonstrated a neuroprotective potential in various animal models.^{15–17} The use of melatonin to prevent delirium in clinical studies is promising. It decreases delirium incidence in elderly patients hospitalised in medical wards by more than 50%, passing from 31% in control group to 12% in melatonin group ($p=0.014$).¹⁸ Concerning the perioperative period, only a few small studies with conflicting results are available, three in non-cardiac surgery,^{19–21} and two in cardiac surgery.^{22 23} A recent meta-analysis²⁴ found no significant difference in the surgical patient subgroup (OR 0.51 (0.25, 1.03) $p=0.06$); however, the method and population varied greatly between studies included (cardiac and non-cardiac surgery, inclusion of two studies using ramelteon and not melatonin, different doses and timing of administration).

This equipoise in the literature emphasises the need for a randomised controlled trial with an improved methodology.

Aims and objectives

The primary aim of the DELIRLESS study is to determine if the use of perioperative melatonin, as compared with a placebo, reduces the postoperative delirium incidence in the first 10 days after surgery, in elderly patients (over 70 years old) being hospitalised for surgery of fractured lower limb. We hypothesise that perioperative melatonin applied from preoperative period up to 5 days after surgery could decrease the incidence of postoperative delirium in elderly patients with lower limb fracture, in comparison with a placebo.

The secondary aims of this trial are presented in the table 1.

METHODS AND ANALYSIS

Design overview

The DELIRLESS study is an investigator-initiated, national multicentric, phase III, superiority, parallel-group, double-blinded, comparative randomised clinical trial, in which patients being hospitalised for surgery of fractured lower limb are allocated in a 1:1 ratio to Melatonin (intervention group) or to Placebo (control group). The trial design is summarised in table 2 and in figure 1. We report the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials statement.²⁵

After inclusion (performed by the investigator or by a medical doctor representing the investigator) and before randomisation, delirium evaluation by the Confusion Assessment Method (CAM) score (followed in case of abnormalities of cognition and attention by a brief interview with a proxy or caregiver of the patient) will be performed in order to exclude secondarily patients already presenting a delirious state. After randomisation (performed by the investigator or by a medical doctor representing the investigator) treatments will start in both groups.

Melatonin 4mg (Circadin 2 tablets) per os or placebo (2 tablets) will be administered to the patients every night between 20:00 and 22:00, from randomisation up to 5 days after surgery. The dose and the administration schedule have been chosen considering the published studies. As Circadin has been administered at 5 mg daily doses in clinical trials over 12 months without significantly changing the nature of the reported adverse reactions, we choose to administrate a dose in the high range of what is commonly done, that is to say 2 tablets of CIRCADIN 2 mg=4mg. The administration of melatonin every night between 20:00 and 22:00 is based on the treatment recommendation for insomnia, that is, to take CIRCADIN 1–2 hours before bedtime and after a meal.

Preoperative treatment with melatonin will be limited to 5 days. If surgery has not been performed 5 days after inclusion, treatment will be stopped and data on these patients will be censored. The patients will be followed for 5 days to detect any event related to the medication. If eventually these patients are operated, the postoperative

Table 1 Secondary endpoints and associated outcomes

| Secondary objectives | Secondary outcomes |
|---|--|
| <ul style="list-style-type: none"> ▶ To evaluate the effect of perioperative melatonin administration on: <ul style="list-style-type: none"> Duration of postoperative delirium incidence Need for postoperative sedative or antipsychotic drugs administration Need for postoperative physical restrain prescription Incidence of postoperative falls Length of hospital stay Day 10 postoperative (or end of hospital stay if shorter) cognitive performance Day 30 postoperative mortality Day 30 postoperative functional status and quality of life ▶ To assess the total cost, the cost-effectiveness and the cost utility of perioperative melatonin administration. ▶ To assess the safety of perioperative melatonin administration. | <ul style="list-style-type: none"> ▶ Number of days CAM positive ▶ Incidence of postoperative sedative or antipsychotic drugs administration from D1 to D10 (or end of hospital stay if shorter) ▶ Incidence of postoperative physical restrain prescription from D1 to D10 (or end of hospital stay if shorter) ▶ Incidence of postoperative falls from D1 to D10 (or end of hospital stay if shorter) ▶ Mini Mental State Examination at D10 postoperative (or end of hospital stay if shorter) ▶ Duration of hospital stay ▶ D30 postoperative mortality ▶ D30 postoperative patient autonomy evaluated by the Katz Index of activities of daily living ▶ D30 postoperative quality of life and QALYs evaluated by EQ5D5L questionnaire; 30days QALYs are the utility weights for the 30-day periodx30/365 ▶ Total hospital costs at D30 calculated as the cumulative costs of all admissions (inpatient and outpatient, home care, rehabilitation) over a 30 days period ▶ Incremental cost effectiveness and cost utility ratios ▶ Occurrence of side effects |

CAM, Confusion Assessment Method; QALYs, quality-adjusted life year.

assessment will be performed, and data included in sensitivity analyses.

In sum, treatment duration may vary with length of preoperative period up to a maximum of a 10 days period.

Perioperative management will follow the 2017 French anaesthesia guidelines for elderly patients. Medical management and data collection will be identical between the two groups in all other aspects.

Mandatory biological assessments added by the protocol are plasmatic creatinine, bilirubin, prothrombin time (and factor V if prothrombin time is below 70%) during the baseline visit, and plasma creatinine, sodium, potassium and chloride levels at D1 postoperative. Other biological tests performed during the follow-up are not mandatory but will be collected.

Study setting and population

Participants will be prospectively recruited among patients being hospitalised for surgery of fractured lower limb. They will be invited to participate by the anaesthesiologists during preoperative consultations in 21 French university and non-university centres (list of study sites can be obtain by contacting the corresponding author). Patients will be considered eligible for randomisation if they fulfil the inclusion criteria and none of the exclusion criteria, as defined in [box 1](#), and if the presence of a delirious state is excluded. The key eligibility criteria include isolated fracture of a lower limb and the need for scheduled orthopaedic surgery for patients 70 years old or older.

Interventions

Experimental group

From randomisation up to 5 days after surgery, melatonin 4mg (Circadin two tablets) per os will be administered to the patients every night between 20h00 and 22h00. If surgery is scheduled the same day of randomisation, the patients will get the first dose 2 hours before surgery.

Control group

From randomisation up to 5 days after surgery, placebo (2 tablets) per os will be administered to the patients every night between 20:00 and 22:00. If surgery is scheduled the same day of randomisation, the patients will get the first dose 2 hours before surgery.

Outcomes

Primary outcome

The primary outcome is the postoperative delirium incidence. Delirium assessment will be performed daily since the first postoperative day until postoperative Day-10 or the end of hospital stay if shorter (ie, D1 to D10, D0 being the day of the surgery). The French validated translation of the CAM score²⁶ for patients hospitalised in surgery, or CAM-ICU score²⁷ (see online supplemental material 1) for patients hospitalised in ICU (Intensive Care Unit) will be used. [Table 3](#) establishes the different time of CAM's assessment and the modalities in order to rate the CAM at baseline, in surgery ward or in ICU.

For the first delirium assessment during baseline visit, that will be performed to exclude patients already delirious, the anesthesiologist will, in order to answer CAM

**Table 2** Summary of the chronology of the study with data collected

| Study period | Enrolment | Allocation | Preoperative treatment | Surgery | Postoperative treatment | Close-out |
|---|-----------|------------|------------------------|---------|-------------------------|-----------|
| Timepoint (days) | D-5 to D0 | D-5 to D0 | D-5 to D0 | D0 | D0 to D5 | D30 |
| Enrolment | | | | | | |
| Eligibility screen | X | | | | | |
| Express consent | X | | | | | |
| Allocation | | X | | | | |
| Interventions | | | | | | |
| Melatonin | | | X | | X | |
| Placebo | | | X | | X | |
| Assessment | | | | | | |
| Baseline variables | | | | | | |
| Demographics | X | | | | | |
| Medical history | X | | | | | |
| Clinical examination | X | | | | | |
| Type of fracture | X | | | | | |
| Current medications | x | | | | | |
| Standard biological assessment | X | | | | | |
| Baseline CAM | X | | | | | |
| Katz Index (preoperative autonomy) | X | | | | | |
| EQ5D5L (preoperative quality of life) | X | | | | | |
| MMSE (preoperative cognition) | X | | | | | |
| Mini-GDS (preoperative depression) | X | | | | | |
| Perioperative data | | | | | | |
| Type of surgical procedure | | | | X | | |
| Duration of surgical procedure | | | | X | | |
| Type of anaesthesia | | | | X | | |
| Duration of anaesthesia | | | | X | | |
| Type of surgical procedure | | | | X | | |
| Intraoperative drugs | | | | X | | |
| Anaesthesia monitoring parameters | | | | X | | |
| Fluid volume administrated | | | | X | | |
| Administration of blood products | | | | X | | |
| All other notable intraoperative events | | | | X | | |
| Time end of surgery-extubation | | | | X | | |

Continued

Table 2 Continued

| Study period | Enrolment | Allocation | Preoperative treatment | Surgery | Postoperative treatment | Close-out |
|---|-----------|------------|------------------------|---------|-------------------------|-----------|
| Destination after operating room (recovery room or intensive care unit) | | | | X | | |
| Duration of stay in recovery room | | | | X | | |
| All drugs used in recovery room | | | | X | | |
| Destination after recovery room | | | | X | | |
| Outcome variables | | | | | | |
| CAM or CAM-ICU | | | | | X | |
| Vital status | | | | | X | X |
| Unit of hospitalisation | | | | | X | |
| Sedative or antipsychotic drugs administration | | | | | X | |
| Physical restrain prescription | | | | | X | |
| Falls | | | | | X | |
| MMSE | | | | | X (D10 only) | |
| Daily consumption of morphine | | | | | X | |
| Anticholinergic drugs administration | | | | | X | |
| Postoperative morbidity | | | | | X | |
| Biological data | | | | | X | |

CAM, Confusion Assessment Method; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination.

feature 1 (acute change or fluctuation) and in case of abnormalities of cognition and attention, contact a proxy, describe the patient state and ask the following question ‘Do you think [name of patient] has been more confused lately?’ (Single Question in Delirium²⁸ have a 80% sensitivity and specificity for delirium diagnosis)

To insure maximal sensitivity and specificity of these testing, several interviewers for each centre will follow a 1-day training procedure with expert pairs. The additional staff costs for CAM and CAM-ICU assessments were included in the budget of DELIRLESS. Therefore, all the scheduled CAM and CAM-ICU questionnaires will be administered by trained staff in all patients, even on weekends and holidays.

Secondary outcomes

See table 1 for the full list of secondary outcomes.

Randomisation and sequence generation

The randomisation will be performed using CleanWEB, an online centralise procedure service running 24 hours/24.

The randomisation sequence will be computer generated in advance by a statistician of the coordinating office. It will be stratified by centre and by type of scheduled post-operative ward (either geriatric perioperative unit or another type of ward). The latter stratification variable was chosen due to a more specialised management of delirium in geriatric perioperative units than in other wards.

Allocation concealment

The number of experimental units per block will be kept confidential to avoid prediction of future patient’s allocation. Only the independent statistician and the computer programmer who will implement the sequence assignment in the secure electronic case report form (eCRF) will have access to the randomization list. Allocation concealment will be ensured, as CleanWeb services will not release the randomization code until the patient has been recruited into the trial.

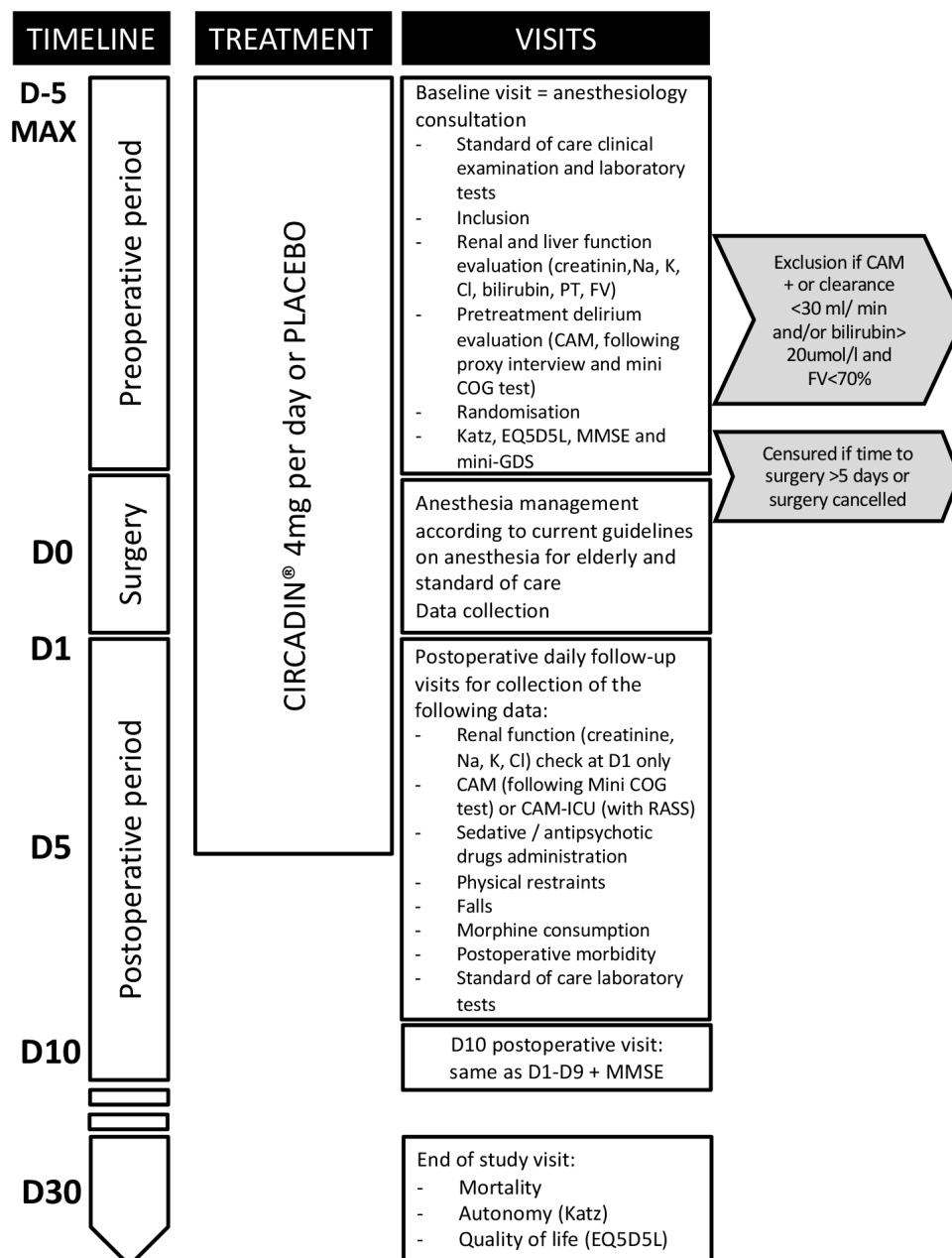


Figure 1 Randomised clinical trial flow diagram. CAM, Confusion Assessment Method; D, day; FV, factor V; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; PT, prothrombin time; RASS, Richmond agitation sedation scale; EQ5D5L, 5 levels 5 dimensions Euro Quality of Life evaluation.

Blinding

Neither the patients nor the medical staff will be aware of the randomisation arm. The rare, mild and non-specific potential side effects of melatonin and its moderate effect on sleep disorders, non-specific in this elderly population and particular setting (postoperative) will not compromise the blinding at individual level. The study statistician, also, will be blinded to the groups.

Statistical considerations

Sample size calculation

In the literature, incidence rates of delirium in elderly populations in control groups in the first week after surgery or hospital admission range from 20.8% to

32.6%.^{19 20 29} We therefore expect a cumulative incidence of delirium of 25% at day 10 after surgery in the control group.

Literature data are discordant on melatonin's effect on the risk of delirium. In medical wards, meta-analyses^{11 30} found in elderly patients a decreased in the incidence of delirium between 60% and 75% with melatonin supplementation. In a postoperative setting the effect seems smaller but there are fewer studies, with discordant results, going from no effect to a 70% decrease of delirium incidence.^{19 20 29} We therefore expect a 40% risk reduction in the melatonin group with respect to placebo, which corresponds to a cumulative incidence of delirium

Box 1 Eligibility criteria

Inclusion criteria

- ▶ Demographic criteria: patient 70 years old or older
- ▶ Diagnostic criteria: isolated fracture of a lower limb
 - Proximal femoral fractures: head, cervical, or trochanteric fractures
 - Periprosthetic hip fracture
 - Femoral shaft fracture
 - Distal femoral fractures: supracondylar or condylar
 - Periprosthetic knee fracture
 - Tibial plateau fracture
- ▶ Treatments/strategies/procedures: scheduled orthopaedic surgery (osteosynthesis or arthroplasty)
- ▶ proxy or caregiver knowing baseline cognitive status of the patient present or reachable by phone for an interview

Exclusion criteria

- ▶ Patient already taking melatonin
- ▶ Contraindications and precaution for use of melatonin administration:
 - Hypersensitivity to the active substance or to any of the excipients of Circadin
 - Liver failure (presence of some of the following clinical and biological symptoms: icterus, asterixis, ascites, known oesophageal varices, total bilirubin >20 µmol/L, FV<70%)
 - Cirrhosis (known histological liver fibrosis)
 - Renal failure with clearance <30 mL/min
 - Autoimmune disease
 - Hereditary galactose intolerance, Lapp lactase deficiency or glucose–galactose malabsorption syndrome
 - Patients taking fluvoxamine, 5-methoxypsoralene or 8-methoxypsoralene, cimetidine, oestrogenotherapy, quinolones, carbamazepime, rifampicine
- ▶ Other concomitant trauma than lower limb fracture
- ▶ Surgery scheduled in more than 5 days
- ▶ Patient under mechanical ventilation
- ▶ Patient refusing to participate
- ▶ Patient not talking/understanding French
- ▶ Patient under guardianship
- ▶ Patient already participating to another interventional study
- ▶ No signed informed consent
- ▶ No affiliation to a social security regime

Secondary exclusion criteria (before randomisation)

- ▶ Diagnosis of delirium at the Confusion Assessment Method assessment at inclusion
- ▶ Creatinin clearance <30 mL/min and/or biological signs of hepatocellular insufficiency (bilirubin>20 µmol/L and factor V<70%) if samples not available during the anesthesiologist consultation and so performed after inclusion.

of 15% at day 10 after surgery in the melatonin group. Adding to this assumption a bilateral type I error of 5% and a power 90%, we need to randomise 718 patients (359/group) in order to have 129 events and to detect a significant difference between arms (including 10% of patients that could not be evaluated). Sample size was computed with a Fine and Gray methods using R package *cmprsk*.³¹ We expect that 10% of included subjects will be secondarily excluded (not randomised) due to presence of delirium at inclusion. Therefore, we need to include 790 patients in order to randomise 718 subjects. Inclusions will continue until 718 patients are randomised.

Statistical analyses

The analyses will follow the intention-to-treat principle.

Postoperative delirium cumulative incidence function (CIF) will be compared at day 10 between the two randomised arms (melatonin vs placebo) by means of a competing risks framework, using the Fine and Grey model, that allows to estimate CIF on the presence of other cause of failure (deceased in our study), altering the probability of experiencing the event of interest, delirium.

The significant level of all statistical analyses will be a 2-sided 5%. All statistical analyses will be performed using SAS software (SAS Institute) V.9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org/>) V.4.0 or later.

Health economics analysis

The economic evaluation is planned, undertaken and analysed according to the intention-to-treat principle, with the primary aim to estimate the 30-day incremental cost-utility and cost effectiveness of melatonin. Because of the short duration of the follow-up (30 days) the difference in quality-adjusted life year is likely to be small; we will therefore add a measure of clinical effectiveness based on a composite of the primary and secondary clinical outcomes: incidence of delirium, need for sedatives, need for physical restraints, fall and death.

All analyses will be conducted by a statistician according to a prespecified statistical analysis plan. A full statistical analysis plan including the health economics analysis has been written and is available in online supplemental material 2.

All analyses results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines and the Consolidated Health Economic Evaluation Reporting Standards guidelines on economic evaluation in healthcare.³²

Data collection and management

Data collection will be done in electronic format, the statistical software CleanWeb for data entry will be used. The software will fulfil the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

We will collect data on primary and secondary endpoints, as well as potential risk factors of delirium (postoperative medication, comorbidities and complications) detailed in [table 2](#).

The data of this study will be available on reasonable request from the corresponding author. The data will not be publicly available due to privacy and ethical restrictions.

Table 3 Delirium assessment

| | Baseline visits assessment | Postoperative assessment D0–D10 | |
|------------------|---|--|--|
| | Before randomisation | In surgery or medical ward | In ICU |
| Modalities | <ol style="list-style-type: none"> Contact the proxy or caregiver Ask him/her if the patient is known for having dementia (if this diagnosis is not already known) Ask him/her if the patient is more confused lately Interview the patient using the Mini COG test Answer the CAM questionnaire | <ol style="list-style-type: none"> Chart review and discussion with nurse in charge about fluctuation and acute change of cognition in the last 24 hours Interview the patient using the Mini COG test Answer the CAM questionnaire | <ol style="list-style-type: none"> Chart review and discussion with nurse in charge about fluctuation and acute change of cognition in the last 24 hours Level of consciousness assessment by RASS CAM-ICU questionnaire (if RASS \geq -3) |
| Pretest | Mini-Cog test (see online supplemental material 1) | Mini-Cog test (see online supplemental material 1) | Richmond Agitation and Sedation Scale RASS \geq -3 (see online supplemental material 1) |
| CAM | Feature 1—Acute change or fluctuation (any symptom) AND Feature 2—Inattention AND EITHER Feature 3—Disorganised thinking OR Feature 4—Altered level of consciousness | Feature 1—Acute change or fluctuation (any symptom) AND Feature 2—Inattention AND EITHER Feature 3—Disorganised thinking OR Feature 4—Altered level of consciousness | Feature 1—Acute change or fluctuation (any symptom) AND Feature 2—Inattention AND EITHER Feature 3—Disorganised thinking OR Feature 4—Altered level of consciousness |
| Primary endpoint | X | Positive CAM | Positive CAM-ICU |

CAM, Confusion Assessment Method.

Patients and public involvement

Patients and public were not involved in any of the phases of this study. Results of the trial will be made available to all participants via ClinicalTrials.gov as well as by email notification.

Trial status

Recruiting. The first inclusion occurs 23 January 2021 and the recruiting period will be 24 months.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this minimal risks and constraints human research study. AP-HP has obtained the favourable opinion of the Comité de Protection des Personnes (CPP) Sud-Est (ref CPP2020-18-99 2019-003210-14) for the study protocol (version DELIRLESS-01.1; 05 February 2020). The AP-HP has sent the CPP approval and the summary of the protocol to the Agence Nationale de Sécurité du Médicament et des Produits de Santé for information. The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol must be sent to the sponsor for approval.

Once approval has been received from the sponsor, it must also obtain approval from the CPP before the amendment can be implemented. The information sheet and the consent form can be revised if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information and consent from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research can be carried out on a person without his/her free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The person will be given a reflection period of at least 15 min between receiving oral and written information, and being asked to sign the consent form (see online supplemental material 3). The person's free and informed written consent will be obtained by the investigator, or by a medical doctor representing the investigator, before the person is enrolled on the trial, during the baseline visit. The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the

doctor representing the investigator, will be given to the individual prior to being enrolled on the trial. In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Subjects may exit the study at any time and for any reason.

Data collection and quality control

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information relating to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. Under no circumstances should the names, addresses and other protected identifiers of the subjects involved be shown.

In any case of premature withdrawals and exits, the investigator must document their reason(s) and try to collect primary endpoint, secondary endpoints and safety assessment, if the participant agrees. If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used excepted if the participant refuses in writing.

To monitor compliance all treatment blisters will be stored after use for counting and auditing. All processing units (used or not) will be stored in the medical ward and sent to the site pharmacy at study end for destruction.

A data monitoring committee has not been convened, on the grounds that the study is low risk. This has been approved by the Sponsor, Steering Committee and the independent Ethical Board. The research data will be collected and monitored using an eCRF through CleanWEB Electronic Observation Book and will be centralised on a server hosted by the AP-HP Operations Department. This research is governed by the CNIL (Commission Nationale de l'Informatique et des Libertés, national commission for informatic and liberty) 'Reference Method for processing personal data for clinical studies' (MR-001, amended). AP-HP, the sponsor, has signed a declaration of compliance with this 'Reference Method'.

Research staff will work with local investigators to obtain data that are as complete and accurate as possible. An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out

at any time by independent individuals appointed by the sponsor. The aims of the audits are to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

Safety considerations

The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.

The investigating doctor may request unblinding for any reason he considers essential.

According to article R.1123-49 of the French Public Health Code (CSP, Code de Santé Publique), the investigator must notify the sponsor without delay on the day when the investigator becomes aware of any serious adverse event which occurs during the trial, related to the studied treatment or not, except those which are listed below as not requiring a notification without delay.

Other events, judged as being 'medically significant', require the investigator to notify the sponsor without delay (clinical or biological events that may suggest toxicity or require an increased monitoring of the subjects exposed):

- ▶ Jaundice, hyperbilirubinaemia three times higher than the upper limit.
- ▶ Aspartate or alamine aminotransferase three times higher than the upper limit.
- ▶ Leukopaenia < 2000/mm³.
- ▶ Thrombocytopenia < 50 000/mm³.

The following adverse events, related to the surgery and/or to a pre-existing illness or condition, are simply recorded in the CRF (eCRF) and do not require the investigator to notify the sponsor without delay. A CRF extraction of these adverse events will be realised every 6 months.

- ▶ Deterioration of a pre-existing illness or condition (for example cardiopulmonary),
- ▶ Surgical complications (for example surgical wound infection, haemorrhage, non-unions, avascular necrosis of the femoral head, dislocation, implant failure or malposition, induced fractures),
- ▶ Venous thrombo-embolism,
- ▶ Gastrointestinal tract bleeding,
- ▶ Urinary tract complications,
- ▶ Perioperative anaemia,
- ▶ Pressure scars,
- ▶ Postoperative delirium,
- ▶ Loss of autonomy and admission to long-term care.

The mortality rate of lower limb fractures in elderly is high, for example, for hip fractures it is 7% at 1 month.³³ If there is any imbalance between the randomisation groups or the mortality rate is higher than expected, affecting the safety of trial subjects and which requires the sponsor to take urgent safety measures, the French

National Agency for Medication will be informed about the emerging safety issue without delay.

Trials oversight committees

Two oversight committees have been established to oversee the conduct of this trial, the Steering Committee and Scientific Committee, the composition of each is listed at the end of this paper.

Publication plan

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The coauthors of the report and the publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the DELIRLESS investigators' in the final manuscript. Rules on publication will follow international recommendations.³⁴

Author affiliations

¹Anesthesiology and Intensive Care, Hôpital Beaujon, Clichy, France

²INSERM, Neurodiderot, Paris, Île-de-France, France

³Unité de recherche Clinique, Hôpital Bichat - Claude-Bernard, Paris, Île-de-France, France

⁴Anesthesiology and Intensive Care, University Hospital Pitié Salpêtrière, Paris, Île-de-France, France

⁵Faculty of Health, Sorbonne Université, Paris, Île-de-France, France

⁶Anesthesiology Reanimation, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, Rhône-Alpes, France

⁷Geriatric medicine, University Hospital Pitié Salpêtrière, Paris, Île-de-France, France

⁸Geriatric Medicine, Hôpital Bichat - Claude-Bernard, Paris, Île-de-France, France

⁹Faculty of Health, Université de Paris, Paris, Île-de-France, France

¹⁰URC Eco, Hôpital Hôtel-Dieu de Paris, Paris, Île-de-France, France

¹¹URC HUPIFO, Hôpital Ambroise-Pare, Boulogne-Billancourt, Île-de-France, France

¹²Anesthesiology, Robert-Debré Mother-Child University Hospital, Paris, Île-de-France, France

Twitter Stéphanie Sigaut @stephsig

Collaborators The Steering Committee is composed of the coordinating Investigator (Dr Stéphanie SIGAUT), the scientific director (Dr Emmanuel WEISS), the methodologist (Camille COUFFIGNAL), the trial's statistician (Marina ESPOSITO-FARESE), the project manager (Estelle MARCAULT), and a representative of the sponsor, named for this study. The scientific committee includes the members of the steering committee, as well as members selected on the basis of outstanding expertise in the field of the study: Pr Serge MOLLIEUX, Pr Jacques BODDAERT, Pr Agathe RAYNAUD SIMON, Pr Vincent DEGOS. DELIRLESS Study Group includes members of steering and scientific committees, and Principal Investigators of each centre: Pr Philippe MONTRAVERS, Pr Vincent PIRIOU, Dr Marion DOUPLAT, Pr Vincent MINVILLE, Dr Gaëtan PLANTEFEVE, Pr Sigismond LASOCKI, Dr Pauline GLASMAN, Dr Marc GARNIER, Dr Patrick SINDA, Dr Baptiste ROSSELL, Dr Maria LAHLOU CASULLI, Pr Karim ASEHNOUNE, Dr Jean Marie BREGET.

Contributors SS contributed to the conception and design of the research protocol, assisted by CC, MJ, ME-F and EM. CP-B, JB, AR-S, SM, EW, SD and VD provided critical input pertaining to the design of the trial interventions and procedures. SS wrote the first draft of the protocol and this manuscript. ME-F designed the statistical analysis plan; ID-Z designed the health economics analysis. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Research and Innovation Delegation (DRCI), Hôpital Saint-Louis, 1, avenue Claude Vellefaux, 75010 PARIS.

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ORCID iD

Stéphanie Sigaut <http://orcid.org/0000-0002-4888-7769>

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