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

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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 proprieties 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 repair[2] 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-analysis[24] 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 4 mg (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=4 mg. 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 censured. 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
► To evaluate the effect of perioperative melatonin administration on: 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.	► 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 4 mg (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 score[26] for patients hospitalised in surgery, or CAM-ICU score[27] (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 Delirium[28] 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 postoperative 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.

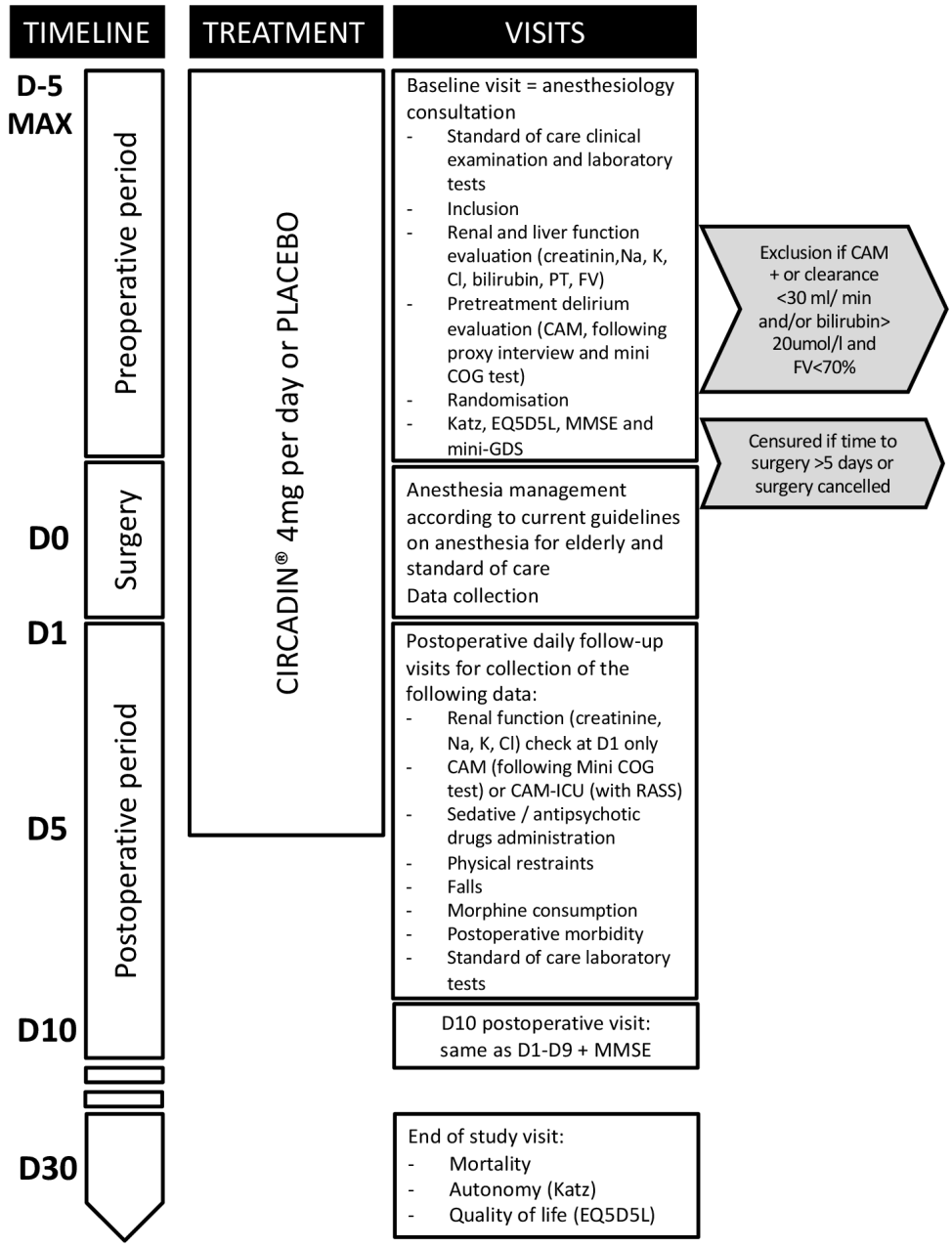

Figure 1 Randomised clinical trial flow diagram. CAM, Confusion Assessment Method; D, day; FV, factor V; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; PT, prothrombin time; RASS, Richmond agitation sedation scale; EQ5D5L, 5 levels 5 dimensions Euro Quality of Life evaluation.

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 umol/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	1. Contact the proxy or caregiver 2. Ask him/her if the patient is known for having dementia (if this diagnosis is not already known) 3. Ask him/her if the patient is more confused lately 4. Interview the patient using the Mini COG test 5. Answer the CAM questionnaire	1. Chart review and discussion with nurse in charge about fluctuation and acute change of cognition in the last 24 hours 2. Interview the patient using the Mini COG test 3. Answer the CAM questionnaire	1. Chart review and discussion with nurse in charge about fluctuation and acute change of cognition in the last 24 hours 2. Level of consciousness assessment by RASS 3. CAM-ICU questionnaire (if RASS ≥ –3)
Pretest	Mini-Cog test (see online supplemental material 1)	Mini-Cog test (see online supplemental material 1)	Richmond Agitation and Sedation Scale RASS ≥ –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 23January 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 15min 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/mm^3.
- Thrombocytopenia<50 000/mm^3.

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]

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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 MOLLIEX, 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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Supplemental material 1: tests used for delirium assessment

CAM: CONFUSION ASSESSMENT METHOD

The Confusion Assessment Method (CAM) was created in 1990 by Dr. Sharon Inouye, and it was intended to be a bedside assessment tool usable by non-psychiatrists to assess for delirium [1]. Delirium is defined in terms of four diagnostic features and is deemed positive when Feature 1 and Feature 2 and either Feature 3 or 4 are present.

CAM Confusion Assessement Method		
	The diagnosis of delirium by CAM requires the presence of **BOTH** features ***A*** and ***B***	
	A = acute onset and fluctuating course	Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: ➢ come and go? ➢ fluctuate during the day? ➢ increase/decrease in severity?
	B = Inattention	Does the patient: ➢ have difficulty focusing attention? ➢ become easily distracted? ➢ have difficulty keeping track of what is said?
	AND the presence of **EITHER** feature **C** or **D**	
	C = Disorganized thinking	Is the patient's thinking ➢ disorganized ➢ incoherent For example, does the patient have ➢ rambling speech/irrelevant conversation? ➢ unpredictable switching of subjects? ➢ unclear or illogical flow of ideas?
	D = Altered level of consciousness	Overall, what is the patient's level of consciousness: ➢ alert (normal) ➢ vigilant (hyper-alert) ➢ lethargic (drowsy but easily roused) ➢ stuporous (difficult to rouse) ➢ comatose (unrousable)

MINI COG TEST

In order to rate the CAM, for each evaluation a formal cognitive testing using the Mini-Cog test will be performed. It is a 3-minute instrument that can increase detection of cognitive impairment in older adults. It consists of two components, a 3-item recall test for memory and a simply scored clock drawing test [2].

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

Scoring:

Word Recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing.
Clock Draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.
Total Score: _____ (0-5 points)	Total score = Word Recall score + Clock Draw score. A cut point of <3 on the Mini-CogTM has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

CAM-ICU : CONFUSION ASSESSMENT METHOD IN INTENSIVE CARE UNIT

The CAM-ICU is an adaptation of the CAM tool for use in ICU patients (e.g., critically ill patients on or off the ventilator) using nonverbal, objective tests derived through a comprehensive literature review and consultation with numerous delirium experts [3]. The CAM-ICU underwent extensive validation in the ICU setting and is, therefore, one of the delirium scores recommended by international guidelines [4].

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course A. Is there evidence of an acute change in mental status from baseline? **B.** Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidence by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Coam Glasgow Scale?	☐	☐
II. Inattention Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)	☐	☐
III. Disorganized thinking Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1-pound weigh more than 2 pounds 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up these many fingers (examiner holds 2 fingers in front of the patient) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient) (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such a rambling or irrelevant conversation, unclear or illogical flow or ideas, or unpredictable switching from subject to subject)	☐	☐
IV. Altered level of consciousness Is the patient level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environment and interacts appropriately Vigilant: hyperalert Lethargic drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally	☐	☐

Stupor: difficult to arouse, unaware of some or all elements, in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stupor subject lapse back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features I and II and either feature III or IV): YES ☐ NO ☐		

RASS = RICHMOND AGITATION-SEDATION SCALE

The Richmond Agitation Sedation Scale (RASS) is a component of the CAM-ICU (Feature 4: Altered Level of Consciousness). The RASS has been shown to be both reliable and valid in critically ill adults with and without mechanical ventilation and sedating medications [5].

RASS is a 10-point scale, with four levels of anxiety or agitation (+1 to +4 [combative]), one level to denote a calm and alert state (0), and 5 levels of sedation (−1 to −5) culminating in unarousable (−5). The values and definitions for each level of agitation and sedation are displayed below:

The Richmond Agitation-Sedation Scale (RASS)		
Score	**Term**	**Description**
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purpose full movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (< 10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but not eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Procedure for RASS assessment 1. Observe patient • Patient is alert, restless, or agitated 2. If nor alert, state patient's name and say to open eyes and look at speaker • Patient awakens with sustained eye opening and eye contact • Patient awakens with eye opening and eye contact but not sustained • Patient has any movement in response to voice but no eue contact 3. When no response to verbal stimulation, physical stimulate patient by shaking shoulder and/or rubbing sternum. • Patient has any movement to physical stimulation • Patient has no response to any stimulation	Score 0 to +4 Score -1 Score -2 Score -3 Score -4 Score -5

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Supplemental Material 2: Full statistical analysis plan

General considerations:
A flow-chart will describe the flow of patients during the study, from inclusion until Day-30, by randomization arm and by type of scheduled postoperative ward, either geriatric perioperative unit or another type of ward (stratification variable).

All variables will be described overall and by randomization arm. Categorical variables will be described by frequencies for all categories, and percentages; continuous variables will be described by their min, max, mean, standard deviation, and interquartile range. Number of missing values will also be described for all variables.

In this randomized control trial, the principal and secondary analyses will follow the intention-to-treat (ITT) principle.

Stratification variables are center and postoperative wards. The last one is a dichotomic variable: either geriatric perioperative unit or another type of ward.

Following the ITT principle, not operated patients will be analyzed according to their initial randomization group. Reasons for not operating include switching to palliative care or transferring to other facilities. For those patients, treatment will be stopped and data will be censored at the decision date of do not operate.

The maximum duration between inclusion and intervention will be of 5 days. Beyond that duration, treatment is stopped. For principal analyses, occurrence of delirium of patients with stopped treatment will be censored at Day-5. If eventually they are operated, sensibility analyses will include their data.

For coma operated patients, for whom CAM or CAM-ICU cannot be assessed, the delirium occurrence will be imputed by a most pejorative outcome of CAM scores on the day of coma onset.

All effect size will be presented together with their 95% confident intervals.

The significant level of all analyses is fixed to a bilateral (alpha) Type I error of 5%.

All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) 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.

Primary endpoint analysis:
Delirium occurrence at time T is defined as the first CAM or CAM-ICU assessment that retained the diagnosis of delirium.
In this population of elderly patients, the risk of death in the context of postoperative acute surgery of fractured lower limb is of 7% at Day-30. Therefore, it will be estimated the concurrent distribution of mortality in both groups while estimating the incidence of the treatment by melatonin on delirium.

Postoperative delirium cumulative incidence function (CIF) will be compared at Day-10 between the two randomized arms (melatonin vs. placebo) by means of a competing risks framework, using the Fine and Grey model [1] that allows to estimate CIF on the presence of concurrent causes of failure, deceased in our study, altering the probability of experiencing the event of interest, delirium. Death is the competing risk under consideration.

Patients alive on Day-10 without delirium occurrence will be censored at Day-10. Those lost to follow up will be censored on the date of latest news. Non operated patients will be censored on the decision date of do not operate.

Secondary endpoints analyses:

1- Following recommendations, cause-specific hazard will be calculated and compared between the study arms for both delirium and mortality at Day-30.
2- Proportion of days where the CAM or CAM-ICU are positive will be compared between randomized arms at Dat-10 using a linear regression adjusted by the stratification variables.
3- Administration at any postoperative time of sedative or antipsychotic drugs, evaluated at Day-10, or at the day of leave if shorter, will be compared between groups using a logistic regression adjusted by the stratification variables.
4- Occurrence of postoperative physical restrain at Day-10, or at the day of leave if shorter, will be compared between groups using a logistic regression adjusted by the stratification variables.
5- Occurrence of postoperative falls at Day-10, or at the day of leave if shorter, will be compared between groups using a logistic regression adjusted by the stratification variables.
6- The Mini Mental State Examination score at Day-10, or at the day of leave if shorter will be compared between randomized arms using a linear regression adjusted by center and type of postoperative. The MMSE score runs from 0 point (worst result) to 30 points (best result). Score of deceased patients will be interpreted as 0 point. Transferred patients will be evaluated before leaving the hospital.
7- Duration of hospital stay at Dat-30 will be compared using a linear regression adjusted by center and type of postoperative ward. Number of days of deceased or transferred patients will be counted until the day of leave.
8- Katz Index of activities of daily living is a score running from 0 point (best result) to 6 points (worst result). Scores of deceased patients will be interpreted as 6 points (worst scores). The score at Day-30 will be compared between randomized arms using a linear regression adjusted by center and type of postoperative ward.
9- Quality of life (utility values derived from the score at EQ-5D-5L questionnaire) will be compared between the randomized arms using a linear regression adjusted by center and type of postoperative ward (see questionnaire in supplementary material 1).
10- Occurrence of side effects at Day-10, or at the day of leave if shorter, will be compared between groups using a logistic regression adjusted by the stratification variables.
11- In order to evaluate morphine consumption and administration of anticholinergic drugs, since those drugs might work as confounding factors, the morphine consumption and anticholinergic drugs until D-10, or the day of leave if shorter, will be used. With respect

to morphine, cumulated morphine consumption will be standardized in equivalent of oral morphine according to the following table [2].

Medication name	Equivalent of oral morphine (mg)
Oral morphine (mg)	1 : 1
Subcutaneous morphine (mg)	1 : 2 (SC morphine x 2 = oral morphine equivalent)
Intravenous morphine IV (mg)	1 : 3 (IV morphine x 3 = oral morphine equivalent)
Oral Oxycodone (mg)	1 : 1,5 (oxycodone x 1,5 = oral morphine equivalent)
Oral hydromorphone (mg)	1 : 5 (hydromorphone x 5 = oral morphine equivalent)
Transdermal buprénorphine (ug/h)	1 : 1,7 (patch dosing x 1,7 = oral morphine equivalent for 24 hours)
Transdermal Fentanyl (ug/h)	1 : 2,4 (patch dosing x 2,4 = oral morphine equivalent for 24 hours)

Morphine and anticholinergic drugs consumption will be compared between groups using a logistic regression adjusted by the stratification variables. If this endpoint is statistically significant between groups, it will be used as adjusting factor for the secondary other endpoints. In-depth analyses about their consumption will be done between groups.

12- **Compliance to treatment** will be assessed using records of unused packaging and medical files. We will confront the dose actually absorbed by the patient to the prescribed and predicted dose (which will consider possible discontinuation of treatment). Comparisons will be performed between randomized arms using a linear regression adjusted by center and type of postoperative ward.

Univariate and then multivariate models will be performed to determine the relative contributions of factors to delirium (potential confounders, in the perspective of further adjustment, if necessary). The selection of variables for these models will be done considering the number of events, significant factors in univariate analyses and those clinically relevant. Of particular interest are: the automatic restraint of patients (or its part contributing to the center effect), age, chronic alcoholism, antipsychotic or sedative treatment.
A sensitivity analysis may be performed based on the time frame of the preoperative period.

Economic evaluation

The outcome measure for the economic evaluation will be the estimation of the cost-effectiveness of melatonin. Because of the short duration of the follow up (30 days) the difference in quality-adjusted life year (QALY) 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. Quality of life will be assessed using the EuroQol EQ-5D-5L questionnaire as now recommended by the French national health authority.

The analysis will follow the French Health Authority and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines on economic evaluation in health care. [3,4]

Trial follow-up: Quality of life (assessed at hospital discharge and at 1 month, postoperative complications and use of hospital resources (emergency room visits, hospital admissions) will be obtained by collection of data during the initial hospital stay and then by telephone call from a clinician or a study nurse, at 1month. In addition, a double checking of the use of hospital-related resources after the initial discharge will be made via hospital databases.

Calculation of costs: Cost calculation will include all the hospital-related costs over a one-month period. Owing to the impact of a delirium on the use of hospital resources (ICU and in-hospital length of stay), the estimation of costs will focus on hospital costs. Primary care-related costs will not be analysed. The rates for the hospital stay will be calculated with respect to the Diagnosis Related Groups, adjusted for the patients' length of stay. Unit costs are presented in the following table.

Type of service/ product	**Unit cost (€)**	**source**
Melatonin	1€ per tablet	French red book (Vidal)
Surgery ward day	700-800	scansante
REA (resuscitation supplement)	804	scansante
STF (intensive care supplement)	402	scansante

Calculation of QALYs: EQ5D5L scores will be converted into utilities using the French value set [5]. QALYs will be calculated using the area under the curve approach. Missing data on EQ-5D score and health-care costs will be imputed with multiple imputations by chained equations, assuming data missing at random.

The value of the melatonin treatment will be determined with respect to 1) the extra cost and 2) its potentially beneficial impact on both quality of life and adverse events. QALY, the commonly used generic measure of disease burden, will be used. The overall cost difference between the standard- and melatonin treatments will be assessed via the calculation of the incremental cost-effectiveness ratio (ICER), expressed as € per QALY:

$$ICER = \frac{C\ melatonin - C\ standard\ management}{QALY\ melatonin - QALY\ standard\ managment}$$

To refine the 95% confidence interval of these parameters, the bootstrapping technique will be used. We will compare the result to the usually applied thresholds of €50,000-100,000/QALY and calculate the probability of cost-effectiveness from the bootstrapped probabilistic sensitivity analysis.

A complete case analysis will be performed on the population for whom all cost and effectiveness (EQ5D5L and 1-month clinical outcomes) and data are available. Secondarily, after imputation of missing data, an intention-to-treat analysis will be performed.

Of note, the sample size calculation has been based upon clinical outcomes, mostly for ethical reasons: the clinical outcome takes precedence over the efficiency of the allocation of healthcare resources. Hence, we input the 718 patients sample size into Glick's formula [6]. This sample size will allow testing for the existence of a difference of €800 and 0.04 QALYs at the €100,000/QALY threshold between standard management and melatonin, respectively [7].

Hospital length of stay, ICU length of stay, will be analysed using Cox proportional-hazards models.

State whether subjects who exit the study prematurely will be replaced and in what proportion: Patients exiting the study prematurely will not be replaced.

Anticipated level of statistical significance: The statistically significant level is fixed for all analyses as a bilateral (alpha) Type I error of 5%.

Statistical criteria for termination of the study: Not applicable.

Method for considering missing, unused or invalid data: Missing data will be described for all variables globally and by treatment group. Missing data for the principal endpoint will be censored at the last date of follow-up or at the day of latest news.

If eventually one of the 10 assessments on delirium is missing, but the following is available and consistent with the previous assessment, the missing data will be imputed by the closest value. If the available data before and after and missing data are discordant, imputation will follow two scenarios (absence or presence of delirium).

Management of modifications made to the analysis plan for the initial strategy: All major modifications to the planned analysis will be submitted to approval of the scientific committee and of the ethics committee (CPP).

Selection of populations: All analyses will follow the intention-to-treat principle.

The primary analysis will be repeated on population per protocol: only patients in the intervention group who absorbed at least 90% of the prescribed treatment before delirium occurrence or competitive event, and patients of the control group who have not received melatonin (or less than 10% of an equivalent dose of melatonin) will be included in this analysis.
Patients wrongly included, secondary excluded or lost to follow-up will not be considered in this analysis. No patient will be reclassified.

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IDRCB : 2019-003210-14 APHP_180594

Titre complet de recherche : **Mélatonine dans la prévention du délirium postopératoire après une chirurgie pour fracture du membre inférieur chez les patients âgés : un essai contrôlé randomisé. Etude DELIRLESS**

Cette recherche est promue par l'Assistance Publique - Hôpitaux de Paris
Délégation à la Recherche Clinique et à l'Innovation
1 avenue Claude Vellefaux
75010 Paris

NOTE D'INFORMATION

Madame, Monsieur,

Le Docteur / Le Professeur (barrée la mention inutile)…….
(nom, prénom), exerçant à l'hôpital ……, vous propose de participer à une recherche.
Il est important de lire attentivement cette note avant de prendre votre décision ; n'hésitez pas à lui demander des explications. Si vous le souhaitez, vous pouvez demander l'avis d'une personne de confiance de votre choix avant de prendre votre décision.
Si vous décidez de participer à cette recherche, un consentement écrit vous sera demandé.

1) Quel est le but de cette recherche ?

Cette recherche porte sur la confusion postopératoire, aussi appelé délirium postopératoire, qui est l'une des complications les plus fréquentes après une intervention chirurgicale chez les patients âgés. Nous pensons qu'un médicament (la mélatonine) pourrait diminuer la survenue de confusion postopératoire. Cependant, des preuves scientifiques supplémentaires sont nécessaires pour valider cette hypothèse.

2) En quoi consiste la recherche ?

Dans la recherche proposée, nous allons évaluer l'effet de ce médicament (la mélatonine) en traitement préventif du délirium postopératoire. Pour cela nous allons traiter une partie des personnes avec le médicament et l'autre partie avec un placebo.
L'attribution du médicament ou du placebo se fera par tirage au sort. Ni vous ni le médecin qui vous suit ne sauront si vous prenez le médicament ou le placebo. Il est prévu d'inclure dans ce protocole de recherche 790 personnes âgées de 70 ans ou plus présentant une fracture entre la hanche et le genou pour laquelle elles doivent être opérées, dans environ une vingtaine d'établissements de soins situés en France.

3) Quel est le calendrier de la recherche ?

La durée prévisionnelle de la recherche est de 2 années et 1 mois et votre participation sera de 36 jours maximum. Après la signature de votre consentement, lors de la consultation d'anesthésie, les examens pour la recherche seront les suivants :

- Un prélèvement sanguin de 2 tubes de sang de 4 mL pour évaluer le fonctionnement de votre foie et votre rein pourra être réalisé si un bilan de moins de 3 mois n'est pas disponible.

Sigaut S, *et al. BMJ Open* 2021; 11:e053908. doi: 10.1136/bmjopen-2021-053908

- une évaluation de la confusion par un bref échange avec un proche ou un soignant vous connaissant et par un questionnaire adapté sera réalisée.

Si les résultats sanguins ne vous permettent pas de prendre le médicament de l'étude ou si le questionnaire détecte une confusion, alors il ne sera pas possible de participer à l'étude.

Si votre participation est validée par ces tests, la visite sera complétée par d'autres questionnaires qui permettent d'évaluer :

- Votre autonomie préopératoire,
- Votre Qualité de vie préopératoire,
- L'existence d'une dépression,
- Votre état cognitif préopératoire.

Puis le tirage au sort sera effectué.
Vous bénéficierez soit du traitement avec le médicament (mélatonine) soit d'un placebo. Dans les 2 cas vous prendrez deux comprimés une fois par jour, les soirs précédant la chirurgie et pendant 5 jours après celle-ci.

Ensuite, pendant les 10 jours suivant l'intervention (ou moins si vous sortez avant de l'hôpital), une évaluation de la confusion par un questionnaire adapté sera réalisée chaque jour. Le dernier jour, une nouvelle évaluation de votre état cognitif sera faite.

Enfin, 30 jours après votre intervention, nous vous contacterons par téléphone pour évaluer grâce à des questionnaires votre autonomie et votre qualité de vie postopératoire.

Votre participation à cette étude implique donc la **prise d'un traitement** (médicament actif ou placebo) pour une durée de 6 à 10 jours en fonction du délai entre la consultation d'anesthésie et la date de la chirurgie.
Nous vous demanderons aussi de **répondre à des questionnaires** :

- Lors de la consultation d'anesthésie : Indice de Katz (autonomie), ED5Q5L (qualité de vie), mini GDS (dépression), CAM (confusion), MMSE (état cognitif)
- Chaque jour pendant les 10 jours suivant votre chirurgie (ou jusqu'au jour de votre sortie) : CAM ou CAM-ICU (confusion) et le dernier jour MMSE (état cognitif)
- 30 jours après la chirurgie, lors d'un appel téléphonique si vous êtes sorti de l'hôpital : Indice de Katz (autonomie), ED5Q5L (qualité de vie)

Si la chirurgie devait avoir lieu plus de 5 jours après la visite d'anesthésie, le traitement serait interrompu et vous seriez exclu secondairement de l'étude.

4) Quels sont les bénéfices liés à votre participation ?

Les bénéfices attendus pour les patients sont une baisse du taux de confusion post opératoire dans le groupe recevant de la mélatonine.

5) Quels sont les traitements autorisés et non autorisés ?

Au moment où commence l'étude vous ne devez pas avoir comme traitement en cours de la fluvoxamine, du 5- ou 8-méthoxypsoralène, de la cimétidine, de l'œstrogénothérapie, des quinolones, du carbamazépime, de la rifampicine. Si ces traitements s'avèrent ensuite absolument nécessaires lors de votre prise en charge sur la période de l'étude, vos médecins pourront vous les prescrire, mais ils risquent d'augmenter ou de diminuer les effets de la mélatonine.

6) Quels sont les risques et les contraintes prévisibles ajoutés par la recherche ?

Les risques prévisibles de la recherche sont les effets indésirables attendus du médicament de l'étude (mélatonine ou Circadin®). Ceux-ci sont listés ci-après avec leur fréquence :

Peu fréquents (moins de 1% des cas) : fatigue, douleur thoraciques, irritabilité, nervosité, agitation, rêves anormaux, cauchemars, impatience, anxiété, maux de tête, migraine, léthargie, hyperactivité psychomotrice, étourdissement, insomnie ou au contraire somnolence, hypertension artérielle, douleurs abdominales, digestion difficile, nausées, ulcération buccale, bouche sèche, sueurs nocturnes, démangeaisons, rougeur cutanée, sécheresse de la peau, douleur de extrémités, prise de poids, augmentation du taux de bilirubine et anomalies du bilan hépatique.

Rares (moins de 0,1% des cas): troubles de l'humeur, agressivité, agitation, désorientation, réveil tôt le matin, état dépressif, augmentation de la libido, malaise, troubles de la mémoire ou de l'attention, syndrome des jambes sans repos, fourmillement des extrémités, troubles de la vue, larmoiement, vertiges, angine de poitrine, palpitations, bouffées de chaleur, reflux gastro-oesophagien, brûlures d'estomac, aphtes, vomissements, ballonnements, gêne abdominale, hypersécrétion salivaire, mauvaise haleine, herpès zoster, eczéma, éruption cutanée généralisée, douleur articulaire ou du cou, crampes nocturnes, priapisme, augmentation des transaminases, baisse du taux de globules blanc et de plaquettes, augmentation du taux de triglycéride, baisse du taux de calcium et de sodium, augmentation du taux des enzymes hépatiques, présence de protéines ou de sucre dans les urines, priapisme, prostatite.

Fréquence indéterminée : réaction d'hypersensibilité, œdème buccal, œdème de la langue, galactorrhée

Les contraintes liées à l'étude sont de prendre le traitement de l'étude pendant votre hospitalisation et de répondre aux questionnaires lors de la visite d'anesthésie, pendant les 10 jours qui suivent la chirurgie et 30 jours après celle-ci soit lors de votre hospitalisation soit par téléphone si vous êtes rentré chez vous.

Si vous acceptez de participer, vous devrez respecter les points suivants :

- Informer le médecin de la recherche, de l'utilisation de tout médicament ainsi que de tout événement survenant pendant la recherche (hospitalisation…)
- Ne pas prendre part à un autre projet de recherche sans l'accord de votre médecin, ceci pour vous protéger de tout accident possible pouvant résulter par exemple d'incompatibilités possibles entre les médicaments étudiés ou d'autres dangers
- Etre affilié(e) à un régime de sécurité sociale ou être bénéficiaire d'un tel régime.

8) Quelles sont les éventuelles alternatives médicales ?

Si vous ne souhaitez pas participer à cette étude, vous bénéficierez de la prise en charge chirurgicale habituelle sans traitement pharmacologique préventif du délirium postopératoire.

9) Quelles sont les modalités de prise en charge médicale à la fin de votre participation ?

Arrêt prématuré du traitement : Il peut y avoir un arrêt prématuré du traitement si vous ne supportez pas le traitement. Dans ce cas vous poursuivrez néanmoins votre participation à l'étude (réponses aux questionnaires) comme prévu initialement.
Vous pouvez aussi arrêter de prendre le traitement et de participer à cette recherche si votre chirurgie est reportée et que le délai entre la consultation d'anesthésie et la chirurgie dépasse les 5 jours.
Arrêt prématuré de la recherche : Si la recherche est interrompue prématurément, la prise du traitement pourra être interrompue. Vous continuerez à être suivi dans le cadre de la recherche jusqu'à la fin de votre participation.
Votre médecin pourra décider à tout moment de l'arrêt de votre participation ; il vous en expliquera les raisons.

10) Si vous participez, comment vont être traitées les données recueillies pour la recherche ?

Dans le cadre de la recherche à laquelle l'AP-HP vous propose de participer, un traitement de vos données personnelles va être mis en œuvre pour permettre d'en analyser les résultats.

Ce traitement est nécessaire à la réalisation de la recherche qui répond à la mission d'intérêt public dont est investie l'AP-HP en tant qu'établissement public de santé hospitalo-universitaire

A cette fin, les données médicales vous concernant et les données relatives à vos habitudes de vie, seront transmises au Promoteur ou aux personnes ou partenaires agissant pour son compte, en France. Ces données seront identifiées par un numéro d'enregistrement. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.
Les données médicales vous concernant pouvant documenter un dossier auprès des autorités compétentes portant sur le médicament évalué dans cette recherche, pourront être transmises à un industriel afin qu'un plus grand nombre de patients puissent bénéficier des résultats de la recherche. Cette transmission sera faite dans les conditions assurant leur confidentialité.

Vos données pourront être utilisées pour des recherches ultérieures ou des analyses complémentaires à la présente recherche en collaboration avec des partenaires privés ou publics, en France ou à l'étranger, dans des conditions assurant leur confidentialité et le même niveau de protection que la législation européenne.
Vous pouvez retirer à tout moment votre consentement à l'utilisation ultérieure de vos données auprès du médecin qui vous suit dans le cadre de cette recherche.

Vos données ne seront conservées que pour une durée strictement nécessaire et proportionnée à la finalité de la recherche. Elles seront conservées dans les systèmes d'information du responsable de traitement jusqu'à deux ans après la dernière publication des résultats de la recherche.

Le fichier informatique utilisé pour cette recherche est mis en œuvre conformément à la règlementation française (loi Informatique et Libertés modifiée) et européenne (au Règlement Général sur la Protection des Données -RGPD). Vous disposez d'un droit d'accès, de rectification et d'opposition au traitement des données couvertes par le secret professionnel utilisées dans le cadre de cette recherche. Ces droits s'exercent auprès du médecin en charge de la recherche qui seul connaît votre identité (identifié en première page du présent document).

Si vous décidez d'arrêter de participer à la recherche, les données recueillies précédemment à cet arrêt seront utilisées conformément à la réglementation, et exclusivement pour les objectifs de cette recherche. En effet, leur effacement serait susceptible de compromettre la validité des résultats de la recherche. Dans ce cas, vos données ne seront absolument pas utilisées ultérieurement ou pour une autre recherche.

En cas de difficultés dans l'exercice de vos droits, vous pouvez saisir le Délégué à la Protection des données de l'AP-HP à l'adresse suivante : protection.donnees.dsi@aphp.fr, qui pourra notamment vous expliquer les voies de recours dont vous disposez auprès de la CNIL.
Vous pouvez également exercer votre droit à réclamation directement auprès de la CNIL (pour plus d'informations à ce sujet, rendez-vous sur le site www.cnil.fr).

11) Comment cette recherche est-elle encadrée ?

L'AP-HP a pris toutes les mesures pour mener cette recherche conformément aux dispositions du Code de la Santé Publique applicables aux recherches impliquant la personne humaine.

L'AP-HP a souscrit une assurance (N° d'adhésion) garantissant sa responsabilité civile et celle de tout intervenant auprès de la compagnie HDI–GERLING par l'intermédiaire de BIOMEDICINSURE dont l'adresse est Parc d'Innovation Bretagne Sud C.P.142 56038 Vannes Cedex.

L'AP-HP a obtenu l'avis favorable du Comité de Protection des Personnes pour cette recherche [*indiquer le nom du CPP*] le *[indiquer la date de la séance au format jj /mm /aaaa]* et une autorisation de l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) le *[indiquer la date au format jj /mm /aaaa].*

12) Quels sont vos droits ?

Votre participation à cette recherche est entièrement libre et volontaire. Votre décision n'entraînera aucun préjudice sur la qualité des soins et des traitements que vous êtes en droit d'attendre. Si vous le souhaitez, vous pouvez demander l'avis d'une personne de confiance de votre choix avant de prendre votre décision.

Avant d'accepter de participer à cette recherche, vous bénéficierez d'un examen médical adapté, dont les résultats vous seront communiqués.

Vous pourrez tout au long de la recherche demander des informations concernant votre santé ainsi que des explications sur le déroulement de la recherche au médecin qui vous suit.

Vous pouvez vous retirer à tout moment de la recherche sans justification, sans conséquence sur la suite de votre traitement ni la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre médecin. A l'issue de ce retrait, vous pourrez être suivi par la même équipe médicale. Dans ce cas, les données collectées jusqu'au retrait seront utilisées pour l'analyse des résultats de la recherche.

Votre dossier médical restera confidentiel et ne pourra être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par l'AP-HP pour la recherche et soumises au secret professionnel.

A l'issue de la recherche et après analyse des données relatives à cette recherche, vous pourrez être informé(e) des résultats globaux en le demandant au médecin qui vous suit dans le cadre de cette recherche.

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.

Après avoir lu toutes ces informations, discuté tous les aspects avec votre médecin et après avoir bénéficié d'un temps de réflexion suffisant, si vous acceptez de participer à la recherche vous devrez signer et dater le formulaire de consentement éclairé se trouvant à la fin de ce document.

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

FORMULAIRE DE CONSENTEMENT

Je soussigné(e), M^me^, M. *[rayer les mentions inutiles]* (*nom, prénom*)……..
accepte librement de participer à la recherche intitulée « Mélatonine dans la prévention du délirium postopératoire après une chirurgie de fracture du membre inférieur chez les patients âgés : un essai contrôlé randomisé. Etude DELIRLESS » organisée par l'Assistance Publique - Hôpitaux de Paris et qui m'est proposée par le Docteur / Le Professeur (*nom, prénom, téléphone*)……, investigateur dans cette recherche.

- J'ai pris connaissance de la note d'information version du 05/02/2020 [5 pages] m'expliquant l'objectif de cette recherche, la façon dont elle va être réalisée et ce que ma participation va impliquer,
- je conserverai un exemplaire de la note d'information et du consentement,
- j'ai reçu des réponses adaptées à toutes mes questions,
- j'ai disposé d'un temps suffisant pour prendre ma décision,
- j'ai compris que ma participation est libre et que je pourrai interrompre ma participation à tout moment, sans encourir la moindre responsabilité et préjudice pour la qualité des soins qui me seront prodigués.
- j'ai été informé que les données recueillies dans le cadre de la recherche peuvent être réutilisées pour des recherches ultérieures, et que je pouvais m'y opposer à tout moment
- Je suis conscient(e) que ma participation pourra aussi être interrompue par le médecin si besoin, il m'en expliquera les raisons,
- avant de participer à cette recherche, j'ai bénéficié d'un examen médical adapté à la recherche, dont les résultats m'ont été communiqués,
- j'ai compris que pour pouvoir participer à cette recherche je dois être affilié(e) à un régime de sécurité sociale ou bénéficiaire d'un tel régime. Je confirme que c'est le cas
- j'ai bien été informé(e) que ma participation à cette recherche durera au maximum 36 jours et que cela implique que je ne pourrai pas envisager de participer à une autre recherche sans en informer le médecin qui me suit pour la recherche,
- mon consentement ne décharge en rien le médecin qui me suit dans le cadre de la recherche ni l'AP-HP de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi.

Signature de la personne participant à la recherche		**Signature du médecin**	
Nom Prénom :		Nom Prénom :	
Date :	Signature :	Date :	Signature :

Ce document est à réaliser en 3 exemplaires, un exemplaire doit être conservé 15 ans par l'investigateur, le deuxième remis à la personne donnant son consentement et le troisième transmis à l'AP-HP sous enveloppe scellée à la fin de la recherche.