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Dexmedetomidine after Cardiac Surgery for Prevention of Delirium (EXACTUM) trial protocol: a multicentre randomised, double-blind, placebo-controlled trial

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ABSTRACT

Introduction Incidence of delirium after cardiac surgery remains high and delirium has a significant burden on short-term and long-term outcomes. Multiple causes can trigger delirium occurence, and it has been hypothesised that sleep disturbances can be one of them. Preserving the circadian rhythm with overnight infusion of low-dose dexmedetomidine has been shown to lower the occurrence of delirium in older patients after non-cardiac surgery. However, these results remain controversial. The aim of this study was to demonstrate the usefulness of sleep induction by overnight infusion of dexmedetomidine to prevent delirium after cardiac surgery.

Methods and analysis Dexmedetomidine after Cardiac Surgery for Prevention of Delirium is an investigator-initiated, randomised, placebo-controlled, parallel, multicentre, double-blinded trial. Nine centres in France will participate in the study. Patients aged 65 years or older and undergoing cardiac surgery will be enrolled in the study. The intervention starts on day 0 (the day of surgery) until intensive care unit (ICU) discharge; the treatment is administered from 20:00 to 08:00 on the next day. Infusion rate is modified by the treating nurse or the clinician with an objective of Richmond Agitation and Sedation Scale score from –1 to +1. The primary outcome is delirium occurrence evaluated with confusion assessment method for the ICU two times per day during 7 days following surgery. Secondary outcomes include incidence of agitation related events, self-evaluated quality of sleep, cognitive evaluation 3 months after surgery and quality of life 3 months after surgery. The sample size is 348.

Ethics and dissemination The study was approved for all participating centers by the French Central Ethics Committee (Comité de Protection des Personnes Ile de France VI, registration number 2018-000850-22). The results will be submitted for publication in peer-reviewed journals.

Trial registration number NCT03477344.

Strengths and limitations of this study

► The Dexmedetomidine after Cardiac Surgery for Prevention of Delirium trial is an investigator-initiated, multicentre, double-blinded randomised controlled trial.

► The studied population is a representative sample of patients undergoing cardiac surgery.

► Delirium will only be assessed with confusion assessment method for the intensive care unit (ICU) two times per day during the 7 days following surgery.

► One main limitation is that patients can only receive allocated treatment during their ICU stay.

► Sample size calculation of this study is based on highly variable incidence of postoperative delirium found in previous studies, exposing the study to be underpowered if the incidence of delirium is lower than expected.

INTRODUCTION

Incidence of delirium is high after cardiac surgery, with a rate of 20%–55%,[1 2] depending on the studies. Delirium is characterised by an acute onset of mental status changes with fluctuating inattention, disorganised thinking and altered level of consciousness. In intensive care unit (ICU) settings, screening tools allow care givers to diagnose delirium accurately. Among the screening tools, the most reliable and widely used is the confusion assessment method for the intensive care unit (CAM-ICU). The CAM-ICU is easy to perform by caregivers and research staff, and it has excellent sensitivity and specificity.[3] Three subtypes of delirium are commonly described: calm, agitated or mixed delirium.

Delirium has an independent negative effect on outcome. Whatever the subtype, delirium is associated with short-term adverse events[4] (eg, prolonged length of stay, prolonged mechanical ventilation and agitation-related events) and worse long-term

outcome.[5] Thereby, patients suffering from delirium in the ICU may experience cognitive impairment and higher morbidity and mortality in the months following ICU discharge.[6]

It is therefore critical to prevent, diagnose and treat delirium in ICU patients. If diagnosis is made easier by screening tools, only few interventions have demonstrated their efficacy to prevent and treat delirium. Several pharmacological strategies to prevent and treat delirium have been tested over the past 10 years. However, methodological limitations and controversial results did not allow formulation of high-grade recommendations. Given the lack of efficacy in preventing or treating delirium of the tested treatment to date, guidelines do not support the use of any drug to treat or prevent delirium. As such, current guidelines support the use of non-pharmacological therapy to prevent delirium while highlighting the low quality of evidence.[7–9]

Although sleep disturbances are common in the ICU, their causal link with delirium remains to be demonstrated. Some physiological studies have shown links between sleep deprivation, inflammation and delirium.[10] Moreover, impairment of sleep architecture and circadian rhythm has been proven to have a negative effect on all physiological functions.[11] As sleep and circadian rhythm are seriously impaired in ICU patients, it seems critical to prevent and treat sleep disturbances in those patients. Dexmedetomidine sedation is associated with neurophysiological patterns more similar to normal sleep patterns[12] compared with other molecules such as gamma-aminobutyric acid (GABA) receptors agonists. Thus, dexmedetomidine seems effective in restoring physiological sleep in ICU patients.[13] Burry and coworkers reported recently in a network meta-analysis study that dexmedetomidine may reduce the occurrence of delirium in a selected population of patients.[14] Furthermore, in a randomised placebo controlled trial,[15] overnight prophylactic low dose of dexmedetomidine decreased delirium incidence in patients aged 65 years and older and admitted to the ICU after non-cardiac surgery. In this study, the delirium-preventing effect of dexmedetomidine was persistent even after treatment discontinuation and ICU discharge. Patients' quality of sleep was self-evaluated as a secondary outcome and was significantly improved in the dexmedetomidine group. However, the primary outcome of this trial was not confirmed in the recently published Dexmedetomidine for Reduction of Atrial Fibrillation and Delirium after Cardiac Surgery (DECADE) study.[16] The DECADE study is a randomised controlled trial testing the effect of low-dose dexmedetomidine infusion on delirium and atrial fibrillation after cardiac surgery. The infusion was started right before the beginning of the surgical procedure and maintained for 24 hours. There were no significant differences in the occurrence of atrial fibrillation nor in the occurrence of delirium. Quality of sleep was not assessed in the DECADE study.

The Dexmedetomidine after Cardiac Surgery for Prevention of Delirium (EXACTUM) trial hypothesises that nocturnal administration of dexmedetomidine prevents postoperative delirium.

MATERIALS AND METHODS

Trial design

The EXACTUM trial is an investigator-initiated, randomised, controlled, parallel, multicentre, double-blinded trial. Nine centres in France will participate in the study. In each centre, more than 500 cardiac surgery cases are performed every year and patients are routinely admitted to an ICU after surgery.

Selection of patients

Inclusion criteria

For inclusion, patients must meet the following criteria:
- Aged 65 years or older.
- Cardiac surgery with or without cardiopulmonary bypass.
- Ability to provide consent.

Exclusion criteria

For any of the following criteria, patients will not be included in the study:
- Documented cognitive failure or dementia, defined by the presence of the diagnosis in medical records.
- Previous inclusion in a study on sedation or analgesia.
- Predicted length of stay in the ICU of <24 hours.
- Alpha 2 agonist allergy or intolerance.
- Emergency surgery in immediate life-threatening situation.
- Uncontrolled hypotension (determined by the treating provider).
- Second-grade or third-grade atrio ventricular block in the absence of a pacemaker.
- Hepatocellular insufficiency defined by the presence of the diagnosis in medical records.
- Altered laboratory tests of hepatic function (transaminases and bilirubin).
- Acute cerebrovascular disease (cerebrovascular disease, defined using medical records; acute cerebrovascular disease, defined as a patient undergoing acute treatment for a recent stroke).
- Current clonidine treatment.
- Patients under guardianship or curatorship.

Recruitment modality

Screening for inclusion is performed in patients with surgical procedure indicated by a cardiologist and a cardiac surgeon (figure 1). In most cases, procedures are elective and patients are seen in a scheduled consultation with an anaesthesiologist a few weeks before surgery. Eligible patients attending a scheduled consultation are asked for consent and included in the study (see patient consent form in online supplemental file 1). In case of semiurgent surgery, patients are admitted in the referent hospital for cardiac surgery in the days following an acute cardiac problem. Eligible patients of this type will be

Time point	Pre inclusion (surgery consultation)	Inclusion visit (anesthesia consultation)	Surgery Day 0	Day 0 to day 7	3 months after surgery (phone call)
Screening	X				
Inclusion/exclusion criterion checking		X			
Informed consent		X			
Medical history		X			
Randomization		X			
Clinical investigation: CAM ICU				2 times per day	
Quality of sleep questionnaire		X			
Sleep quality self-evaluation				Once a day	
Intervention			X		X
Dexmedetomidine or Placebo			Start of treatment administration	End of administration between day 2 and day 7	
Observance				X	
Adverse events and severe adverse events			X	X	X

Figure 1 Study calendar. CAM-ICU, confusion assessment method for the intensive care unit.

screened on their arrival in the hospital and approached for consent.

Randomisation

A randomisation list will be created by the data management unit of the Brest University Hospital. Randomisation will be centralised, web-based and accessible 24 hours a day according to the allocation list. A blocked randomisation with randomly selected block sizes will be performed. Randomisation will be stratified on centres and modality of surgery between on and off pump. Patients will be randomised either in the dexmedetomidine group or the placebo group (figure 2). After randomisation, patients will participate in the study until 3 months after surgery when the last follow-up takes place (figure 1).

Blinding and treatment suspension

Experimental treatment is dexmedetomidine diluted at 100 µg/mL conditioned in vials of 2 mL. The placebo is sodium chloride diluted at 9 g/L conditioned in vials of 2 mL. The size and shape of the two vials and the colour and texture of the two treatments are strictly identical. Blinding will be performed by the pharmacist at the coordinating centre by erasing the original label of the vials and then labelling them accordingly to study treatment.

The receipt, blinding, labelling, storage and distribution of treatment will be centralised in the pharmacy of the coordinating centre and dispatched to the pharmacy of each participating centre (figure 3).

The treatment can be interrupted if it is supposed to be responsible for adverse effects. The supposed ineffectiveness of the treatment to promote sleep is not a valid reason to stop the treatment infusion.

As dexmedetomidine is a short-acting drug with no antidote, the first intervention in the presence of a suspected serious adverse event is the discontinuation of the infusion. A treatment interruption is not a valid reason for unblinding. Unblinding is only allowed if knowledge of the allocated treatment will influence patient care. If unblinding is wished by a clinician in charge of a patient
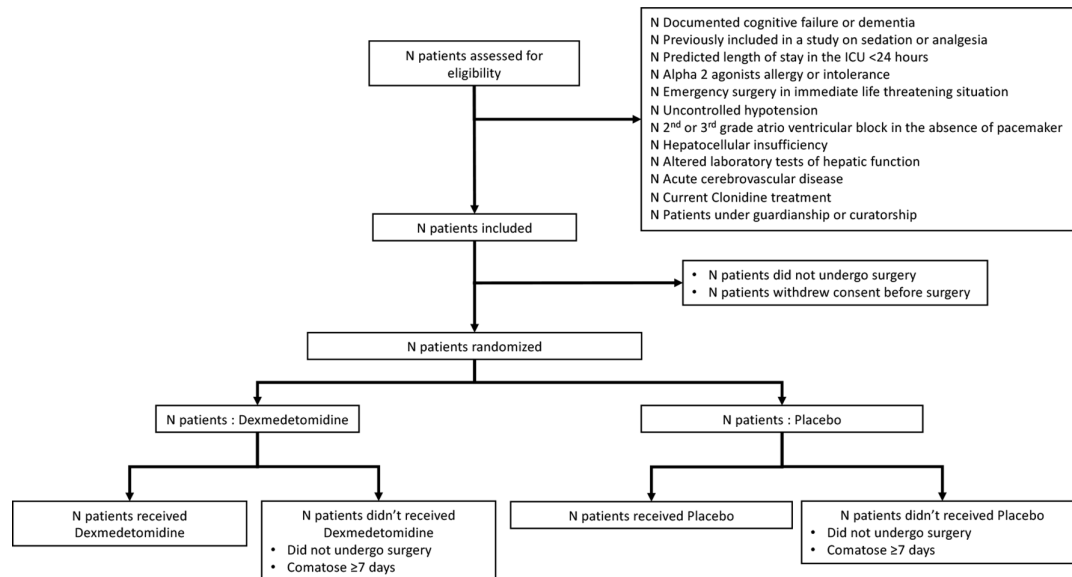
Figure 2 Consolidated Standards of Reporting Trials diagram of the study. ICU, intensive care unit.

enrolled in the study, the reason for unblinding must be validated by the principal investigator.

A list of known side effects of dexmedetomidine is provided to clinicians in charge of the participant in the protocol. All adverse events must be declared, whether they are known side effects or not.

Known dexmedetomidine side effects

Metabolic disorder

Common (1%–10%): hyperglycaemia and hypoglycaemia.

Uncommon (0.1%–1.0%): metabolic acidosis and hypoalbuminaemia.

Psychiatric disorder

Common (1%–10%): agitation.

Uncommon (0.1%–1.0%): hallucination.

Cardiac effects

Very common (10% or more): bradycardia.

Common (1%–10%): myocardial infarction and tachycardia.

Uncommon (0.1%–1.0%): atrioventricular blockade, cardiac output decrease and cardiac arrest.

Vascular effects

Very common (10% or more): hypotension and hypertension.

Respiratory disorder

Common (1%–10%): respiratory depression.

Uncommon (0.1%–1.0%): dyspnoea and apnoea.

Gastrointestinal disorder

Common (1%–10%): nausea, vomiting and dry mouth.

Uncommon (0.1%–1.0%): abdominal distension.

Renal and urinary tract effects

Frequency not reported: polyuria.

General effects and administration site

Common (1%–10%): withdrawal syndrome and hyperthermia.

Uncommon (0.1%–1.0%): treatment inefficacy and thirst.

Participant withdrawal

Patients can withdraw consent at any time point of the study without justification needed. Patients will be excluded from the trial if they withdraw consent; as a result, the treatment will no longer be infused to the
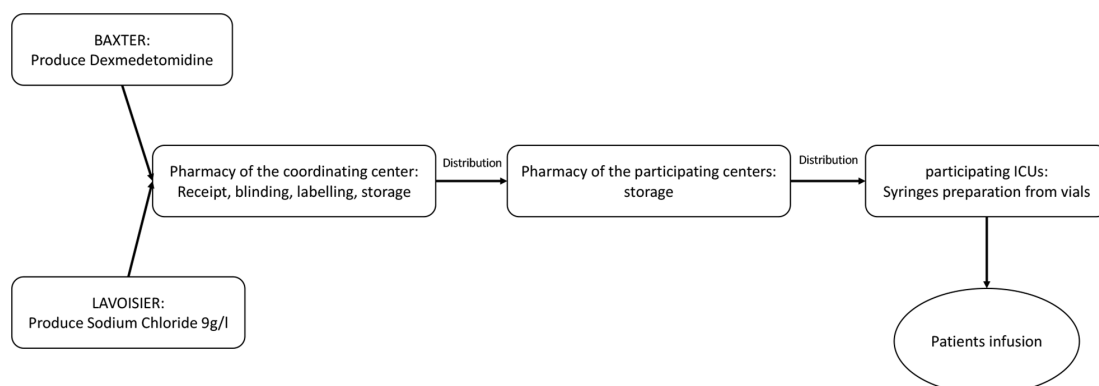

Figure 3 Management of the study treatment from production to infusion. ICU, intensive care unit.

patient. If the patient does not object to use their data concerning primary outcome, these data will be collected.

Trial intervention
Standard care
Patients are admitted intubated in the ICU after surgery. Fast tracking in cardiac surgery principles are applied in participating centres. Sedation is stopped unless patients are severely shocked (uncontrolled hypotension and decreased tissue perfusion) or hypothermic; therefore, in most patients, weaning from mechanical ventilation is effective in the following hours after surgery. Multimodal analgesia is a standard of care in the participating centres. In the participating centres, delirium prevention relies on the ABCDEF bundle[17]; medical and paramedical staff are trained to diagnose delirium with the CAM-ICU.

Modality of experimental treatment administration
In the experimental group: dexmedetomidine is diluted to 0.4 µg/mL and administered with electric syringe. From day 0 (the day of surgery), the treatment is administered from 20:00 to 08:00 on the next day. Minimal dose is 0.1 µg/kg/hour and maximum dose is 1.4 µg/kg/hour. Starting dose is 0.1 µg/kg/hour. Infusion rate is modified by the treating nurse or the clinician by 0.1 µg/kg/hour every hour with an objective of Richmond Agitation and Sedation Scale (RASS) from −1 to +1. The treatment is administered in the same way until the patient ICU discharge or after 7 days of ICU stay. Dexmedetomidine can only be prescribed and administered to patients in ICU or HDU (High Dependency Unit) settings as it requires close surveillance and monitoring of the patients due to its potential harmful side effects. Therefore, once patients are transferred to a surgical ward, the experimental treatment is no longer administered.

In the particular case of a patient admitted in the ICU after surgery between 20:00 and midnight, day 0 is considered the next calendar day and the treatment administration is debuted at 20:00 on that day.

In the placebo group, the treatment is sodium chloride 0.9% administered with electric syringe. Infusion follows the same rules as in the experimental group.

The infusion of the treatment in an ICU setting is mandatory. Given the risk of haemodynamic and cardiac side effects of the treatment, surveillance during infusion must include continuous cardiac monitoring and continuous or intermittent blood pressure monitoring.

Concomitant treatment allowed
Clinicians are allowed to use whatever treatment deemed necessary for the patient.

Unauthorised concomitant treatment
Open-label use of the experimental treatment dexmedetomidine is not authorised. Clonidine has similar pharmacological targets and effects as dexmedetomidine; it is therefore not authorised to use clonidine during the study.

Summary of outcomes
Primary outcome
Delirium occurrence was evaluated with CAM-ICU two times per day during the 7 days following surgery. CAM-ICU evaluation will be performed by clinicians in charge of the patient or by research staff. All staff members performing CAM-ICU have been trained with the French version of the CAM-ICU Training Manual. If the patient leaves the ICU before the seventh day after surgery, delirium evaluation with CAM-ICU is continued two times per day in the ward. Reasons for not performing CAM-ICU will be recorded.

The choice of the CAM ICU to assess delirium took into account limitations and strengths of the test: CAM-ICU does not have a sensitivity of 100% and a specificity of 100%. Gold standard of delirium diagnosis is an expert evaluation based on DSM V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) criteria for delirium. This kind of evaluation takes time and was not feasible in the setting of our study. Conversely, CAM-ICU is quick and easy to perform by trained personals and still has an excellent sensitivity and specificity compared with the gold standard.[3] CAM-ICU has been widely used in high-quality studies to assess delirium.[15 16]

Secondary outcome
Agitation evaluated with RASS in the 7 days following surgery

Occurrence of agitation-related adverse events in the 7 days following surgery:
► Unplanned extubation.
► Medical device removal.
► Falling out of bed.
► ICU runaway.
► Immobilisation device removal.
► Self-aggression or aggression towards medical staff.

Number of agitation-related adverse events in the 7 days following surgery.

ICU length of stay.

Hospital length of stay.

Self-evaluation of sleep quality with Numerical Scale from 0 to 10.

Quality of sleep evaluated daily with Leeds Sleep Evaluation Questionnaire until day 7 after surgery.

In-hospital mortality.

All-cause 3-month mortality.

Quality of life 3 months after surgery evaluated with the Medical Outcome Study Short Form 36 (SF-36).

Cognitive function evaluated with Cognitive Failure Questionnaire (CFQ) 3 months after surgery.

Occurrence of post-traumatic stress disorder detected by Post Traumatic Stress Disorder Checklist (PCL-5) 3 months after surgery.

Statistical analysis
Baseline characteristics of patients will be described with usual parameters: frequency, mean, SD, median and interquartile rank. Baseline characteristics will be compared

with parametric tests: Student t-test for continuous variables and χ^2 test for categorical variables. Non-parametric tests will be used if conditions for validity of these tests are not met: Wilcoxon test for continuous variables and Fisher's exact test for categorical variables.

Primary outcome analysis will be performed with χ^2 test in intention to treat. No interim analysis will be performed. Multivariate analysis with logistic regression accounting for potential confounders will be made.

Secondary outcome analysis will be performed in intention to treat, with Student t-test for continuous variables and χ^2 for categorical variables. Multivariate analysis with logistic regression accounting for stratification criteria will also be performed. The randomisation will be stratified on centres and modality of surgery between on and off pump.

Subgroup analysis will be performed on the following subgroups of patients:
- Cardiopulmonary bypass surgery.
- Off-pump surgery.
- Valvular surgery.
- Coronary bypass surgery.
- Combined surgery with coronary bypass and valvular surgery.

A supplemental per protocol analysis will be performed on an exploratory basis on patients who received the treatment at least once.

Ancillary analysis

Preplanned ancillary analysis will be performed
- To evaluate the effect of the intervention on supraventricular arrhythmias.
- To describe the incidence of post-traumatic stress disorder in the population studied and evaluate the effect of the intervention on its occurrence.

Sample size calculation

In three randomised controlled trials on postoperative delirium in elderly patients undergoing cardiac surgery, delirium incidence varied from 13.7% to 34.0%.[18–20] Based on this literature, we hypothesised a delirium incidence of 25% in the population studied. In two of the three studies, the magnitude of the treatment effect was a 50% decrease of postoperative delirium and subsyndromal delirium.[18 19] Therefore, a 50% decrease in incidence of delirium was chosen to remain in line with the previous publications. Using a one-sided alpha=0.05% and 90% power, a sample size of 332 is needed. Considering a loss-to-follow-up rate of 5%, we plan to enrol 348 patients.

A one-sided alpha was chosen because no publication reported any worsening of the patient's outcome compared with placebo. A two-sided alpha estimate is more robust but requires a bigger sample size.

Monitoring

Monitoring will be performed by Clinical Research Associates from Brest University Hospital Research Management Unit and by CLINACT, a contract research organisation. Monitoring will follow Good Clinical Practice principles.

The following data will be monitored on all the case report forms:
- Included and excluded patients.
- Written informed consent.
- Eligibility criteria.
- Primary outcome.
- Severe adverse events.
- Management of the study treatment and therapeutic adherence.

Case report forms of at least 10% of all participating patients will be fully monitored. Those fully monitored cases will be spread over the nine participating centres.

Trial status

Patients from nine ICUs are expected to be included in the study. A 3 years' period had been expected to be necessary to include all patients in the study. The first patient has been included on 4 January 2019 and randomised on 15 February 2019. The last patient has been included in the study and the last follow-up was performed in July 2021.

Closing of the database is scheduled in December 2021.

Track record

Data will be recorded in the electronic case report form by trial staff. Characteristics at baseline will be gathered: site of inclusion, age, gender, weight, height, medical history, body mass index, Euroscore, American Society of Anesthesiologists classification, SF-36, CFQ and PCL-5 before surgery. Characteristics related to the surgery will be gathered: type of intervention, mode of intervention (with or without bypass) duration of intervention, duration of bypass, anaesthesia drugs, transfusion, vasopressors and fluid requirement. During hospitalisation, the following data will be assessed: arrythmia occurrence, fluid balance, blood tests results, including liver function tests, daily SOFA score and concomitant hypnotics, sedatives and analgesic medication use, length of ICU stay, length of hospital stay and days at home at 30 days.

The patient will be contacted by phone 3 months after surgery to assess the following data: SF-36 scores, CFQ and PCL-5.

To ensure confidentiality of participants' personal information, data will be key-coded using alphanumerical numbers.

ETHICS AND DISSEMINATION

The study was approved for all participating centres by the French Central Ethics Committee (Comité de Protection des Personnes Ile de France VI) with the registration number 2018-000850-22. Written consent was required from all participants before the surgery.

The results will be submitted for publication in peer reviewed journals.

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REFERENCES

1 Brown CH, Probert J, Healy R, *et al*. Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology* 2018;129:406–16.
2 McPherson JA, Wagner CE, Boehm LM, *et al*. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med* 2013;41:405–13.
3 Ely EW, Margolin R, Francis J, *et al*. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001;29:1370–9.
4 Ely EW, Shintani A, Truman B, *et al*. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753.
5 Salluh JIF, Wang H, Schneider EB, *et al*. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015;350:h2538.
6 Pandharipande PP, Girard TD, Jackson JC, *et al*. Long-Term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–16.
7 Devlin JW, Skrobik Y, Gélinas C, *et al*. Executive summary: clinical practice guidelines for the prevention and management of pain, Agitation/Sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:1532–48.
8 Baron R, Binder A. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. *Ger Med Sci GMS E-J* 2015;2015:Doc19.
9 Barr J, Fraser GL, Puntillo K, *et al*. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263–306.
10 Munster BCvan, Aronica E, Zwinderman AH, *et al*. Neuroinflammation in delirium: a postmortem case-control study. *Rejuvenation Res* 2011;14:615–22.
11 Pisani MA, Friese RS, Gehlbach BK, *et al*. Sleep in the intensive care unit. *Am J Respir Crit Care Med* 2015;191:731–8.
12 Akeju O, Brown EN. Neural oscillations demonstrate that general anesthesia and sedative states are neurophysiologically distinct from sleep. *Curr Opin Neurobiol* 2017;44:178–85.
13 Wu X-H, Cui F, Zhang C, *et al*. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. *Anesthesiology* 2016;125:979–91.
14 Burry LD, Cheng W, Williamson DR, *et al*. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. *Intensive Care Med* 2021;47:943–60.
15 Su X, Meng Z-T, Wu X-H, *et al*. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016;388:1893–902.
16 Turan A, Duncan A, Leung S, *et al*. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (decade): a randomised placebo-controlled trial. *Lancet* 2020;396:177–85.
17 Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. *Crit Care Med* 2017;45:321–30.
18 Djaiani G, Silverton N, Fedorko L, *et al*. Dexmedetomidine *versus* propofol sedation reduces delirium after cardiac surgery: a randomized controlled trial. *Anesthesiology* 2016;124:362–8.
19 Hakim SM. Early treatment with risperidone for Subsyndromal delirium after on-pump cardiac surgery in the elderly. *Perioper Med*;11.
20 Gamberini M, Bolliger D, Lurati Buse GA, *et al*. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. *Crit Care Med* 2009;37:1762–8.