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Inased (Inhaled Sedation in ICU) trial protocol: a multicentre randomised open-label trial

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Keywords: ICU, sedation, volatile anesthetics, delirium

Abstract

Introduction

The use of sedation in ICUs is necessary and ubiquitous. The impact of sedation strategy on outcome, particularly when delivered early after initiation of mechanical ventilation, is unknown. Evidence is increasing that volatile anesthetic agents could be associated with better outcome. Their use in delirium prevention is unknown.

Methods and analysis

This study is an investigator-initiated, prospective, multicentre, two-arm, randomised, control, open trial comparing inhaled sedation strategy versus intra-venous (IV) sedation strategy in mechanically ventilated patients in ICU. Two hundred and fifty patients will be randomly assigned to the IV sedation group or inhaled sedation group, with a 1:1 ratio in two groups according to the sedation strategy. The primary outcome is the occurrence of delirium assessed using daily confusion assessment method for the ICU (CAM-ICU). Secondary outcomes include cognitive and functional outcomes at 3 and 12 months.

Ethics and dissemination

The study has been approved by the ethics committee (CCP Ouest) and national authorities (ANSM) CPP/ANSM. The results will be submitted for publication in peer-reviewed journals.

Trial registration number

NCT04341350

Strengths and limitations of this study

This study is a multicentre, randomised, controlled and open-label trial adequately powered to determine whether inhaled sedation strategy in ICU reduces delirium.

This study will be the largest randomised controlled trial never conducted on the use of inhaled sedation strategy in ICU and may help to establish strong recommendations on sedation strategy with a high level of evidence.

Treatment's benefits include reduced delirium incidence, reduced risk of cognitive consequences and enhanced quality of life.

The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

Introduction

Background and rationale

The use of sedative drugs in intensive care units (ICUs) is essential and ubiquitous. Sedatives are administered to critically ill patients to relieve anxiety, reduce the stress of mechanical ventilation and prevent agitation-related harm [1]. However, sedative drugs and their active metabolites can accumulate, leading to prolonged deep sedation, respiratory depression, immune suppression, and hypotension. Under-sedation leads to agitation, hypercatabolism, self-harm and unplanned extubation [2]. Over-sedation may increase the duration of mechanical ventilation, thereby increasing the risk of ventilator acquired pneumonia [3]. Yet, these drugs, used as part of sedation titration protocol or daily sedation stop protocol, have improved patient outcomes [4–6].

However all these drug regimen, by uncertain mechanisms, favor the occurrence of ICU delirium. ICU delirium and ICU delirium duration are independent factors associated with the duration of mechanical ventilation, ICU length of stay and 6 month mortality [7, 8]. It has been demonstrated that patients who survive admission to ICU but who have experienced delirium suffer moderate to severe cognitive impairment at 6 months and show persistent depression, anxiety and post-traumatic stress 1 year after hospitalization leading to public health burden [9–12].

Benzodiazepine use is to be avoided within the ICU [1]. If propofol has a more favourable pharmacokinetics than benzodiazepine, its prolonged exposure can lead to hypotension, respiratory depression, hypertriglyceridaemia, pancreatitis and to the often lethal propofol infusion syndrome [13, 14].

New sedative drugs have been tested for patients under mechanical ventilation. Dexmedetomidine (alpha 2 adrenergic receptor agonist), as an example, seems to reduce the delirium duration, the coma duration and even mortality in septic patients [15]. However, dexmedetomidine is often insufficient to deeply sedate patients and a recent multicenter trial enrolling 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction at day 90 [16, 17].Side effects were multiplied by 10 in this study.

Halogenated gases have been used for a long time in anesthesia. Thanks to technical innovations, they can be used on ICU ventilators [18]. They are easy to titrate, produce no active metabolites, and are predominantly cleared unchanged by pulmonary exhalation. Several studies on selected populations have shown the feasibility and the benefits of this use, in particular, the absence of accumulation, the absence of tachyphylaxis, the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the wake up speed and the analgesia effect [18–21]. The duration of use of isoflurane is long and range up to 96 hours in the study by Sackey *et al*. [22], up to 348 hours in the study by L'Her *et al.* [18], up to 323 hours in the study by Krannich *et al.* [23]. Despite these extended times, the

duration of mechanical ventilation and lenghth of stay in the intensive care unit are shorter in the study by Krannich *et al.*, extubations are made earlier in the study by Jerath *et al.*, response to simple orders and the extubation are obtained earlier in the study by Sackey *et al.* [22–24]. Safety use for the staff in charge of the patient has been established [25, 26].. Recommendations for use have been issued [27]. In addition, their potential neuroprotective effect would make it an anesthetic of choice in the prevention of ICU delirium [28, 29]. Schoen *et al.* report that sevoflurane improved short-term post-operative cognitive ability in patients undergoing circulatory assisted heart surgery compared to propofol [30]. Dabrowski *et al.* have confirmed in patients undergoing bypass surgery that sevoflurane and isoflurane attenuate levels of MMP-9, GFAP, specific biochemical markers of brain injury [31]. The use of isoflurane preferentially over sevoflurane is justified by the absence of wake-up gain by the use of sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or pharmacodynamic differences between the molecules during their use in general anesthesia and a more pronounced bronchodilator effect of isoflurane [32–34]. Sevoflurane induced diabetes insipidus is of concern too [35]. To the best of our knowledge, no study has yet examined this potential clinical effect in the ICU setting.

Objectives

We aim to conduct a prospective multicentre randomised controlled trial comparing two sedation strategies in ICU with the hypothesis that inhaled sedation strategy would decrease delirium occurrence.

Primary objective

Determine the impact on the delirium occurrence of an inhaled sedation strategy versus an intra-venous sedation strategy in ICU mechanically ventilated patients.

Trial design

The INASED study is an investigator-initiated, prospective, multicentre, randomised, open-label trial comparing inhaled versus intra-venous sedation in ICU mechanically ventilated patients. Patients will be assigned to the IV sedation group or the inhaled sedation group, with a 1:1 ratio.

Methods: participants, interventions and outcomes

Study setting

The INASED study will take place in 10 ICUs in France.

Inclusion criteria

Patients eligible to be enrolled in this trial are adult ICU patients (>18 years) within 24 h of intubation and who are expected to require mechanical ventilation and sedation for at least 24 h; patient requiring immediate ongoing sedative medication for comfort, safety, and to facilitate the delivery of life support measures.

Exclusion criteria

Age less than 18 years; patient that has been intubated for more than 24-hours in the ICU; Admission for a cardiac arrest, a traumatic brain injury, and/or a stroke; patient that is unable to complete the neuropsychological test due to aphasia, deafness, blindness or dementia; contraindication to isoflurane (personal or familial history of malignant hyperthermia; liver failure with prothrombin < 30%; acute or chronic neuromuscular disease); occurrence of a severe ARDS (P/F ratio<150), a PaCO2>50mmHg at the time of randomization; death is deemed to be imminent or inevitable during the ICU admission; pregnancy or breastfeeding woman; patient under guardianship or curatorship

Intervention

Patients that are eligible for inclusion will be randomised and assigned to one of the two following groups (Fig. 1): (1) The patients assigned to control group will receive continuously IV propofol (2) The patients assigned to interventional group will receive continuously inhaled isoflurane. Sedation and pain management in both arms will be guided using an explicit bedside nurse driven sedation-analgesia algorithm. Sedation in both arms will be titrated every 2 hours to target a Richmond Agitation Sedation Scale of (-2;1) (or as clinically indicated) until extubation or tracheostomy [36]. Supplemental sedatives can be used, always at the lowest effective dose, to optimize sedation and achieve the level of sedation specified by the treating clinician at any time when allocated treatment alone is insufficient to provide patient comfort and safety, provide rescue sedation for immediate control of sudden breakthrough agitation at any time. Benzodiazepines will not be administered to any patient, unless deemed mandatory by the treating clinician for conditions such as convulsions, palliation, procedural anaesthesia, concomitant neuromuscular blockade or refractory agitation. Patients will be reviewed daily for assessment of withdrawing sedation to assist ventilator weaning (resolving the underlying pathology that led to mechanical ventilation; FiO2<50%; PEEP 5 to 8 cm H2O; hemodynamic stability with mean arterial pressure >60 mmHg, which maybe assisted with stable doses of vasoactive drug support) and extubated according to predefined criteria. Pain scores will be monitored every 2 hours in both groups using the Behavorial Pain Scale (BPS), the Face Legs Activity Cry Consolability or the VICOMORE and/or numerical pain score. Pain will be managed in both arms using intravenous opioids aiming for pain scores. In both groups, light sedation is encouraged (RASS -2; 1). Whatever the treatment arm allocated, ABCDEF bundle will be used [38].

Control group: IV sedation

The patients assigned to the control group will receive continuously IV propofol. Sedation and pain management will be guided using an explicit bedside nurse driven sedation-opioïd analgesia algorithm.

Interventional group: inhaled sedation

Isoflurane will be infused into the AnaConDa device, which is placed between the endotracheal tube and the ventilator breathing circuit. Isoflurane is placed in a standard syringe pump. The AnaConDa is placed in the breathing circuit between the Y-piece and the ET-tube. Liquid isoflurane is delivered from the syringe through the agent line into the AnaConDa where it is vaporised within the device. The gas monitor samples the gas from the AnaConDa port and displays the exhaled anaesthetic concentration in Fet% or MAC values (which indicates the concentration of the drug). Due to AnaConDa's design, most of the exhaled anaesthetic agent is adsorbed and reflected to the patient upon inspiration. Thus, AnaConDa recycles more than 90 % of the expired volatile agent, which facilitates low infusion rates. The residual anaesthetic agent passes through the ventilator and exits through the exhaust where it is captured in the FlurAbsorb. The device is changed every 24 h. When patients are being prepared for extubation, study sedation drugs will be discontinued, and the AnaConDa device will be removed from the breathing circuit to facilitate a quick drug washout.

Staff education and training

This trial involves centers where the use of volatile sedation may be uncommon. Thus, education of medical, nursing and respiratory therapy staff regarding the use of volatile agents is supported by the development of a web-based teaching program. Training sessions with a dedicated nurse include information regarding the use of the AnaConDa device, equipment set-up, and safety monitoring.

Masking protocol

It is not possible to blind local investigators to allocation as it is obvious clinically which patients are receiving inhaled sedation. Blinding of outcome data assessment is, however, ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Equipment licensing and approvals

The AnaConDa device is licensed for use in Europe and isoflurane use in ICU is permitted (EC certificate CE 667826).

Duration of treatment

In both groups, patients will be treated for a minimal duration of 24 hours. Sedation continuation will be decided on an individual basis, according to the patient clinical status and will continue until no longer indicated up to a 14-days maximum after enrolment. If sedation is deemed necessary beyond 14 days after enrolment, the choice of sedative regimen will be determined solely by the treating clinician.

Outcomes

Primary outcome

The primary outcome is the occurrence of delirium (yes / no) up until ICU discharge assessed using the confusion assessment method for the ICU (CAM-ICU)..

Secondary outcomes

Secondary outcome variables include the following:

ICU outcomes:

Number of days with vasopressors or inotropic agents

Number of days with sedation

Cumulative dose and duration of anesthetics drugs

Maximum dose of vasopressors or inotropic agents

Ventilation free days at 28 days following randomisation

Proportion of RASS measurements in target range

Incidence and duration of delirium (delirium free days at 28 days). Additionally, we consider a positive CAM-ICU assessment to be hyperactive delirium if the corresponding RASS is >0 and hypoactive delirium if the corresponding RASS is <0

Number of days until RASS 0; -1 is reach

Mortality at ICU discharge, at 28 days

Length of ICU stay

Requirement of physical restraints, of patients with unplanned extubation, unplanned catheter, urinary probe or gastric probe removal

Self or hetero-aggressive act

Hospital outcome

Mortality at hospital discharge

Length of hospital stay

Readmission to ICU

Discharge destination

Post-hospital outcomes

Cost-effectiveness; institutional perspective and cost of lives saved (if positive).

Cognitive function, psychological state and health related quality of life at 3 and 12 months

Sample size

We determined that enrolment of 250 patients would provide a power of 80% to show a reduction by half (30% versus 15%) in the rate of delirium occurrence between the control group using IV sedation and the interventional group using inhaled sedation at a two-sided alpha level of 0.05, accounting for 3% lost to follow-up.

Recruitment

The initial duration of patient enrolment expected is 2 years, starting in july 2020. 2020: approval by an independent ethics committee. 2020-2022: inclusion of patients. 2022: end of inclusions, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database. 2023: data analysis, writing of the manuscript and submission for publication.

Methods: assignment of intervention, data collection, management and analysis

Allocation and sequence intervention

A computer-generated, centre stratified randomisation is performed in a 1:1 ratio, using a centralised web-based management system (Cleannfile). The strategy assigned to the patient (IV or inhaled sedation) will be initiated immediately after randomisation.

Data collection and management

Data will be collected on a Case Report Form (e-CRF) by a trained investigator or research assistant at each centre. A blank copy of the e-CRF can be printed from the e-CRF. This enables the investigator or research assistant to fill it out with the data of the included patients, which will be captured. Once data collection has been completed, the investigator or research assistant shall sign and date the copy. This document will constitute an integral

part of the patient's medical records; as such, it shall be retained permanently. Data recorded in the e-CRF that originate in source documents must be consistent with each other; if they are not, the differences have got to be justified and documented. Blinded and patient identifiable data are stored separately in secure databases. All patient identifiable data are stored by the coordinating centre. Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. At time of inclusion, the following data will be collected:

Patient demographics, APACHE (Acute Physiology and Chronic Health Evaluation) score, SOFA score, hemodynamic variables and vasoactive drug support, ventilation mechanics, laboratory investigations, clinical ICU complications, length of stay, and mortality will be recorded by daily patient assessment and review of paper and electronic health records. Delirium will be assessed twice daily using the Confusion Assessment Method (CAM-ICU)[39]. All these parameters will be collected each day from day 1 to ICU discharge.

For cognitive function, psychological state and health related quality of life evaluation, HADS, PTSD Checklist 14, SF36, iQCODE, IADL and CANTAB tests will be performed at ICU discharge, 3 and 12 months by investigator or research assistant.

Statistical methods

All the analyses will be performed by an independent statistician, following a predefined statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a blind review of the data and final database lock. All the analyses will be conducted using SAS V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value equal or less than 0.05 will be considered as statistically significant.

Descriptive analysis of patient groups at baseline

Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described. The baseline characteristics of the study participants will be described according to their randomization group. Analysis pertaining to the main criteria of evaluation

The frequency of delirium occurrence will be compared between the two groups using a Chi-square test or an exact Fisher test if required. The probability of delirium occurrence will then be modeled (secondary analysis) using a multivariate logistic regression.

Analysis pertaining to the secondary criteria of evaluation

Secondary criteria of evaluation will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the $\chi 2$ test (or Fisher's exact test) for qualitative

variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses.

Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

Predetermined subgroup analysis

Duration of delirium will be compared between the two groups among patients who suffered from delirium, using the Student's t-test or the Mann-Whitney U test if required.

Data monitoring

An investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the data recorded.

Ethics and dissemination

Consent or assent

The patient will be included after having provided a written informed consent to the investigator according to the decision of the central ethics committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. Where it is not possible or practicable for the patient or the substitute decision maker to consider the study and give consent within an appropriate timeframe, the patient may be enrolled without prior consent, provided the procedure is in accord with the requirements of the site's Human Research Ethics Committee and applicable legislation. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Declaration of interest

The study is promoted by the University Hospital of Brest. Sedana Medical funded the promoter for study monitoring and will provide sedation equipment and monitoring for all the participating centres, but will have no other involvement in the study, data analysis, the writing of the manuscript, or in the decision to submit the manuscript.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The protocol is reported according to the SPIRIT guidelines. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users.

Patient and public involvement

Patients and public were not involved in the study.

Discussion

International guidelines on sedation and delirium in ICU have been written [1]. Concerning sedation, four messages are important:

using light sedation versus deep sedation, however there is no consensus on the definition of light, moderate, and deep sedation,

using a daily sedative interruption protocol or a nurse-protocolised sedation protocol,

using propofol or dexmedetomidine over benzodiazepines even if there is no difference between propofol and benzodiazepine use for delirium prevention and even if the pooled analysis of all evaluated studies in these guidelines did not show a significant benefit of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical ventilation extubation, ICU length of stay and the risk for delirium,

monitor sedation.

Since the publication of these guidelines, the SPICE study a recent multicenter trial enrolling 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction at day 90, showed that sedation targets were difficult to obtain with dexmedetomidine as the sole agent of sedation and that adverse effects were multiplied by ten [17].

Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term outcomes has been defined as one of the top trials to perform in the next years by a multinational, interprofessional board [40].

Delirium during sedation administration is frequent. Rapidly improving cognitive state concerns only a minority of delirium sedated patients (14%). Majority of delirium under sedation patient has a worse long-term prognosis [41]. These results have been confirmed in

a large study showing that delirium associated with sedation was the most common type of delirium in ICU, but also the most strongly associated with long –term cognitive impairment. All of these results stress the importance of carrying out this study [42].

The INASED study is the first randomised, controlled and open-label trial adequately powered to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are as broad as possible. This strategy maximises recruitment rates and improves the generalisation of results. Both groups have sedation strategy and nurse driven protocol. All patients will be treated using the ABCDEF bundle which implies less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting depth of sedation, type of sedative drug, and duration of use. At last, extubation criteria will be predefined.

Given the current data and potential of isoflurane sedation to improve patient outcomes, INASED is a well-designed, adequately powered RCT within a homogeneous population to truly understand the potential clinical effects of this sedation modality.

Trial status

The trial has already achieved many milestones. The study is funded by Sedana Medical and promoted by the University Hospital of Brest. Research ethics committee approval was obtained in april 2020. It is registered with the American registry of trials (https:// clinicaltrials.gov/; NCT04341350). No patient has yet been included, and expected starting point of the study is July 2020.

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Contributors

PB and ELH designed the study and wrote the manuscript together. EN provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size. All authors contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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The study is funded by Sedana Medical, and promoted by the University Hospital of Brest.

Disclaimer

The firm Sedana provides therapy equipment and monitoring to all the participating centres but has no other involvement in the study.

Competing interests

PB reports financial support (travel expanse coverage to attend scientific meetings) from Sedana Medical.

MJ is coordinating investigator of the ”Sevoflurane for Sedation in ARds” (SESAR) trial of inhaled sevoflurane in ARDS, co-funded by the French Ministry of Health, the ESA, and Sedana Medical, has received a fee from Sedana Medical for participation to a French advisory board, has received a fee for an educational seminar on mechanical ventilation, by GE Healthcare.

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AWT reports financial support (payment for lectures and travel expanse coverage to attend scientific meetings) from Fisher & Paykel, Covidien, Maquet - Getinge and GE Healthcare.

SJ reports receiving consulting fees from Drager, Medtronic, Baxter,Fresenius Medical and Fisher & Paykel.

ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to automated oxygen administration. He is also a consultatnt for Sedana Medical, GE Healthcare and Smiths Medical.

Ethic approval

The study has been approved by the CPP Nord-Ouest 1 est with the registration number 19.12.20.72129.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Open access

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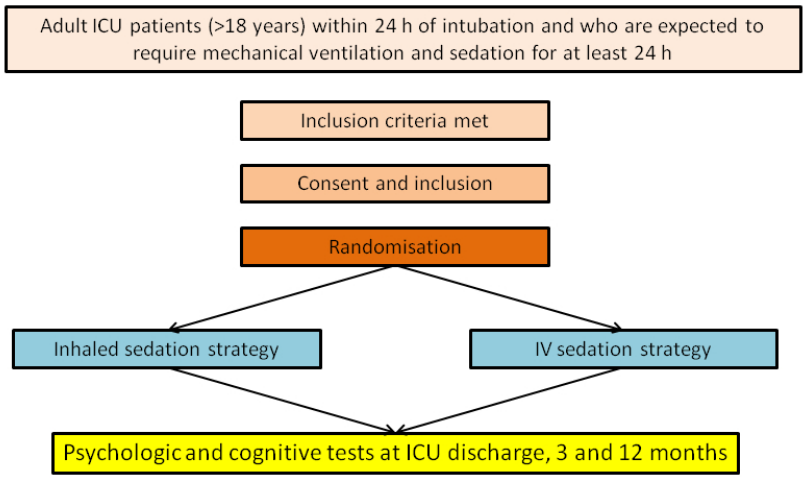

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Inased (Inhaled Sedation in ICU) trial protocol: a multicentre randomised open-label trial

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Abstract

Introduction

The use of sedation in ICUs is necessary and ubiquitous. The impact of sedation strategy on outcome, particularly when delivered early after initiation of mechanical ventilation, is unknown. Evidence is increasing that volatile anesthetic agents could be associated with better outcome. Their use in delirium prevention is unknown.

Methods and analysis

This study is an investigator-initiated, prospective, multicentre, two-arm, randomised, control, open trial comparing inhaled sedation strategy versus intra-venous (IV) sedation strategy in mechanically ventilated patients in ICU. Two hundred and fifty patients will be randomly assigned to the IV sedation group or inhaled sedation group, with a 1:1 ratio in two groups according to the sedation strategy. The primary outcome is the occurrence of delirium assessed using twice a day confusion assessment method for the ICU (CAM-ICU). Secondary outcomes include cognitive and functional outcomes at 3 and 12 months.

Ethics and dissemination

The study has been approved by the ethics committee (CCP Ouest) and national authorities (ANSM) CPP/ANSM. The results will be submitted for publication in peer-reviewed journals.

Trial registration number

NCT04341350

Strengths and limitations of this study

Isoflurane sedation has many advantages for ICU sedation. Its potential neuroprotective role could be beneficial in the prevention of delirium.

This study is a multicentre, randomised, controlled and open-label trial adequately powered to determine whether inhaled sedation strategy in ICU reduces delirium.

This study will be the largest randomised controlled trial ever conducted on the impact on delirium of the use of inhaled sedation strategy in ICU and may help to establish strong recommendations on sedation strategy with a high level of evidence.

The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

Introduction

Background and rationale

The use of sedative drugs in intensive care units (ICUs) is essential and ubiquitous. Sedatives are administered to critically ill patients to relieve anxiety, reduce the stress of mechanical ventilation and prevent agitation-related harm [1]. However, sedative drugs and their active metabolites can accumulate, leading to prolonged deep sedation, respiratory depression, immune suppression, and hypotension. Under-sedation leads to agitation, hypercatabolism, self-harm and unplanned extubation [2]. Over-sedation may increase the duration of mechanical ventilation, thereby increasing the risk of ventilator acquired pneumonia [3]. Yet, these drugs, used as part of sedation titration protocol or daily sedation stop protocol, have improved patient outcomes [4–6].

However all these drug regimen, by uncertain mechanisms, favor the occurrence of ICU delirium. ICU delirium and ICU delirium duration are independent factors associated with the duration of mechanical ventilation, ICU length of stay and 6 month mortality [7, 8]. It has been demonstrated that patients who survive admission to ICU but who have experienced delirium suffer moderate to severe cognitive impairment at 6 months and show persistent depression, anxiety and post-traumatic stress 1 year after hospitalization leading to public health burden [9–12].

Benzodiazepine use is to be avoided within the ICU [1]. If propofol has a more favourable pharmacokinetics than benzodiazepine, its prolonged exposure can lead to hypotension, respiratory depression, hypertriglyceridaemia, pancreatitis and to the often lethal propofol infusion syndrome [13, 14].

New sedative drugs have been tested for patients under mechanical ventilation. Dexmedetomidine (alpha 2 adrenergic receptor agonist), as an example, seems to reduce the delirium duration, the coma duration and even mortality in septic patients [15]. However, dexmedetomidine is often insufficient to deeply sedate patients and a recent multicenter trial enrolling 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual sedation care failed to show a mortality reduction at day 90 [16, 17]. Side effects were multiplied by 10.

Halogenated gases have been used for a long time in anesthesia. Thanks to technical innovations, they can be used on ICU ventilators [18]. They are easy to titrate, produce no active metabolites, and are predominantly cleared unchanged by pulmonary exhalation. Several studies on selected populations have shown the feasibility and the benefits of this use in ICU [18–21]. Safety use for the staff in charge of the patient has been established [22, 23].

To the best of our knowledge, no study has yet prospectively examined the potential clinical effect of Isoflurane sedation on delirium in the ICU setting.

Objectives

We aim to conduct a prospective multicentre randomised controlled trial comparing two sedation strategies in ICU with the hypothesis that inhaled sedation strategy would decrease delirium occurrence.

Primary objective

Determine the impact on the delirium occurrence of an inhaled sedation strategy versus an intra-venous sedation strategy in ICU mechanically ventilated patients.

Trial design

The INASED study is an investigator-initiated, prospective, multicentre, randomised, open-label trial comparing inhaled versus intra-venous sedation in ICU mechanically ventilated patients. Patients will be assigned to the IV sedation group or the inhaled sedation group, with a 1:1 ratio.

Methods: participants, interventions and outcomes

Study setting

The INASED study will take place in 10 ICUs in France.

Inclusion criteria

Patients eligible to be enrolled in this trial are adult ICU patients (>18 years) within 24 h of intubation and who are expected to require mechanical ventilation for at least 24 h; patient requiring immediate ongoing sedative medication for comfort, safety, and to facilitate the delivery of life support measures.

Exclusion criteria

Age less than 18 years; patient that has been intubated for more than 24-hours in the ICU; admission for a cardiac arrest, a traumatic brain injury, and/or a stroke; patient that is unable to complete the neuropsychological test due to aphasia, deafness, blindness or dementia; contraindication to isoflurane (personal or familial history of malignant hyperthermia; liver failure with prothrombin < 30%; acute or chronic neuromuscular disease); occurrence of a severe ARDS (P/F ratio<100), a PaCO2>50mmHg at the time of randomization; death is deemed to be imminent or inevitable during the ICU admission; pregnancy or breastfeeding woman; patient under guardianship or curatorship.

Intervention

Patients that are eligible for inclusion will be randomised and assigned to one of the two following groups (Fig. 1): (1) The patients assigned to control group will receive continuously IV propofol (2) The patients assigned to interventional group will receive continuously inhaled isoflurane. Sedation and pain management in both arms will be guided using an explicit bedside nurse driven sedation-analgesia algorithm. Sedation in both arms will be titrated every 2 hours to target a Richmond Agitation Sedation Scale of (-2;1) (or as clinically indicated) until extubation or tracheostomy [24]. Supplemental sedatives can be used, always at the lowest effective dose, to optimize sedation and achieve the level of sedation specified by the treating clinician at any time when allocated treatment alone is insufficient to provide patient comfort and safety, provide rescue sedation for immediate control of sudden breakthrough agitation at any time. Benzodiazepines will not be administered to any patient, unless deemed mandatory by the treating clinician for conditions such as convulsions, palliation, procedural anaesthesia, concomitant neuromuscular blockade or refractory agitation. Patients will be reviewed daily for assessment of withdrawing sedation to assist ventilator weaning (resolving the underlying pathology that led to mechanical ventilation; FiO2<50%; PEEP 5 to 8 cm H2O; hemodynamic stability with mean arterial pressure>60 mmHg, which maybe assisted with stable doses of vasoactive drug support) and extubated according to predefined criteria. Pain scores will be monitored every 2 hours in both groups using the Behavorial Pain Scale (BPS), the Face Legs Activity Cry Consolability or the VICOMORE and/or numerical pain score. Pain treatment is based on the ABCDEF bundle [25]. It uses the nurse driven analgesia protocol of each ward involved in the study. It uses a pain assessment score (BPS, VICOMORE, FLACC), local or regional anesthesia, non-opioïd adjuncts (acetaminophen, NSAIDs, nefopam), opioïds (per os opioïds, bolus of sufentanyl followed by continuous infusion if necessary, continuous infusion of remifentanyl). We decided to avoid morphine use for analgesia-based sedation because of its long half-life of action and its accumulation. In both groups, light sedation is encouraged (RASS -2; 1). Whatever the treatment arm allocated, ABCDEF bundle will be used [25].

Control group: IV sedation

The patients assigned to the control group will receive continuously IV propofol. Sedation and pain management will be guided using an explicit bedside nurse driven sedation-opioïd analgesia algorithm.

Interventional group: inhaled sedation

Isoflurane will be infused into the AnaConDa device, which is placed between the endotracheal tube and the ventilator breathing circuit. Isoflurane is placed in a standard syringe pump. The AnaConDa is placed in the breathing circuit between the Y-piece and the ET-tube. Liquid isoflurane is delivered from the syringe through the agent line into the AnaConDa where it is vaporised within the device. In order to limit the dead space, INASED

study will only use 50mL AnaConDa S filters. The gas monitor samples the gas from the AnaConDa port and displays the exhaled anaesthetic concentration in Fet% or MAC values (which indicates the concentration of the drug). Due to AnaConDa's design, most of the exhaled anaesthetic agent is adsorbed and reflected to the patient upon inspiration. Thus, AnaConDa recycles more than 90 % of the expired volatile agent, which facilitates low infusion rates. The residual anaesthetic agent passes through the ventilator and exits through the exhaust where it is captured in the FlurAbsorb. The device is changed every 24 h. When patients are being prepared for extubation, study sedation drugs will be discontinued, and the AnaConDa device will be removed from the breathing circuit to facilitate a quick drug washout. Gas-scavenging is performed with a commercially available canister connected to the ventilator output. The canister contains 500g of activated charcoal and removes isoflurane from the expired air up to a weight increase of 150 g, which provides 24 hours with the AnaConDa.

Staff education and training

This trial involves centers where the use of volatile sedation may be uncommon. Thus, education of medical, nursing and respiratory therapy staff regarding the use of volatile agents is supported by the development of a web-based teaching program. Training sessions with a dedicated nurse include information regarding the use of the AnaConDa device, equipment set-up, and safety monitoring.

Masking protocol

It is not possible to blind local investigators to allocation as it is obvious clinically which patients are receiving inhaled sedation: AnaConDa is connected to the endotracheal tube and requires the use of exhaled isoflurane monitor and a syringe driver As the INASED study uses a nurse driven protocol, withdrawing of sedation is not initiated by the medical investigator but by the nurse in charge of the patient, based on this pre-specified protocol. This is similar to what is used for spontaneous breathing trial (SBT), which are triggered daily by the nurse without medical consent if all the pre-specified criteria are met [26]. If SBT fails, patient is not extubated. If it succeeds, patient is extubated. Blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Equipment licensing and approvals

The AnaConDa device is licensed for use in Europe and isoflurane use in ICU is permitted (EC certificate CE 667826).

Duration of treatment

In both groups, patients will be treated for a minimal duration of 24 hours. Sedation continuation will be decided on an individual basis, according to the patient clinical status and

will continue until no longer indicated up to a 14-days maximum after enrolment. If sedation is deemed necessary beyond 14 days after enrolment, the choice of sedative regimen will be determined solely by the treating clinician.

Outcomes

Primary outcome

The primary outcome is the occurrence of delirium (yes / no) up until ICU discharge assessed using the confusion assessment method for the ICU (CAM-ICU). As delirium is fluctuating, CAM-ICU is to be evaluated twice a day, first time in the morning during first daily medical examination, second time in the evening at the beginning of the night shift. We decided not to evaluate delirium during the night in order to avoid sleep disorders within our patients and to respect the ABCDEF bundle.

Secondary outcomes

Secondary outcome variables include the following:

ICU outcomes:

- Number of days with vasopressors or inotropic agents
- Number of days with sedation
- Cumulative dose and duration of anesthetics drugs
- Maximum dose of vasopressors or inotropic agents
- Ventilation free days at 28 days following randomisation
- Proportion of RASS measurements in target range
- Incidence and duration of delirium (delirium free days at 28 days). Additionally, we consider a positive CAM-ICU assessment to be hyperactive delirium if the corresponding RASS is >0 and hypoactive delirium if the corresponding RASS is <0
- Number of days until RASS 0; -1 is reach
- Mortality at ICU discharge, at 28 days
- Length of ICU stay
- Requirement of physical restraints, of patients with unplanned extubation, unplanned catheter, urinary probe or gastric probe removal
- Self or hetero-aggressive act

Hospital outcome

Mortality at hospital discharge

Length of hospital stay

Readmission to ICU

Discharge destination

Post-hospital outcomes

Cost-effectiveness; institutional perspective and cost of lives saved (if positive).

Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months using two kinds of scores:

1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60 minutes medical consultation (those tests were also used in the Spice functional and neuro-psychological outcomes SPICEFANS substudy [17].

2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental activities of daily living) performed by a clinical research associate.

Sample size

We determined that enrolment of 250 patients would provide a power of 80% to show a reduction by half (30% versus 15%) in the rate of delirium occurrence between the control group using IV sedation and the interventional group using inhaled sedation at a two-sided alpha level of 0.05, accounting for 3% lost to follow-up.

Recruitment

The initial duration of patient enrolment expected is 2 years, starting in july 2020. 2020: approval by an independent ethics committee. 2020-2022: recruitment period. 2022: end of recruitment, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database. 2023: data analysis, writing of the manuscript and submission for publication.

Methods: assignment of intervention, data collection, management and analysis

Allocation and sequence intervention

A computer-generated, centre stratified randomisation is performed in a 1:1 ratio, using a centralised web-based management system (Cleannfile). The strategy assigned to the patient (IV or inhaled sedation) will be initiated immediately after randomisation.

Data collection and management

Data will be collected on a Case Report Form (e-CRF) by a trained investigator or research assistant at each centre. A blank copy of the e-CRF can be printed from the e-CRF. This enables the investigator or research assistant to fill it out with the data of the included patients, which will be captured. Once data collection has been completed, the investigator or research assistant shall sign and date the copy. This document will constitute an integral part of the patient's medical records; as such, it shall be retained permanently. Data recorded in the e-CRF that originate in source documents must be consistent with each other; if they are not, the differences have got to be justified and documented. Blinded and patient identifiable data are stored separately in secure databases. All patient identifiable data are stored by the coordinating centre. Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. At time of inclusion, the following data will be collected:

Patient demographics, APACHE (Acute Physiology and Chronic Health Evaluation) score, SOFA score, hemodynamic variables and vasoactive drug support, ventilation mechanics, laboratory investigations, clinical ICU complications, length of stay, and mortality will be recorded by daily patient assessment and review of paper and electronic health records. Delirium will be assessed twice daily using the Confusion Assessment Method (CAM-ICU)[27]. All these parameters will be collected each day from day 1 to ICU discharge.

Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months using two kinds of scores:

1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60 minutes medical consultation (those tests were also used in the Spice functional and neuro-psychological outcomes SPICEFANS substudy [17].

2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental activities of daily living) performed by a clinical research associate.

Statistical methods

All the analyses will be performed by an independent statistician, following a predefined statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a blind review of the data and final database lock. All the analyses will be conducted using SAS V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value equal

or less than 0.05 will be considered as statistically significant. All tests, except for the primary outcome, will be exploratory.

Descriptive analysis of patient groups at baseline

Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described. The baseline characteristics of the study participants will be described according to their randomization group.

Analysis pertaining to the main criteria of evaluation

The frequency of delirium occurrence will be compared between the two groups using a Chi-square test or an exact Fisher test if required. The probability of delirium occurrence will then be modeled (secondary analysis) using a multivariate logistic regression.

Analysis pertaining to the secondary criteria of evaluation

Secondary criteria of evaluation will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the $\chi 2$ test (or Fisher's exact test) for qualitative variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses.

Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

Predetermined subgroup analysis

Duration of delirium will be compared between the two groups among patients who suffered from delirium, using the Student's t-test or the Mann-Whitney U test if required.

Data monitoring

An investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the data recorded.

Ethics and dissemination

Consent or assent

The patient will be included after having provided a written informed consent to the investigator according to the decision of the central ethics committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is

completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Declaration of interest

The study is promoted by the University Hospital of Brest. Sedana Medical funded the promoter for study monitoring and will provide sedation equipment and monitoring for all the participating centres, but will have no other involvement in the study, data analysis, the writing of the manuscript, or in the decision to submit the manuscript.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The protocol is reported according to the SPIRIT guidelines. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users.

Patient and public involvement

Patients and public were not involved in the study.

Discussion

International guidelines on sedation and delirium in ICU have been written [1]. Concerning sedation, four messages are important:

using light sedation versus deep sedation, however there is no consensus on the definition of light, moderate, and deep sedation,

using a daily sedative interruption protocol or a nurse-driven sedation protocol,

using propofol or dexmedetomidine over benzodiazepines even if there is no difference between propofol and benzodiazepine use for delirium prevention and even if the pooled analysis of all evaluated studies in these guidelines did not show a significant benefit of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical ventilation extubation, ICU length of stay and the risk for delirium,

monitor sedation.

Since the publication of these guidelines, the SPICE study, a recent multicenter trial enrolling 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction at day 90, showed that sedation targets were difficult to obtain with dexmedetomidine as the sole agent of sedation and that adverse effects were multiplied by ten [17]. The NONSEDA study (comparing a no sedation group versus a light sedation group [RASS-2;-3]) enrolled 710 patients. Mortality at 90 days did not differ significantly between those assigned to a plan of no sedation and those assigned to a plan of light sedation. 14% of screened patients declined to participate and about one third patient should have been sedated during the first 24 hours in the no sedation group [28].

Delirium during sedation administration is frequent. Rapidly improving cognitive state concerns only a minority of delirium sedated patients (14%). Majority of delirium under sedation patient has a worse long-term prognosis [29]. These results have been confirmed in a large study showing that delirium associated with sedation was the most common type of delirium in ICU, but also the most strongly associated with long-term cognitive impairment [30]. Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term outcomes has been defined as one of the top trials to perform in the next years by a multinational, interprofessional board [31].

Potential benefits of isoflurane use in ICU are the absence of accumulation or tachyphylaxis, the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the wake up speed and the analgesia effect [18, 20, 21, 32]. The duration of use of isoflurane is long and range up to 96 hours in the study by Sackey et al. [33], up to 348 hours in the study by L'Her et al. [18], up to 323 hours in the study by Krannich et al. [34]. Despite these extended times, the duration of mechanical ventilation and lenghth of stay in the intensive care unit are shorter in the study by Krannich et al., extubations are made earlier in the study by Jerath et al., response to simple orders and the extubation are obtained earlier in the study by Sackey et al.[33–35]. RCTs examining volatile anesthesics effects and safety aspects in ICU are currently recruiting (NCT01983800). Inhaled sedation has shown decrease of epithelial injury and inflammation in ARDS [20]. Those results should however be confirmed in a randomized clinical trial (NCT04235608). Safety use for the staff in charge of the patient has been established [22, 23]. Recommendations for use have been issued [36]. Inhaled volatile anesthetics to conserve intravenous sedatives agents have proven to be effective during the COVID-19 pandemic [37, 38, NCT04383730]. In addition, their potential neuroprotective effect would make it an anesthetic of choice in the prevention of ICU delirium [39, 40]. Schoen et al. report that sevoflurane improved short-term post-operative cognitive ability in patients undergoing circulatory assisted heart surgery compared to propofol [41]. Dabrowski et al. have confirmed in patients undergoing bypass surgery that sevoflurane and isoflurane attenuate levels of MMP-9, GFAP, specific biochemical markers of brain injury [42].

All of these results stress the importance of carrying out this study whose hypothesis is that inhaled sedation strategy would decrease delirium occurrence. The use of isoflurane preferentially over sevoflurane is justified by the absence of wake-up gain by the use of sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or pharmacodynamic differences between the molecules during their use in general anesthesia and a more pronounced bronchodilator effect of isoflurane[43–45]. Sevoflurane induced diabetes insipidus is of concern too [46].

The INASED study is the first randomised, controlled and open-label trial adequately powered to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are as broad as possible. This strategy maximises recruitment rates and improves the generalisation of results. All patients will be treated using the ABCDEF bundle which implies less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting depth of sedation, type of sedative drug, and duration of use. It is not possible to blind local investigators to allocation treatment. However withdrawing of sedation, SBT, extubation will follow a nurse-driven protocol. Blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Given the current data and potential of isoflurane sedation to improve patient outcomes, INASED is a well-designed, adequately powered RCT within a homogeneous population to truly understand the potential clinical effects of this sedation modality.

Trial status

The trial has already achieved many milestones. The study is funded by Sedana Medical and promoted by the University Hospital of Brest. Research ethics committee approval was obtained in april 2020. It is registered with the American registry of trials (https:// clinicaltrials.gov/; NCT04341350). Starting point of the study was August 2020. 12 patients have been included.

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Contributors

PB and ELH designed the study and wrote the manuscript together. EN provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. PYE, SE, AWT, CG, GG, FR, OH, SJ contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

The firm Sedana provides therapy equipment and monitoring to all the participating centres but has no other involvement in the study.

Competing interests

PB reports financial support (travel expanse coverage to attend scientific meetings) from Sedana Medical.

SE declares receiving consulting fees, unrestricted research grants and equipment research support from Aerogen Ltd, unrestricted research grant from Fisher & Paykel, unrestricted research grant form Hamilton medical, consulting fees from La Diffusion Technique Française.

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SJ reports receiving consulting fees from Drager, Medtronic, Baxter,Fresenius Medical and Fisher & Paykel.

ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to automated oxygen administration. He is also a consultant for Sedana Medical, GE Healthcare and Smiths Medical.

Ethic approval

The study has been approved by the CPP Nord-Ouest 1 with the registration number 19.12.20.72129.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Open access

Figure legend:

Intervention. Patients that are eligible for inclusion will be randomised and assigned to one of the two groups (inhaled or IV sedation). Outcomes will be evaluated during ICU stay, at discharge and at 3 and 12 months.

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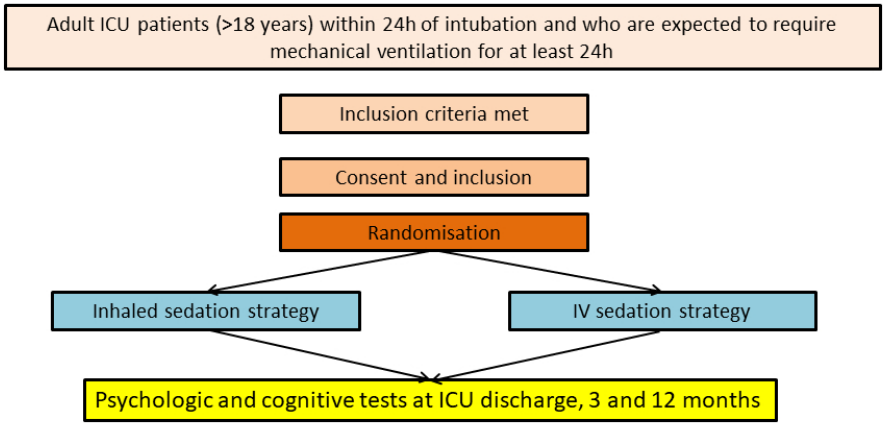

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Inased (Inhaled Sedation in ICU) trial protocol: a multicenter randomized open-label trial

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Inased (Inhaled Sedation in ICU) trial protocol: a multicenter randomized open-label trial

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Keywords: ICU, sedation, volatile anesthetics, delirium

Abstract

Introduction

The use of sedation in ICUs is necessary and ubiquitous. The impact of sedation strategy on outcome, particularly when delivered early after initiation of mechanical ventilation, is unknown. Evidence is increasing that volatile anesthetic agents could be associated with better outcome. Their use in delirium prevention is unknown.

Methods and analysis

This study is an investigator-initiated, prospective, multicenter, two-arm, randomized, controlled, open trial comparing inhaled sedation strategy versus intra-venous (IV) sedation strategy in mechanically ventilated patients in ICU. Two hundred and fifty patients will be randomly assigned to the IV sedation group or inhaled sedation group, with a 1:1 ratio in two groups according to the sedation strategy. The primary outcome is the occurrence of delirium assessed using twice a day confusion assessment method for the ICU (CAM-ICU). Secondary outcomes include cognitive and functional outcomes at 3 and 12 months.

Ethics and dissemination

The study has been approved by the ethics committee (CPP Ouest) and national authorities (ANSM). The results will be submitted for publication in peer-reviewed journals.

Trial registration number

NCT04341350

Strengths and limitations of this study

The INASED study is a multicenter, randomized, controlled and open-label trial, comparing two sedation strategies.

The primary outcome is the occurrence of delirium up until ICU discharge.

Neurocognitive evaluation will be performed for at least 3-months after ICU discharge, which will enable investigators to evaluate patients' outcome on a strong indicator.

The main limitation of the study is that considering the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

However, blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Introduction

Background and rationale

The use of sedative drugs in intensive care units (ICUs) is essential and ubiquitous. Sedatives are administered to critically ill patients to relieve anxiety, reduce the stress of mechanical ventilation and prevent agitation-related harm [1]. However, sedative drugs and their active metabolites can accumulate, leading to prolonged deep sedation, respiratory depression, immune suppression, and hypotension. Under-sedation leads to agitation, hypercatabolism, self-harm and unplanned extubation [2]. Over-sedation may increase the duration of mechanical ventilation, thereby increasing the risk of ventilator acquired pneumonia [3]. Yet, these drugs, used as part of sedation titration protocol or daily sedation stop protocol, have improved patient outcomes [4–6].

However all these drug regimen, by uncertain mechanisms, favor the occurrence of ICU delirium. ICU delirium and ICU delirium duration are independent factors associated with the duration of mechanical ventilation, ICU length of stay and 6 month mortality [7]. It has been demonstrated that patients who survived admission to ICU but who have experienced delirium suffer moderate to severe cognitive impairment at 6 months and show persistent depression, anxiety and post-traumatic stress 1 year after hospitalization, leading to public health burden [8–12].

Halogenated gases have been used for a long time in anesthesia. Thanks to technical innovations, they can be used on ICU ventilators. They are easy to titrate, produce no active metabolites, and are predominantly cleared unchanged by pulmonary exhalation. Several studies on selected populations have shown the feasibility and the benefits of its use in ICU [13–16]. Safety use for the staff in charge of the patient has been established [17, 18].

To the best of our knowledge, no study has yet prospectively examined the potential clinical effect of isoflurane sedation on delirium in the ICU setting.

Objectives

We aim to conduct a prospective multicenter randomized controlled trial comparing two sedation strategies in ICU with the hypothesis that inhaled sedation strategy would decrease delirium occurrence.

Primary objective

Determine the impact on the delirium occurrence of an inhaled sedation strategy versus an intra-venous sedation strategy in ICU mechanically ventilated patients.

Trial design

The INASED study is an investigator-initiated, prospective, multicenter, randomized, open-label trial comparing inhaled versus intra-venous sedation in ICU mechanically ventilated

patients. Patients will be assigned to the IV sedation group or the inhaled sedation group, with a 1:1 ratio.

Methods: participants, interventions and outcomes

Study setting

The INASED study will take place in 10 ICUs in France.

Inclusion criteria

Patients eligible to be enrolled in this trial are adult ICU patients (>18 years) within 24 hours of intubation and who are expected to require mechanical ventilation for at least 24 hours; patient requiring immediate ongoing sedative medication for comfort, safety, and to facilitate the delivery of life support measures.

Exclusion criteria

Age less than 18 years; patient that has been intubated for more than 24 hours in the ICU; admission for a cardiac arrest, a traumatic brain injury, and/or a stroke; patient that is unable to complete the neuropsychological test due to aphasia, deafness, blindness or dementia; contraindication to isoflurane (personal or familial history of malignant hyperthermia; liver failure with prothrombin < 30%; acute or chronic neuromuscular disease); occurrence of a severe ARDS (P/F ratio<100), a PaCO2>50mmHg at the time of randomization; death deemed to be imminent or inevitable during the ICU admission; pregnancy or breastfeeding woman; patient under guardianship or curatorship.

Intervention

Patients that are eligible for inclusion will be randomized and assigned to one of the two following groups (Figure 1): (1) The patients assigned to control group will receive continuous infusion of IV propofol (2) The patients assigned to interventional group will receive continuously inhaled isoflurane with use of AnaConDa (Sedana Medical, Uppsala, Sweden). Sedation and pain management in both arms will be guided using an explicit bedside nurse driven sedation-analgesia algorithm. Sedation in both arms will be titrated every 2 hours to target a Richmond Agitation Sedation Scale of (-2;1) (or as clinically indicated) until extubation or tracheostomy [19]. Supplemental sedatives can be used, always at the minimum effective dose, to optimize sedation and achieve the level of sedation specified by the treating clinician at any time when allocated treatment alone is insufficient to provide patient comfort and safety, provide rescue sedation for immediate control of sudden breakthrough agitation at any time. Benzodiazepines will not be administered to any patient, unless deemed mandatory by the treating clinician for conditions such as convulsions, palliation, procedural anesthesia, concomitant neuromuscular blockade or refractory agitation. Patients will be reviewed daily

for assessment of withdrawing sedation to assist ventilator weaning (resolving the underlying pathology that led to mechanical ventilation; FiO2<50%; PEEP 5 to 8 cm H2O; hemodynamic stability with mean arterial pressure>60 mmHg, which maybe assisted with stable doses of vasoactive drug support) and extubated according to predefined criteria. Pain scores will be monitored every 2 hours in both groups using the Behavorial Pain Scale (BPS), the Face Legs Activity Cry Consolability or the VICOMORE and/or numerical pain score. Pain treatment is based on the ABCDEF bundle [20], which uses the nurse driven analgesia protocol of each ward involved in the study with a pain assessment score (BPS, VICOMORE, FLACC), local or regional anesthesia, non-opioid adjuncts (acetaminophen, NSAIDs, nefopam), opioids (per os opioids, bolus of sufentanyl followed by continuous infusion if necessary, continuous infusion of remifentanyl). We decided to avoid morphine use for analgesia-based sedation because of its long half-life of action and its accumulation [21]. In both groups, light sedation is encouraged (RASS -2; 1). Whatever the treatment arm allocated, ABCDEF bundle will be used [20].

Control group: IV sedation

The patients assigned to the control group will receive continuously IV propofol. Sedation and pain management will be guided using an explicit bedside nurse driven sedation opioid analgesia algorithm.

Interventional group: inhaled sedation

Isoflurane will be infused into the AnaConDa device (Sedana Medical, Uppsala, Sweden), which is placed between the endotracheal tube and the ventilator breathing circuit. Isoflurane is placed in a standard syringe pump. The AnaConDa is placed in the breathing circuit between the Y-piece and the ET-tube. Liquid isoflurane is delivered from the syringe through the dedicated line into the AnaConDa where it is vaporized within the device. In order to limit the dead space, INASED study will only use 50mL AnaConDa S filters. The gas monitor samples the gas from the AnaConDa port and displays the exhaled anesthetic concentration in Fet% or MAC values (which indicates the concentration of the drug). Due to AnaConDa's design, most of the exhaled anesthetic agent is adsorbed and reflected to the patient upon inspiration [22]. Thus, AnaConDa recycles more than 90 % of the expired volatile agent, which facilitates low infusion rates. The residual anesthetic agent passes through the ventilator and exits through the exhaust where it is captured in the FlurAbsorb. The device is changed every 24 h. When patients are being prepared for extubation, study sedation drugs will be discontinued, and the AnaConDa device will be removed from the breathing circuit to facilitate a quick drug washout. Gas-scavenging is performed with a commercially available canister connected to the ventilator output. The canister contains 500g of activated charcoal and removes isoflurane from the expired air up to a weight increase of 150g, which provides 24 hours with the AnaConDa.

Staff education and training

This trial involves centers where the use of volatile sedation may be uncommon. Thus, education of medical, nursing and respiratory therapy staff regarding the use of volatile agents is supported by the development of a web-based teaching program. Training sessions with a dedicated nurse include information regarding the use of the AnaConDa device, equipment set-up, and safety monitoring.

Masking protocol

It is not possible to blind local investigators to allocation as it is obvious which patients are receiving inhaled sedation: AnaConDa is connected to the endotracheal tube and requires the use of exhaled isoflurane monitor and a syringe driver. As the INASED study uses a nurse driven protocol, withdrawing of sedation is not initiated by the medical investigator but by the nurse in charge of the patient, based on this pre-specified protocol. This is similar to what is used for spontaneous breathing trial (SBT), which are triggered daily by the nurse without medical consent if all the pre-specified criteria are met [23]. If SBT fails, patient is not extubated. If it succeeds, patient is extubated. Blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group. Physicians treating the patients will be blinded for the final evolution of the neuro-cognitive assessment. However, the study remains an open-blinded study while physicians will be aware of the sedation group.

Equipment licensing and approvals

The AnaConDa device is licensed for use in Europe and isoflurane use in ICU is permitted (EC certificate CE 667826).

Duration of treatment

In both groups, patients will be treated for a minimal duration of 24 hours. Sedation continuation will be decided on an individual basis, according to the patient clinical status and will continue until no longer indicated up to a 14-days maximum after enrolment. If sedation is deemed necessary beyond 14 days after enrolment, the choice of sedative regimen will be determined solely by the treating clinician.

Outcomes

Primary outcome

The primary outcome is the occurrence of delirium (yes / no) up until ICU discharge assessed using the confusion assessment method for the ICU (CAM-ICU) [24]. As delirium is fluctuating, CAM-ICU has to be evaluated twice a day, first time in the morning during first daily medical examination, second time in the evening at the beginning of the night shift. We decided not to evaluate delirium during the night in order to avoid sleep disorders within our patients and to follow recommendation of the ABCDEF bundle [20].

Secondary outcomes

Secondary outcome variables include the following:

ICU outcomes:

- Number of days with vasopressors or inotropic agents
- Number of days with sedation
- Cumulative dose and duration of anesthetics drugs
- Maximum dose of vasopressors or inotropic agents
- Ventilation free days at 28 days following randomization
- Proportion of RASS measurements in target range
- Incidence and duration of delirium (delirium free days at 28 days). Additionally, we consider a positive CAM-ICU assessment to be hyperactive delirium if the corresponding RASS is >0 and hypoactive delirium if the corresponding RASS is <0
- Number of days until RASS 0; -1 is reach
- Mortality at ICU discharge, at 28 days
- Length of ICU stay
- Requirement of physical restraints, of patients with unplanned extubation, unplanned catheter, urinary probe or gastric probe removal
- Self or hetero-aggressive act

Hospital outcome

- Mortality at hospital discharge
- Length of hospital stay

Readmission to ICU

Discharge destination

Post-hospital outcomes

Cost-effectiveness; institutional perspective and cost of lives saved (if positive).

Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months using two kinds of scores:

1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60 minutes medical consultation (those tests were also used in the Spice functional and neuro-psychological outcomes SPICEFANS substudy [25]).

2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental activities of daily living) performed by a clinical research associate.

Sample size

We determined that enrolment of 250 patients would provide a power of 80% to show a reduction by half (30% versus 15%) in the rate of delirium occurrence between the control group using IV sedation and the interventional group using inhaled sedation at a two-sided alpha level of 0.05, accounting for 3% lost to follow-up.

Recruitment

The initial duration of patient enrolment expected is 2 years, starting in July 2020. 2020: approval by an independent Ethics Committee. 2020-2022: recruitment period. 2022: end of recruitment, monitoring of participating centers and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database. 2023: data analysis, writing of the manuscript and submission for publication.

Methods: assignment of intervention, data collection, management and analysis

Allocation and sequence intervention

A computer-generated, center stratified randomization is performed in a 1:1 ratio, using a centralized web-based management system (Cleannfile). The strategy assigned to the patient (IV or inhaled sedation) will be initiated immediately after randomization.

Data collection and management

Data will be collected on a Case Report Form (e-CRF) by a trained investigator or research assistant at each center. A blank copy of the e-CRF can be printed from the e-CRF. This enables the investigator or research assistant to fill it out with the data of the included patients, which will be captured. Once data collection has been completed, the investigator or research assistant shall sign and date the copy. This document will constitute an integral part of the patient's medical records; as such, it shall be retained permanently. Data recorded in the e-CRF that originate in source documents must be consistent with each other; if they are not, the differences have to be justified and documented. Blinded and patient identifiable data are stored separately in secure databases. All patient identifiable data are stored by the coordinating center. Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. At time of inclusion, the following data will be collected:

Patient demographics, APACHE (Acute Physiology and Chronic Health Evaluation) score, SOFA score, hemodynamic variables and vasoactive drug support, ventilation mechanics, laboratory investigations, clinical ICU complications, length of stay, and mortality will be recorded by daily patient assessment and review of paper and electronic health records. Delirium will be assessed twice daily using the Confusion Assessment Method (CAM-ICU). All these parameters will be collected each day from day 1 to ICU discharge.

Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months using two kinds of scores:

1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60 minutes medical consultation (those tests were also used in the Spice functional and neuro-psychological outcomes SPICEFANS substudy [25].

2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental activities of daily living) performed by a clinical research associate.

Statistical methods

All the analyses will be performed by an independent statistician, following a predefined statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a blind review of the data and final database lock. All the analyses will be conducted using SAS V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value equal or less than 0.05 will be considered as statistically significant. All tests, except for the primary outcome, will be exploratory.

Descriptive analysis of patient groups at baseline

Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described. The baseline characteristics of the study participants will be described according to their randomization group.

Analysis pertaining to the main criteria of evaluation

The frequency of delirium occurrence will be compared between the two groups using a Chi-square test or an exact Fisher test if required. The probability of delirium occurrence will then be modeled (secondary analysis) using a multivariate logistic regression.

Analysis pertaining to the secondary criteria of evaluation

Secondary criteria of evaluation will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the $\chi 2$ test (or Fisher's exact test) for qualitative variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses.

Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

Predetermined subgroup analysis

Duration of delirium will be compared between the two groups among patients who suffered from delirium, using the Student's t-test or the Mann-Whitney U test if required.

Data monitoring

An investigator at each center will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants will regularly monitor all the centers on site to check adherence to the protocol and the accuracy of the data recorded.

Ethics and dissemination

Consent or assent

The patient will be included after having provided a written informed consent to the investigator according to the decision of the central Ethics Committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial. Her/his consent will again be necessary for the continuation of the study.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is promoted by the University Hospital of Brest. Sedana Medical funded the promoter for study monitoring and will provide sedation equipment and monitoring for all the participating centers, but will have no other involvement in the study, data analysis, the writing of the manuscript, or in the decision to submit the manuscript.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The protocol is reported according to the SPIRIT guidelines. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicize and explain the research to clinicians, commissioners and service users.

Patient and public involvement

Patients and public were not involved in the study.

Discussion

International guidelines on sedation and delirium in ICU have been developed and formulated by national and international Societies [1]. Concerning sedation, four messages are important:

using light sedation versus deep sedation, however there is no consensus on the definition of light, moderate, and deep sedation,

using a daily sedative interruption protocol or a nurse-driven sedation protocol,

using propofol or dexmedetomidine over benzodiazepines even if there is no difference between propofol and benzodiazepine use for delirium prevention and even if the pooled analysis of all evaluated studies in these guidelines did not show a significant benefit of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical ventilation extubation, ICU length of stay and the risk for delirium,

monitor sedation.

Benzodiazepine use is to be avoided within the ICU [1]. If propofol has a more favorable pharmacokinetics than benzodiazepine, its prolonged exposure can lead to hypotension, respiratory depression, hypertriglyceridaemia, pancreatitis and to the often lethal propofol infusion syndrome [26, 27].

Dexmedetomidine (alpha 2 adrenergic receptor agonist) seems to reduce the delirium duration, the coma duration and even mortality in septic patients [28, 29]. However, dexmedetomidine is often insufficient to deeply sedate [29]. Since the publication of these guidelines, the SPICE study, a recent multicenter trial enrolling 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction at day 90, showed that sedation targets were difficult to obtain with dexmedetomidine as the sole agent of sedation and that adverse effects were multiplied by ten [25].

The NONSEDA study (comparing a no sedation group versus a light sedation group [RASS-2;-3]) enrolled 710 patients. Mortality at 90 days did not differ significantly between those assigned to a plan of no sedation and those assigned to a plan of light sedation. 14% of screened patients declined to participate and about one third patient should have been sedated during the first 24 hours in the no sedation group [30].

Delirium during sedation administration is frequent. Rapidly improving cognitive state concerns only a minority of delirium sedated patients (14%). Majority of delirium under sedation patient has a worse long-term prognosis [31]. These results have been confirmed in a large study showing that delirium associated with sedation was the most common type of delirium in ICU, but also the most strongly associated with long-term cognitive impairment [32]. Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term outcomes has been defined as one of the top trials to perform in the next years by a multinational, interprofessional board [33].

Potential benefits of isoflurane use in ICU are the absence of accumulation or tachyphylaxis, the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the wake up speed and the analgesia effect [13, 15, 16, 34]. The duration of use of isoflurane is long and range up to 96 hours in the study by Sackey et al. [35], up to 348 hours in the study by L'Her et al. [13], up to 323 hours in the study by Krannich et al. [36]. Despite these extended times, the duration of mechanical ventilation and length of stay in the intensive care unit are shorter in the study by Krannich et al., extubations were performed earlier in the study by Jerath et al., response to simple orders and the extubation are obtained earlier in the study by Sackey et al. [35–37]. RCTs examining volatile anesthesics effects and safety aspects in ICU are currently recruiting (NCT01983800) or have been published demonstrating the safety and acceptability in limited experience ICUs [38]. Inhaled sedation has shown decrease of epithelial injury and inflammation in ARDS [15]. Those results should however be confirmed in a randomized clinical trial (NCT04235608). Safety use for the staff in charge of the patient has been established [17, 18]. Recommendations for use have been issued [39]. Inhaled

volatile anesthetics to conserve intravenous sedatives agents have proven to be effective during the COVID-19 pandemic [40, 41, NCT04383730]. In addition, their potential neuroprotective effect would make it an anesthetic of choice in the prevention of ICU delirium [42, 43]. Schoen et al. report that sevoflurane improved short-term post-operative cognitive ability in patients undergoing circulatory assisted heart surgery compared to propofol [44]. Dabrowski et al. have confirmed in patients undergoing bypass surgery that sevoflurane and isoflurane attenuate levels of MMP-9, GFAP, specific biochemical markers of brain injury [45].

All of these results stress the importance of carrying out this study whose hypothesis is that inhaled sedation strategy would decrease delirium occurrence. The use of isoflurane preferentially over sevoflurane is justified by the absence of wake-up gain by the use of sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or pharmacodynamic differences between the molecules during their use in general anesthesia and a more pronounced bronchodilator effect of isoflurane [46–48]. Sevoflurane induced diabetes insipidus is of concern in context of long-term sedation [49].

The INASED study is the first randomized, controlled and open-label trial adequately powered to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are as broad as possible. This strategy maximizes recruitment rates and improves the generalization of results. All patients will be treated using the ABCDEF bundle which implies less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting depth of sedation, type of sedative drug, and duration of use [20]. It is not possible to blind local investigators to allocation treatment. However withdrawing of sedation, SBT, extubation will follow a nurse-driven protocol. Blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Given the current data and potential of isoflurane sedation to improve patient outcomes, INASED is a well-designed, adequately powered RCT within a homogeneous population to truly understand the potential clinical effects of this sedation modality.

Trial status

The trial has already achieved many milestones. The study is funded by Sedana Medical and promoted by the University Hospital of Brest. Research Ethics Committee approval was obtained in April 2020. It is registered with the American registry of trials (https:// clinicaltrials.gov/; NCT04341350). Starting point of the study was August 2020. 18 patients have been included.

Contributors

PB and ELH designed the study and wrote the manuscript together. EN provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. PYE, SE, AWT, CG, GG, FR, OH, SJ contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

Funding

The study is funded by Sedana Medical which did not interfere with the design of the trial and have no other involvement in the study, data analysis, the writing of the manuscript, or in the decision to submit the manuscript. The study is promoted by the University Hospital of Brest.

Disclaimer

The firm Sedana provides therapy equipment and monitoring to all the participating centers but has no other involvement in the study.

Competing interests

PB reports financial support (travel expanse coverage to attend scientific meetings) from Sedana Medical.

SE declares receiving consulting fees, unrestricted research grants and equipment research support from Aerogen Ltd, unrestricted research grant from Fisher & Paykel, unrestricted research grant form Hamilton medical, consulting fees from La Diffusion Technique Française.

AWT reports financial support (payment for lectures and travel expanse coverage to attend scientific meetings) from Fisher & Paykel, Covidien, Maquet - Getinge and GE Healthcare.

SJ reports receiving consulting fees from Drager, Medtronic, Baxter,Fresenius Medical and Fisher & Paykel.

ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to automated oxygen administration. He is also a consultant for Sedana Medical, GE Healthcare and Smiths Medical.

Ethic approval

The study has been approved by the CPP Nord-Ouest 1 with the registration number 19.12.20.72129.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Open access

Figure 1 legend:

Intervention. Patients that are eligible for inclusion will be randomized and assigned to one of the two groups (inhaled or IV sedation). Outcomes will be evaluated during ICU stay, at discharge and at 3 and 12 months.

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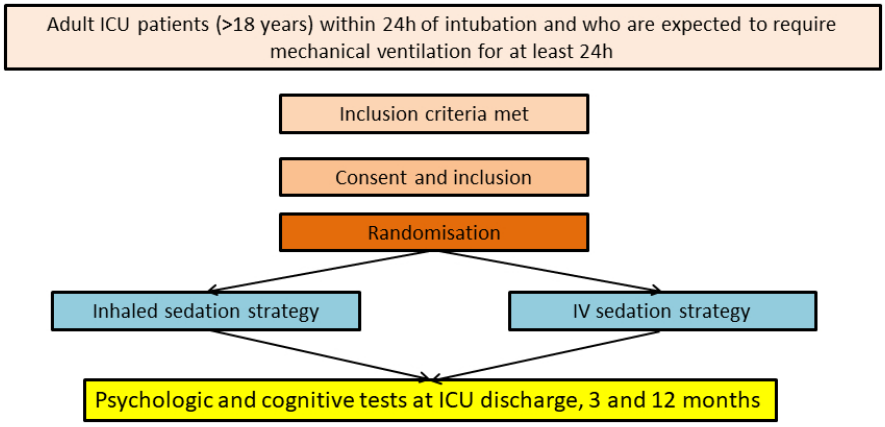

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Inased (Inhaled Sedation in ICU) trial protocol: a multicenter randomized open-label trial

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Inased (Inhaled Sedation in ICU) trial protocol: a multicenter randomized open-label trial

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Abstract

Introduction

The use of sedation in ICUs is necessary and ubiquitous. The impact of sedation strategy on outcome, particularly when delivered early after initiation of mechanical ventilation, is unknown. Evidence is increasing that volatile anesthetic agents could be associated with better outcome. Their use in delirium prevention is unknown.

Methods and analysis

This study is an investigator-initiated, prospective, multicenter, two-arm, randomized, control, open trial comparing inhaled sedation strategy versus intra-venous (IV) sedation strategy in mechanically ventilated patients in ICU. Two hundred and fifty patients will be randomly assigned to the IV sedation group or inhaled sedation group, with a 1:1 ratio in two groups according to the sedation strategy. The primary outcome is the occurrence of delirium assessed using twice a day confusion assessment method for the ICU (CAM-ICU). Secondary outcomes include cognitive and functional outcomes at 3 and 12 months.

Ethics and dissemination

The study has been approved by the Regional Ethics Committee (CPP Ouest) and national authorities (ANSM). The results will be submitted for publication in peer-reviewed journals.

Trial registration number

NCT04341350

Strengths and limitations of this study

The INASED study is a multicenter, randomized, controlled and open-label trial, comparing two sedation strategies.

The primary outcome is the occurrence of delirium up until ICU discharge.

Neurocognitive evaluation will be performed for at least 3-months after ICU discharge, which will enable investigators to evaluate patients' outcome on a strong indicator.

The main limitation of the study is that considering the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

However, blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Introduction

Background and rationale

The use of sedative drugs in intensive care units (ICUs) is essential and ubiquitous. Sedatives are administered to critically ill patients to relieve anxiety, reduce the stress of mechanical ventilation and prevent agitation-related harm [1]. However, sedative drugs and their active metabolites can accumulate, leading to prolonged deep sedation, respiratory depression, immune suppression, and hypotension. Under-sedation leads to agitation, hypercatabolism, self-harm and unplanned extubation [2]. Over-sedation may increase the duration of mechanical ventilation, exposing patient to ventilator acquired pneumonia [3]. Yet, these drugs, used as part of sedation titration protocol or daily sedation stop protocol, have improved patient outcomes [4–6].

However all these drug regimen, by uncertain mechanisms, favor the occurrence of ICU delirium. ICU delirium and ICU delirium duration are independent factors associated with the duration of mechanical ventilation, ICU length of stay and 6 month mortality [7, 8]. It has been demonstrated that patients who survive admission to ICU but who have experienced delirium suffer moderate to severe cognitive impairment at 6 months and show persistent depression, anxiety and post-traumatic stress 1 year after hospitalization leading to public health burden [9–12].

Halogenated gases have been used for a long time in anesthesia. Thanks to technical innovations, they can be used with ICU ventilators [13]. Their dose adjustment is simple, they have no active metabolites and are cleared by breathing. Several studies on selected populations have shown the feasibility and the benefits of this use in ICU [13–16]. Safety use for the staff in charge of the patient has been established [17, 18].

To the best of our knowledge, no study has yet prospectively examined the potential clinical effect of isoflurane sedation on delirium as the primary outcome in the ICU setting.

Objectives

We aim to conduct a prospective multicenter randomized controlled trial comparing two sedation strategies in ICU with the hypothesis that inhaled sedation strategy would decrease delirium occurrence.

Primary objective

Determine the impact on the delirium occurrence of an inhaled sedation strategy versus an intra-venous sedation strategy in ICU mechanically ventilated patients.

Trial design

The INASED study is an investigator-initiated, prospective, multicenter, randomized, open-label trial comparing inhaled versus intra-venous sedation in ICU mechanically ventilated

patients. Patients will be assigned to the IV sedation group or the inhaled sedation group, with a 1:1 ratio.

Methods: participants, interventions and outcomes

Study setting

The INASED study will take place in 10 ICUs in France.

Inclusion criteria

Patients eligible to be enrolled in this trial are adult ICU patients (>18 years) within 24 hours of intubation and who are expected to require mechanical ventilation for at least 24 hours; patient requiring immediate ongoing sedative medication for comfort, safety, and to facilitate the delivery of life support measures.

Exclusion criteria

Age less than 18 years; patient that has been intubated for more than 24 hours in the ICU; admission for a cardiac arrest, a traumatic brain injury, and/or a stroke; patient that is unable to complete the neuropsychological test due to aphasia, deafness, blindness or dementia; contraindication to isoflurane (personal or familial history of malignant hyperthermia; liver failure with prothrombin < 30%; acute or chronic neuromuscular disease); occurrence of a severe ARDS (P/F ratio<100), a PaCO2>50mmHg at the time of randomization; death is deemed to be imminent or inevitable during the ICU admission; pregnancy or breastfeeding woman; patient under guardianship or curatorship.

Intervention

As in the VALTS trial, two sedation strategy will be compared: one with volatile agent (isoflurane), the other with IV sedative (propofol) [19]. Patients that are eligible for inclusion will be randomized and assigned to one of the two following groups (Fig. 1): (1) The patients assigned to control group will receive continuous infusion of IV propofol (2) The patients assigned to interventional group will receive continuously inhaled isoflurane with use of AnaConDa (Sedana Medical, Uppsala, Sweden). Sedation and pain management in both arms will be guided using a standardized nurse-driven bedside protocol. Sedation in both arms will be titrated every hour to reach a Richmond Agitation Sedation Scale of (-2;1) (or as clinically indicated) until extubation [20]. Supplemental sedatives can be used, always at the minimum effective dose, to optimize sedation and achieve the level of sedation specified by the treating clinician at any time when allocated treatment alone is insufficient to provide patient comfort and safety, provide rescue sedation for immediate control of sudden breakthrough agitation at any time. Benzodiazepines will not be administered to any patient, unless deemed mandatory by the treating clinician for conditions such as convulsions, palliation, procedural

anesthesia, concomitant neuromuscular blockade or refractory agitation. Patients will be reviewed daily for assessment of withdrawing sedation to assist ventilator weaning (resolving the underlying pathology that led to mechanical ventilation; FiO2<50%; PEEP 5 to 8 cm H2O; hemodynamic stability with mean arterial pressure>60 mmHg, which maybe assisted with stable doses of vasoactive drug support) and extubated according to predefined criteria. Pain scores will be monitored every 2 hours in both groups using the Behavorial Pain Scale (BPS), the Face Legs Activity Cry Consolability or the VICOMORE and/or numerical pain score. Pain treatment is based on the ABCDEF bundle [21]. It uses the nurse driven analgesia protocol of each ward involved in the study. It uses a pain assessment score (BPS, VICOMORE, FLACC), local or regional anesthesia, non-opioid adjuncts (acetaminophen, NSAIDs, nefopam), opioids (per os opioids, bolus of sufentanyl followed by continuous infusion if necessary, continuous infusion of remifentanyl). We decided to avoid morphine use for analgesia-based sedation because of its long half-life of action and its accumulation [22]. In both groups, light sedation is encouraged (RASS -2; 1). Whatever the treatment arm allocated, ABCDEF bundle will be used [21].

Control group: IV sedation

The patients assigned to the control group will receive continuously IV propofol. Sedation and pain management will be guided using an explicit bedside nurse driven sedation opioid analgesia algorithm.

Interventional group: inhaled sedation

Isoflurane will be infused into the AnaConDa device (Sedana Medical, Uppsala, Sweden), which is placed between the endotracheal tube and the ventilator breathing circuit. Isoflurane is placed in a standard syringe pump. The AnaConDa is placed in the breathing circuit between the Y-piece and the ET-tube. Liquid isoflurane is delivered from the syringe through the dedicated line into the AnaConDa where it is vaporized within the device. In order to limit the dead space, INASED study will only use 50mL AnaConDa S filters. The gas monitor samples the gas from the AnaConDa port and displays the exhaled anesthetic concentration in Fet% or MAC values (which indicates the concentration of the drug). Due to AnaConDa's design, most of the exhaled anesthetic agent is adsorbed and reflected to the patient upon inspiration [23]. Thus, AnaConDa recycles more than 90 % of the expired volatile agent, which facilitates low infusion rates. The residual anesthetic agent passes through the ventilator and exits through the exhaust where it is captured in the FlurAbsorb. The AnaConDa is changed every 24 h. When patients are being prepared for extubation, Isoflurane will be discontinued, and the AnaConDa device will be removed from the breathing circuit to facilitate rapid drug elimination. Gas-scavenging is performed with a commercially available canister connected to the ventilator output. The canister contains 500g of activated charcoal and removes isoflurane from the expired air up to a weight increase of 150 g, which provides 24 hours with the AnaConDa.

Staff education and training

This trial involves centers where the use of volatile sedation may be uncommon. Thus, education of medical, nursing and respiratory therapy staff regarding the use of volatile agents is supported by the development of a web-based teaching program. Training sessions with a dedicated nurse include information regarding the use of the AnaConDa device, equipment set-up, and safety.

Masking protocol

It is not possible to blind local investigators to allocation as it is obvious which patients are receiving inhaled sedation: AnaConDa is connected to the endotracheal tube and requires the use of exhaled isoflurane monitor and a syringe driver. As the INASED study uses a nurse driven protocol, withdrawing of sedation is not initiated by the medical investigator but by the nurse in charge of the patient, based on this pre-specified protocol. This is similar to what is used for spontaneous breathing trial (SBT), which are triggered daily by the nurse without medical consent if all the pre-specified criteria are met [24]. If SBT fails, patient is not extubated. If it succeeds, patient is extubated. Blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group. Physicians treating the patients will be blinded for the final evolution of the neuro-cognitive assessment. However, the study remains an open-blinded study while physicians will be aware of the sedation group.

Equipment licensing and approvals

The AnaConDa device is licensed for use in Europe and isoflurane use in ICU is permitted (EC certificate CE 667826).

Duration of treatment

In both groups, patients will be treated for a minimal duration of 24 hours. Sedation continuation will be decided on an individual basis, according to the patient clinical status and will continue until no longer indicated up to a 14-days maximum after enrolment. If sedation is deemed necessary beyond 14 days after enrolment, the choice of sedative regimen will be determined solely by the treating clinician.

Outcomes

Primary outcome

The primary outcome is the occurrence of delirium (yes / no) up until ICU discharge assessed using the confusion assessment method for the ICU (CAM-ICU). As delirium is fluctuating, CAM-ICU is to be evaluated twice a day, first time in the morning during first daily medical examination, second time in the evening at the beginning of the night shift. We decided not to evaluate delirium during the night in order to avoid sleep disorders within our patients and to follow recommendation of the ABCDEF bundle [21].

Secondary outcomes

Secondary outcome variables include the following:

ICU outcomes:

Number of days with vasopressors or inotropic agents

Number of days with sedation

Cumulative dose and duration of anesthetics drugs

Maximum dose of vasopressors or inotropic agents

Ventilation free days at 28 days following randomization

Proportion of RASS measurements in target range

Incidence and duration of delirium (delirium free days at 28 days). Additionally, we consider a positive CAM-ICU assessment to be hyperactive delirium if the corresponding RASS is >0 and hypoactive delirium if the corresponding RASS is <0

Number of days until RASS 0; -1 is reach

Mortality at ICU discharge, at 28 days

Length of ICU stay

Requirement of physical restraints, of patients with unplanned extubation, unplanned catheter, urinary probe or gastric probe removal

Self or hetero-aggressive act

Hospital outcome

Mortality at hospital discharge

Length of hospital stay

Readmission to ICU

Discharge destination

Post-hospital outcomes

Cost-effectiveness; institutional perspective and cost of lives saved (if positive).

Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months using two kinds of scores:

1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60 minutes medical consultation (those tests were also used in the Spice functional and neuro-psychological outcomes SPICEFANS substudy [25]).

2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental activities of daily living) performed by a clinical research associate.

Sample size

We determined that enrolment of 250 patients would provide a power of 80% to show a reduction by half (30% versus 15%) in the rate of delirium occurrence between the control group using IV sedation and the interventional group using inhaled sedation at a two-sided alpha level of 0.05, accounting for 3% lost to follow-up.

Recruitment

The initial duration of patient enrolment expected is 2 years, starting in July 2020. 2020: approval by an independent Ethics Committee. 2020-2022: recruitment period. 2022: end of recruitment, monitoring of participating centers and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database. 2023: data analysis, writing of the manuscript and submission for publication.

Methods: assignment of intervention, data collection, management and analysis

Allocation, data collection and monitoring will be carried out according to the same methods described in the HIGH-WEAN protocol [26].

Allocation and sequence intervention

A computer-generated, center stratified randomization is performed in a 1:1 ratio, using a centralized web-based management system (Cleannfile). The strategy assigned to the patient (IV or inhaled sedation) will be initiated immediately after randomization.

Data collection and management

Data will be collected on a Case Report Form (e-CRF) by a trained investigator or research assistant at each center. A blank copy of the e-CRF can be printed from the e-CRF. This enables the investigator or research assistant to fill it out with the data of the included patients, which will be captured. Once data collection has been completed, the investigator or research assistant shall sign and date the copy. This document will constitute an integral part of the patient's medical records; as such, it shall be retained permanently. Data recorded in the e-CRF that originate in source documents must be consistent with each other; if they are not, the differences have got to be justified and documented. Blinded and patient identifiable data are stored separately in secure databases. All patient identifiable data are stored by the coordinating center. Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. At time of inclusion, the following data will be collected:

Patient characteristics, severity scores (Acute Physiology and Chronic Health Evaluation score, SOFA score), hemodynamics, vasoactive drug support, ventilation mechanics, laboratory findings, clinical ICU complications, length of stay, and mortality will be recorded. Delirium will be assessed twice daily using the Confusion Assessment Method (CAM-ICU)[27]. All these parameters will be collected each day from day 1 to ICU discharge.

Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months using two kinds of scores:

1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60 minutes medical consultation (those tests were also used in the Spice functional and neuro-psychological outcomes SPICEFANS substudy [25].

2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental activities of daily living) performed by a clinical research associate.

Statistical methods

All the analyses will be performed by an independent statistician, following a predefined statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a blind review of the data and final database lock. All the analyses will be conducted using SAS V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value equal or less than 0.05 will be considered as statistically significant. All tests, except for the primary outcome, will be exploratory.

Descriptive analysis of patient groups at baseline

Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described. The baseline characteristics of the study participants will be described according to their randomization group.

Analysis pertaining to the main criteria of evaluation

The frequency of delirium occurrence will be compared between the two groups using a Chi-square test or an exact Fisher test if required. The probability of delirium occurrence will then be modeled (secondary analysis) using a multivariate logistic regression.

Analysis pertaining to the secondary criteria of evaluation

Secondary criteria of evaluation will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the $\chi 2$ test (or Fisher's exact test) for qualitative variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses.

Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

Predetermined subgroup analysis

Duration of delirium will be compared between the two groups among patients who suffered from delirium, using the Student's t-test or the Mann-Whitney U test if required.

Data monitoring

An investigator at each center will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the e-CRF. Research assistants will regularly monitor all the centers on site to check adherence to the protocol and the accuracy of the data recorded.

Ethics and dissemination

Consent or assent

The patient will be included after having provided a written informed consent to the investigator according to the decision of the central Ethics Committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial. Her/his consent will again be necessary for the continuation of the study.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is promoted by the University Hospital of Brest. Sedana Medical funded the promoter for study monitoring and will provide sedation equipment and monitoring for all the participating centers, but will have no other involvement in the study, data analysis, the writing of the manuscript, or in the decision to submit the manuscript.

Access to data

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Dissemination policy

The protocol is reported according to the SPIRIT guidelines. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicize and explain the research to clinicians, commissioners and service users.

Patient and public involvement

Patients and public were not involved in the study.

Discussion

International guidelines on sedation and delirium in ICU have been developed and formulated by national and international Societies [1]. Concerning sedation, four messages are important:

using light sedation versus deep sedation, however there is no consensus on the definition of light, moderate, and deep sedation,

using a daily sedative interruption protocol or a nurse-driven sedation protocol,

using propofol or dexmedetomidine over benzodiazepines even if there is no difference between propofol and benzodiazepine use for delirium prevention and even if the pooled analysis of all evaluated studies in these guidelines did not show a significant benefit of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical ventilation extubation, ICU length of stay and the risk for delirium,

monitor sedation.

Benzodiazepine use is to be avoided within the ICU [1]. If propofol has a more favorable pharmacokinetics than benzodiazepine, its prolonged exposure can lead to hypotension,

respiratory depression, hypertriglyceridaemia, pancreatitis and to the often lethal propofol infusion syndrome [28, 29].

Dexmedetomidine (alpha 2 adrenergic receptor agonist) seems to reduce the delirium duration, the coma duration and even mortality in septic patients [30, 31]. However, dexmedetomidine is often insufficient to deeply sedate [31]. Since the publication of these guidelines, the SPICE study, a recent multicenter trial enrolling 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction at day 90, showed that sedation targets were difficult to obtain with dexmedetomidine as the sole agent of sedation and that adverse effects were multiplied by ten [25].

The NONSEDA study (comparing a no sedation group versus a light sedation group [RASS-2;-3]) enrolled 710 patients. Mortality at 90 days did not differ significantly between those assigned to a plan of no sedation and those assigned to a plan of light sedation. 14% of screened patients declined to participate and about one third patient should have been sedated during the first 24 hours in the no sedation group [32].

Delirium during sedation administration is frequent. Rapidly improving cognitive state concerns only a minority of delirium sedated patients (14%). Majority of delirium under sedation patient has a worse long-term prognosis [33]. These results have been confirmed in a large study showing that delirium associated with sedation was the most common type of delirium in ICU, but also the most strongly associated with long-term cognitive impairment [34]. Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term outcomes has been defined as one of the top trials to perform in the next years by a multinational, interprofessional board [35].

Potential benefits of isoflurane use in ICU are the absence of accumulation or tachyphylaxis, the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the wake up speed and the analgesia effect The duration of use of isoflurane is long and range up to 96 hours in the study by Sackey et al. [36], up to 348 hours in the study by L'Her et al. [13], up to 323 hours in the study by Krannich et al. [37]. Despite these extended times, the duration of mechanical ventilation and lenghth of stay in the intensive care unit are shorter in the study by Krannich et al., extubations were performed earlier in the study by Jerath et al., response to simple orders and the extubation are obtained earlier in the study by Sackey et al.[36–38]. RCTs examining volatile anesthesics effects and safety aspects in ICU are currently recruiting (NCT01983800) or have been published demonstrating the safety and acceptability in ICUs with limited experience of using volatile anesthesics-based sedation [39] . Inhaled sedation has shown decrease of epithelial injury and inflammation in ARDS [14]. Those results should however be confirmed in a randomized clinical trial (NCT04235608). Safety use for the staff in charge of the patient has been established [17, 18]. Recommendations for use have been issued [40]. Inhaled volatile anesthetics to conserve intravenous sedatives agents have proven to be effective during the COVID-19 pandemic [41, 42, NCT04383730]. In addition, their

potential neuroprotective effect would make it an anesthetic of choice in the prevention of ICU delirium [43, 44]. Schoen et al. report that sevoflurane improved short-term post-operative cognitive ability in patients undergoing circulatory assisted heart surgery compared to propofol [45]. Dabrowski et al. have confirmed in patients undergoing bypass surgery that sevoflurane and isoflurane attenuate levels of MMP-9, GFAP, specific biochemical markers of brain injury [46].

All of these results stress the importance of carrying out this study whose hypothesis is that inhaled sedation strategy would decrease delirium occurrence. The use of isoflurane preferentially over sevoflurane is justified by the absence of wake-up gain by the use of sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or pharmacodynamic differences between the molecules during their use in general anesthesia and a more pronounced bronchodilator effect of isoflurane[47–49]. Sevoflurane induced diabetes insipidus is of concern in context of long-term sedation [50].

The INASED study is the first randomized, controlled and open-label trial adequately powered to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are as broad as possible. This strategy maximizes recruitment rates and improves the generalization of results. All patients will be treated using the ABCDEF bundle which implies less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting depth of sedation, type of sedative drug, and duration of use [21]. It is not possible to blind local investigators to allocation treatment. However withdrawing of sedation, SBT, extubation will follow a nurse-driven protocol. Blinding of outcome data assessment is ensured as the cognitive function is evaluated by a research assistant that will not be aware of patient assignment group.

Given the current data and potential of isoflurane sedation to improve patient outcomes, INASED is a well-designed, adequately powered RCT within a homogeneous population to truly understand the potential clinical effects of this sedation modality.

Trial status

The study is funded by Sedana Medical and promoted by the University Hospital of Brest. Research Ethics Committee approval was obtained in April 2020. It is registered with the American registry of trials (https:// clinicaltrials.gov/; NCT04341350). Starting point of the study was August 2020. 20 patients have been included.

Contributors

PB and ELH designed the study and wrote the manuscript together. EN provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and

estimated the sample size. PYE, SE, AWT, CG, GG, FR, OH, SJ contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

Funding

The study is funded by Sedana Medical which did not interfere with the design of the trial and have no other involvement in the study, data analysis, the writing of the manuscript, or in the decision to submit the manuscript. The study is promoted by the University Hospital of Brest.

Disclaimer

The firm Sedana provides therapy equipment and monitoring to all the participating centers but has no other involvement in the study.

Competing interests

PB reports financial support (travel expanse coverage to attend scientific meetings) from Sedana Medical.

SE declares receiving consulting fees, unrestricted research grants and equipment research support from Aerogen Ltd, unrestricted research grant from Fisher & Paykel, unrestricted research grant form Hamilton medical, consulting fees from La Diffusion Technique Française.

AWT reports financial support (payment for lectures and travel expanse coverage to attend scientific meetings) from Fisher & Paykel, Covidien, Maquet - Getinge and GE Healthcare.

SJ reports receiving consulting fees from Drager, Medtronic, Baxter,Fresenius Medical and Fisher & Paykel.

ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to automated oxygen administration. He is also a consultant for Sedana Medical, GE Healthcare and Smiths Medical.

Ethic approval

The study has been approved by the CPP Nord-Ouest 1 with the registration number 19.12.20.72129.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

Open access

Figure legend:

Intervention. Patients that are eligible for inclusion will be randomized and assigned to one of the two groups (inhaled or IV sedation). Outcomes will be evaluated during ICU stay, at discharge and at 3 and 12 months.

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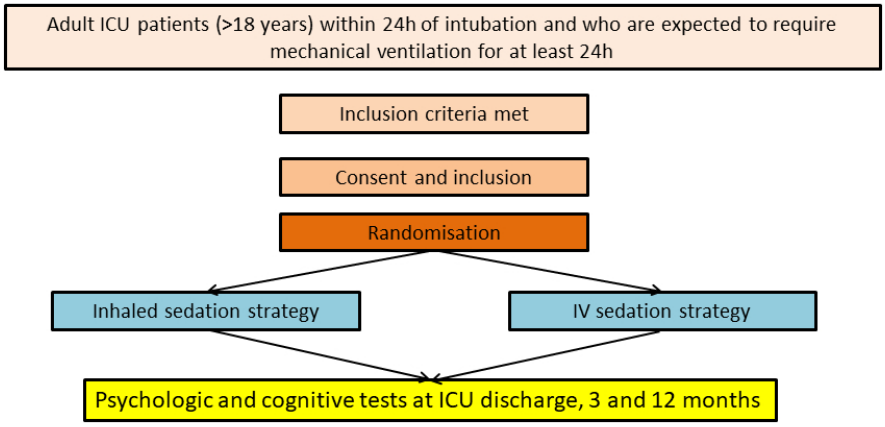

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