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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 ever 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

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

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28 We aim to conduct a prospective multicentre randomised controlled trial comparing two
29 sedation strategies in ICU with the hypothesis that inhaled sedation strategy would decrease
30 delirium occurrence.
31
32

33 Primary objective

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35 Determine the impact on the delirium occurrence of an inhaled sedation strategy versus an
36 intra-venous sedation strategy in ICU mechanically ventilated patients.
37
38

39 Trial design

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41 The INASED study is an investigator-initiated, prospective, multicentre, randomised, open-
42 label trial comparing inhaled versus intra-venous sedation in ICU mechanically ventilated
43 patients. Patients will be assigned to the IV sedation group or the inhaled sedation group,
44 with a 1:1 ratio.
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50 **Methods: participants, interventions and outcomes**

51 Study setting

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53 The INASED study will take place in 10 ICUs in France.
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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 Behavioral 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-opioid 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 anaesthetics 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

1
2
3 Mortality at hospital discharge

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5 Length of hospital stay

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7 Readmission to ICU

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9 Discharge destination

10
11 Post-hospital outcomes

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

14
15 Cognitive function, psychological state and health related quality of life at 3 and 12
16
17 months

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19 Sample size

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21
22 We determined that enrolment of 250 patients would provide a power of 80% to show a
23
24 reduction by half (30% versus 15%) in the rate of delirium occurrence between the control
25
26 group using IV sedation and the interventional group using inhaled sedation at a two-sided
27
28 alpha level of 0.05, accounting for 3% lost to follow-up.

29 Recruitment

30
31 The initial duration of patient enrolment expected is 2 years, starting in July 2020. 2020:
32
33 approval by an independent ethics committee. 2020-2022: inclusion of patients. 2022: end
34
35 of inclusions, monitoring of participating centres and queries to investigators; blind review
36
37 to determine protocol violation, to define intention-to-treat and per-protocol analysis
38
39 populations; new queries to investigators, cleaning and closure of the database. 2023: data
40
41 analysis, writing of the manuscript and submission for publication.

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

43 Allocation and sequence intervention

44
45 A computer-generated, centre stratified randomisation is performed in a 1:1 ratio, using a
46
47 centralised web-based management system (Cleannfile). The strategy assigned to the
48
49 patient (IV or inhaled sedation) will be initiated immediately after randomisation.

50 Data collection and management

51
52 Data will be collected on a Case Report Form (e-CRF) by a trained investigator or research
53
54 assistant at each centre. A blank copy of the e-CRF can be printed from the e-CRF. This
55
56 enables the investigator or research assistant to fill it out with the data of the included
57
58 patients, which will be captured. Once data collection has been completed, the investigator
59
60 or research assistant shall sign and date the copy. This document will constitute an integral

1
2
3 part of the patient's medical records; as such, it shall be retained permanently. Data
4 recorded in the e-CRF that originate in source documents must be consistent with each
5 other; if they are not, the differences have got to be justified and documented. Blinded and
6 patient identifiable data are stored separately in secure databases. All patient identifiable
7 data are stored by the coordinating centre. Site staff will be available to facilitate the
8 monitoring visits and ensure that all required documentation is available for review. At time
9 of inclusion, the following data will be collected:
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11
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13
14 Patient demographics, APACHE (Acute Physiology and Chronic Health Evaluation) score,
15 SOFA score, hemodynamic variables and vasoactive drug support, ventilation mechanics,
16 laboratory investigations, clinical ICU complications, length of stay, and mortality will be
17 recorded by daily patient assessment and review of paper and electronic health records.
18 Delirium will be assessed twice daily using the Confusion Assessment Method (CAM-
19 ICU)[39]. All these parameters will be collected each day from day 1 to ICU discharge.
20
21
22

23 For cognitive function, psychological state and health related quality of life evaluation,
24 HADS, PTSD Checklist 14, SF36, IQCODE, IADL and CANTAB tests will be performed at ICU
25 discharge, 3 and 12 months by investigator or research assistant.
26
27
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29

30 **Statistical methods**

31
32 All the analyses will be performed by an independent statistician, following a predefined
33 statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a
34 blind review of the data and final database lock. All the analyses will be conducted using SAS
35 V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value
36 equal or less than 0.05 will be considered as statistically significant.
37
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39

40 Descriptive analysis of patient groups at baseline

41
42 Wrongly included subjects as well as those lost to follow-up will be described. Deviations
43 from the protocol will be described. The baseline characteristics of the study participants will
44 be described according to their randomization group. Analysis pertaining to the main criteria
45 of evaluation
46
47
48

49 The frequency of delirium occurrence will be compared between the two groups using a Chi-
50 square test or an exact Fisher test if required. The probability of delirium occurrence will
51 then be modeled (secondary analysis) using a multivariate logistic regression.
52
53

54 Analysis pertaining to the secondary criteria of evaluation

55
56 Secondary criteria of evaluation will be compared between the two treatment groups by
57 means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous
58 quantitative variables and by means of the χ^2 test (or Fisher's exact test) for qualitative
59
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1
2
3 variables. Linear models and logistics models will be used to compare the two groups in
4 multivariate analyses.
5

6
7 Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional
8 hazards model.
9

10 Predetermined subgroup analysis

11
12 Duration of delirium will be compared between the two groups among patients who
13 suffered from delirium, using the Student's t-test or the Mann-Whitney U test if required.
14
15

16 Data monitoring

17
18 An investigator at each centre will be responsible for daily patient screening, enrolling
19 patients in the study, ensuring adherence to the protocol and completing the e-CRF.
20 Research assistants will regularly monitor all the centres on site to check adherence to the
21 protocol and the accuracy of the data recorded.
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27 **Ethics and dissemination**

28 Consent or assent

29
30
31 The patient will be included after having provided a written informed consent to the
32 investigator according to the decision of the central ethics committee. If the patient is not
33 able to understand the information given, he/she can be included if the same procedure is
34 completed with a next of kin. Where it is not possible or practicable for the patient or the
35 substitute decision maker to consider the study and give consent within an appropriate
36 timeframe, the patient may be enrolled without prior consent, provided the procedure is in
37 accord with the requirements of the site's Human Research Ethics Committee and applicable
38 legislation. After the patient's recovery, he/she will be asked if he/she agrees to continue the
39 trial.
40
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44

45 Confidentiality

46
47 Data will be handled according to French law. All original records will be archived at trial
48 sites for 15 years. The clean database file will be anonymised and kept for 15 years.
49

50 Declaration of interest

51
52
53 The study is promoted by the University Hospital of Brest. Sedana Medical funded the
54 promoter for study monitoring and will provide sedation equipment and monitoring for all
55 the participating centres, but will have no other involvement in the study, data analysis, the
56 writing of the manuscript, or in the decision to submit the manuscript.
57
58

59 Access to data

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2
3 All investigators will have access to the final data set. Participant-level data sets will be made
4 accessible on a controlled access basis.
5

6 7 Dissemination policy

8
9 The protocol is reported according to the SPIRIT guidelines. Findings will be published in
10 peer-reviewed journals and presented at local, national and international meetings and
11 conferences to publicise and explain the research to clinicians, commissioners and service
12 users.
13
14

15 16 Patient and public involvement

17
18 Patients and public were not involved in the study.
19
20
21

22 23 Discussion

24 International guidelines on sedation and delirium in ICU have been written [1]. Concerning
25 sedation, four messages are important:
26

27 using light sedation versus deep sedation, however there is no consensus on the
28 definition of light, moderate, and deep sedation,
29

30 using a daily sedative interruption protocol or a nurse-protocolised sedation protocol,
31

32 using propofol or dexmedetomidine over benzodiazepines even if there is no
33 difference between propofol and benzodiazepine use for delirium prevention and even if the
34 pooled analysis of all evaluated studies in these guidelines did not show a significant benefit
35 of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical
36 ventilation extubation, ICU length of stay and the risk for delirium,
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39
40

41 monitor sedation.
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43

44 Since the publication of these guidelines, the SPICE study a recent multicenter trial enrolling
45 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual
46 sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction
47 at day 90, showed that sedation targets were difficult to obtain with dexmedetomidine as
48 the sole agent of sedation and that adverse effects were multiplied by ten [17].
49

50
51 Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term
52 outcomes has been defined as one of the top trials to perform in the next years by a
53 multinational, interprofessional board [40].
54
55

56
57 Delirium during sedation administration is frequent. Rapidly improving cognitive state
58 concerns only a minority of delirium sedated patients (14%). Majority of delirium under
59 sedation patient has a worse long-term prognosis [41]. These results have been confirmed in
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1
2
3 a large study showing that delirium associated with sedation was the most common type of
4 delirium in ICU, but also the most strongly associated with long –term cognitive impairment.
5 All of these results stress the importance of carrying out this study [42].
6
7

8 The INASED study is the first randomised, controlled and open-label trial adequately
9 powered to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion
10 criteria are as broad as possible. This strategy maximises recruitment rates and improves the
11 generalisation of results. Both groups have sedation strategy and nurse driven protocol. All
12 patients will be treated using the ABCDEF bundle which implies less variation in study
13 quality, analgesic regimens, use of daily sedation breaks, reporting depth of sedation, type of
14 sedative drug, and duration of use. At last, extubation criteria will be predefined.
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18 Given the current data and potential of isoflurane sedation to improve patient outcomes,
19 INASED is a well-designed, adequately powered RCT within a homogeneous population to
20 truly understand the potential clinical effects of this sedation modality.
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26 **Trial status**

27
28 The trial has already achieved many milestones. The study is funded by Sedana Medical and
29 promoted by the University Hospital of Brest. Research ethics committee approval was
30 obtained in april 2020. It is registered with the American registry of trials ([https://](https://clinicaltrials.gov/)
31 clinicaltrials.gov/; NCT04341350). No patient has yet been included, and expected starting
32 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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Disclaimer

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Competing interests

PB reports financial support (travel expense 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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12

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15

16
17 ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to
18 automated oxygen administration. He is also a consultant for Sedana Medical, GE
19 Healthcare and Smiths Medical.
20
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22 23 24 **Ethic approval**

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26 The study has been approved by the CPP Nord-Ouest 1 est with the registration number
27 19.12.20.72129.
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30 31 32 **Provenance and peer review**

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34 Not commissioned; externally peer reviewed.
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37 38 39 **Data sharing statement**

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41 All investigators will have access to the final data set. Participant-level data sets will be made
42 accessible on a controlled access basis.
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45 46 47 **Open access**

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References

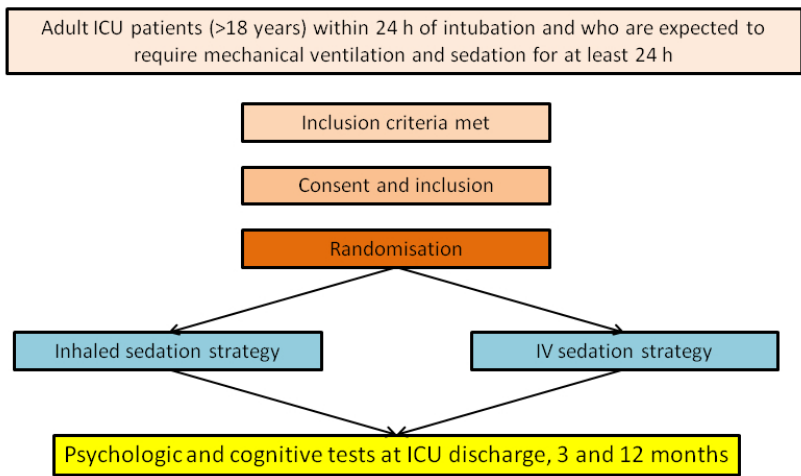
1. Devlin JW, Skrobik Y, Gélinas C, *et al.* Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018;46:e825–e873.
2. Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. *Crit Care* 2009;13:R204.
3. Devlin JW. The pharmacology of oversedation in mechanically ventilated adults. *Curr Opin Crit Care* 2008;14:403–407.
4. De Jonghe B, Bastuji-Garin S, Fangio P, *et al.* Sedation algorithm in critically ill patients without acute brain injury. *Crit Care Med* 2005;33:120–127
5. Arias-Rivera S, Sánchez-Sánchez M del M, Santos-Díaz R, *et al.* Effect of a nursing-implemented sedation protocol on weaning outcome. *Crit Care Med* 2008;36:2054–2060.
6. Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
7. Pandharipande PP, Girard TD, Jackson JC, *et al.* Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
8. Mehta S, Cook D, Devlin JW, *et al.* Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557–566.
9. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med* 2007;33:1506–1518.
10. Wade DM, Howell DC, Weinman JA, *et al.* Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16:R192.
11. Wolters AE, Peelen LM, Welling MC, *et al.* Long-Term Mental Health Problems After Delirium in the ICU. *Crit Care Med* 2016;44:1808–1813.
12. Vasilevskis EE, Chandrasekhar R, Holtze CH, *et al.* The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient. *Med Care* 2018;56:890–897.
13. Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des* 2004;10:3639–3649.
14. Hemphill S, McMenemy L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth* 2019;122:448–459.

- 1
2
3 15. Pandharipande PP, Pun BT, Herr DL, *et al.* Effect of sedation with dexmedetomidine vs
4 lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS
5 randomized controlled trial. *JAMA* 2007;298:2644–2653.
6
7
- 8 16. Ruokonen E, Parviainen I, Jakob SM, *et al.* Dexmedetomidine versus
9 propofol/midazolam for long-term sedation during mechanical ventilation. *Intensive*
10 *Care Med* 2009;35:282–290.
11
- 12 17. Shehabi Y, Howe BD, Bellomo R, *et al.* Early Sedation with Dexmedetomidine in
13 Critically Ill Patients. *N Engl J Med* 2019;380:2506–2517.
14
- 15 18. L'her E, Dy L, Pili R, *et al.* Feasibility and potential cost/benefit of routine isoflurane
16 sedation using an anesthetic-conserving device: a prospective observational study.
17 *Respir Care* 2008;53:1295–1303
18
- 19 19. Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic
20 Agents Compared With Standard Intravenous Midazolam/Propofol Sedation in
21 Ventilated Critical Care Patients: A Meta-analysis and Systematic Review of Prospective
22 Trials. *Anesth Analg.* 2017; 124(4):1190-1199.
23
- 24 20. Jabaudon M, Boucher P, Imhoff E, *et al.* Sevoflurane for Sedation in Acute Respiratory
25 Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med*
26 2017; 195:792–800.
27
- 28 21. Mesnil M, Capdevila X, Bringuier S, *et al.* Long-term sedation in intensive care unit: a
29 randomized comparison between inhaled sevoflurane and intravenous propofol or
30 midazolam. *Intensive Care Med* 2011;37:933–941.
31
- 32 22. Sackey PV, Martling C-R, Carlswärd C, *et al.* Short- and long-term follow-up of intensive
33 care unit patients after sedation with isoflurane and midazolam--a pilot study. *Crit Care*
34 *Med* 2008;36:801–806.
35
- 36 23. Krannich A, Leithner C, Engels M, *et al.* Isoflurane Sedation on the ICU in Cardiac Arrest
37 Patients Treated With Targeted Temperature Management: An Observational
38 Propensity-Matched Study. *Crit Care Med* 2017;45:e384–e390.
39
- 40 24. Jerath A, Beattie SW, Chandy T, *et al.* Volatile-based short-term sedation in cardiac
41 surgical patients: a prospective randomized controlled trial. *Crit Care Med*
42 2015;43:1062–1069.
43
- 44 25. Sackey PV, Martling C-R, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane
45 consumption during intensive care unit sedation with the Anesthetic Conserving
46 Device. *Crit Care Med* 2005;33:585–590.
47
- 48 26. Herzog-Niescery J, Vogelsang H, Gude P, *et al.* The impact of the anesthetic conserving
49 device on occupational exposure to isoflurane among intensive care healthcare
50 professionals. *Minerva Anesthesiol* 2018;84:25–32.
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 - 60
27. Herzog-Niescery J, Seipp H-M, Weber TP, Bellgardt M. Inhaled anesthetic agent sedation in the ICU and trace gas concentrations: a review. *J Clin Monit Comput* 2018;32:667–675.
28. Chen S, Lotz C, Roewer N, Broscheit J-A. Comparison of volatile anesthetic-induced preconditioning in cardiac and cerebral system: molecular mechanisms and clinical aspects. *Eur J Med Res* 2018;23:10.
29. Wang Y-Z, Li T-T, Cao H-L, Yang W-C. Recent advances in the neuroprotective effects of medical gases. *Med Gas Res* 2019;9:80–87.
30. Schoen J, Husemann L, Tiemeyer C, *et al.* Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. *Br J Anaesth* 2011;106:840–850.
31. Dabrowski W, Rzecki Z, Czajkowski M, *et al.* Volatile anesthetics reduce biochemical markers of brain injury and brain magnesium disorders in patients undergoing coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2012;26:395–402.
32. Nyktari V, Papaioannou A, Volakakis N, *et al.* Respiratory resistance during anaesthesia with isoflurane, sevoflurane, and desflurane: a randomized clinical trial. *Br J Anaesth* 2011;107:454–461.
33. Freiermuth D, Mets B, Bolliger D, *et al.* Sevoflurane and Isoflurane-Pharmacokinetics, Hemodynamic Stability, and Cardioprotective Effects During Cardiopulmonary Bypass. *J Cardiothorac Vasc Anesth* 2016;30:1494–1501.
34. Zorrilla-Vaca A, Núñez-Patiño RA, Torres V, Salazar-Gomez Y. The Impact of Volatile Anesthetic Choice on Postoperative Outcomes of Cardiac Surgery: A Meta-Analysis. *Biomed Res Int* 2017:7073401.
35. L’Heudé M, Poignant S, Elaroussi D, *et al.* Nephrogenic diabetes insipidus associated with prolonged sedation with sevoflurane in the intensive care unit. *Br J Anaesth* 2019;122:e73–e75.
36. Sessler CN, Gosnell MS, Grap MJ, *et al.* The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–1344.
37. Tonnelier J-M, Prat G, Le Gal G, *et al.* Impact of a nurses’ protocol-directed weaning procedure on outcomes in patients undergoing mechanical ventilation for longer than 48 hours: a prospective cohort study with a matched historical control group. *Crit Care* 2005;9:R83-89.
38. Pun BT, Balas MC, Barnes-Daly MA, *et al.* Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med* 2019;47:3–14.

- 1
- 2
- 3 39. Ely EW, Inouye SK, Bernard GR, *et al.* Delirium in mechanically ventilated patients:
4 validity and reliability of the confusion assessment method for the intensive care unit
5 (CAM-ICU). JAMA 2001;286:2703–2710.
6
- 7
- 8 40. Pandharipande PP, Ely EW, Arora RC, *et al.* The intensive care delirium research agenda:
9 a multinational, interprofessional perspective. Intensive Care Med 2017;43:1329–1339.
10
- 11 41. Patel SB, Poston JT, Pohlman A, *et al.* Rapidly reversible, sedation-related delirium
12 versus persistent delirium in the intensive care unit. Am J Respir Crit Care Med
13 2014;189:658–665.
14
- 15 42. Girard TD, Thompson JL, Pandharipande PP, *et al.* Clinical phenotypes of delirium
16 during critical illness and severity of subsequent long-term cognitive impairment: a
17 prospective cohort study. Lancet Respir Med 2018;6:213–222.
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Inased (Inhaled Sedation in ICU) trial protocol: a multicentre randomised open-label trial

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Inhaled (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; $FiO_2 < 50\%$; 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 Behavioral 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-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. 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-opioid 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

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

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

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

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51 The AnaConDa device is licensed for use in Europe and isoflurane use in ICU is permitted (EC
52 certificate CE 667826).
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54 Duration of treatment

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

9 Primary outcome

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

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23 Secondary outcome variables include the following:
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25 ICU outcomes:

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27 Number of days with vasopressors or inotropic agents
28

29
30 Number of days with sedation
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32
33 Cumulative dose and duration of anesthetics drugs
34

35
36 Maximum dose of vasopressors or inotropic agents
37

38
39 Ventilation free days at 28 days following randomisation
40

41
42 Proportion of RASS measurements in target range
43

44
45 Incidence and duration of delirium (delirium free days at 28 days). Additionally, we
46 consider a positive CAM-ICU assessment to be hyperactive delirium if the
47 corresponding RASS is >0 and hypoactive delirium if the corresponding RASS is <0
48

49
50 Number of days until RASS 0; -1 is reach
51

52
53 Mortality at ICU discharge, at 28 days
54

55
56 Length of ICU stay
57

58
59 Requirement of physical restraints, of patients with unplanned extubation, unplanned
60 catheter, urinary probe or gastric probe removal
61

62
63 Self or hetero-aggressive act
64

65 Hospital outcome

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3 Mortality at hospital discharge

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5 Length of hospital stay

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7 Readmission to ICU

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9 Discharge destination

10
11 Post-hospital outcomes

12
13 Cost-effectiveness; institutional perspective and cost of lives saved (if positive).

14
15 Cognitive function and functional outcome will be evaluated at discharge, 3- and 12
16 months using two kinds of scores:

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18
19
20 1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60
21 minutes medical consultation (those tests were also used in the Spice functional
22 and neuro-psychological outcomes SPICEFANS substudy [17].
23
24 2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and
25 Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental
26 activities of daily living) performed by a clinical research associate.
27
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33 Sample size

34
35 We determined that enrolment of 250 patients would provide a power of 80% to show a
36 reduction by half (30% versus 15%) in the rate of delirium occurrence between the control
37 group using IV sedation and the interventional group using inhaled sedation at a two-sided
38 alpha level of 0.05, accounting for 3% lost to follow-up.
39
40

41
42 Recruitment

43
44 The initial duration of patient enrolment expected is 2 years, starting in July 2020. 2020:
45 approval by an independent ethics committee. 2020-2022: recruitment period. 2022: end of
46 recruitment, monitoring of participating centres and queries to investigators; blind review to
47 determine protocol violation, to define intention-to-treat and per-protocol analysis
48 populations; new queries to investigators, cleaning and closure of the database. 2023: data
49 analysis, writing of the manuscript and submission for publication.
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55 **Methods: assignment of intervention, data collection, management and analysis**

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57 Allocation and sequence intervention
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3 A computer-generated, centre stratified randomisation is performed in a 1:1 ratio, using a
4 centralised web-based management system (Cleannfile). The strategy assigned to the patient
5 (IV or inhaled sedation) will be initiated immediately after randomisation.
6
7

8 Data collection and management 9

10 Data will be collected on a Case Report Form (e-CRF) by a trained investigator or research
11 assistant at each centre. A blank copy of the e-CRF can be printed from the e-CRF. This enables
12 the investigator or research assistant to fill it out with the data of the included patients, which
13 will be captured. Once data collection has been completed, the investigator or research
14 assistant shall sign and date the copy. This document will constitute an integral part of the
15 patient's medical records; as such, it shall be retained permanently. Data recorded in the e-
16 CRF that originate in source documents must be consistent with each other; if they are not,
17 the differences have got to be justified and documented. Blinded and patient identifiable data
18 are stored separately in secure databases. All patient identifiable data are stored by the
19 coordinating centre. Site staff will be available to facilitate the monitoring visits and ensure
20 that all required documentation is available for review. At time of inclusion, the following data
21 will be collected:
22
23

24 Patient demographics, APACHE (Acute Physiology and Chronic Health Evaluation) score, SOFA
25 score, hemodynamic variables and vasoactive drug support, ventilation mechanics, laboratory
26 investigations, clinical ICU complications, length of stay, and mortality will be recorded by daily
27 patient assessment and review of paper and electronic health records. Delirium will be
28 assessed twice daily using the Confusion Assessment Method (CAM-ICU)[27]. All these
29 parameters will be collected each day from day 1 to ICU discharge.
30
31

32 Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months
33 using two kinds of scores:
34
35

36 1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60
37 minutes medical consultation (those tests were also used in the Spice functional and neuro-
38 psychological outcomes SPICEFANS substudy [17].
39
40

41 2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety
42 and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental
43 activities of daily living) performed by a clinical research associate.
44
45

46 **Statistical methods** 47 48

49 All the analyses will be performed by an independent statistician, following a predefined
50 statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a
51 blind review of the data and final database lock. All the analyses will be conducted using SAS
52 V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value equal
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3 or less than 0.05 will be considered as statistically significant. All tests, except for the primary
4 outcome, will be exploratory.
5

6 Descriptive analysis of patient groups at baseline

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8
9 Wrongly included subjects as well as those lost to follow-up will be described. Deviations from
10 the protocol will be described. The baseline characteristics of the study participants will be
11 described according to their randomization group.
12

13 Analysis pertaining to the main criteria of evaluation

14
15
16 The frequency of delirium occurrence will be compared between the two groups using a Chi-
17 square test or an exact Fisher test if required. The probability of delirium occurrence will then
18 be modeled (secondary analysis) using a multivariate logistic regression.
19

20 Analysis pertaining to the secondary criteria of evaluation

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22
23 Secondary criteria of evaluation will be compared between the two treatment groups by
24 means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous
25 quantitative variables and by means of the χ^2 test (or Fisher's exact test) for qualitative
26 variables. Linear models and logistics models will be used to compare the two groups in
27 multivariate analyses.
28

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31 Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional
32 hazards model.
33

34 Predetermined subgroup analysis

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37 Duration of delirium will be compared between the two groups among patients who suffered
38 from delirium, using the Student's t-test or the Mann-Whitney U test if required.
39

40 Data monitoring

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

52 Consent or assent

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56 The patient will be included after having provided a written informed consent to the
57 investigator according to the decision of the central ethics committee. If the patient is not able
58 to understand the information given, he/she can be included if the same procedure is
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3 completed with a next of kin. After the patient's recovery, he/she will be asked if he/she
4 agrees to continue the trial.
5

6 7 Confidentiality

8
9 Data will be handled according to French law. All original records will be archived at trial sites
10 for 15 years. The clean database file will be anonymised and kept for 15 years.
11

12 13 Declaration of interest

14
15 The study is promoted by the University Hospital of Brest. Sedana Medical funded the
16 promoter for study monitoring and will provide sedation equipment and monitoring for all the
17 participating centres, but will have no other involvement in the study, data analysis, the
18 writing of the manuscript, or in the decision to submit the manuscript.
19

20 21 Access to data

22
23 All investigators will have access to the final data set. Participant-level data sets will be made
24 accessible on a controlled access basis.
25

26 27 Dissemination policy

28
29 The protocol is reported according to the SPIRIT guidelines. Findings will be published in peer-
30 reviewed journals and presented at local, national and international meetings and
31 conferences to publicise and explain the research to clinicians, commissioners and service
32 users.
33

34 35 Patient and public involvement

36
37 Patients and public were not involved in the study.
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42 43 Discussion

44
45 International guidelines on sedation and delirium in ICU have been written [1]. Concerning
46 sedation, four messages are important:
47

48 using light sedation versus deep sedation, however there is no consensus on the
49 definition of light, moderate, and deep sedation,
50

51 using a daily sedative interruption protocol or a nurse-driven sedation protocol,
52

53 using propofol or dexmedetomidine over benzodiazepines even if there is no
54 difference between propofol and benzodiazepine use for delirium prevention and even if the
55 pooled analysis of all evaluated studies in these guidelines did not show a significant benefit
56 of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical
57 ventilation extubation, ICU length of stay and the risk for delirium,
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1
2
3 monitor sedation.
4

5 Since the publication of these guidelines, the SPICE study, a recent multicenter trial enrolling
6 4000 patients and comparing dexmedetomidine as the sole or primary sedative to usual
7 sedation care (propofol, midazolam, or other sedatives) failed to show a mortality reduction
8 at day 90, showed that sedation targets were difficult to obtain with dexmedetomidine as the
9 sole agent of sedation and that adverse effects were multiplied by ten [17]. The NONSEDA
10 study (comparing a no sedation group versus a light sedation group [RASS-2;-3]) enrolled 710
11 patients. Mortality at 90 days did not differ significantly between those assigned to a plan of
12 no sedation and those assigned to a plan of light sedation. 14% of screened patients declined
13 to participate and about one third patient should have been sedated during the first 24 hours
14 in the no sedation group [28].
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20 Delirium during sedation administration is frequent. Rapidly improving cognitive state
21 concerns only a minority of delirium sedated patients (14%). Majority of delirium under
22 sedation patient has a worse long-term prognosis [29]. These results have been confirmed in
23 a large study showing that delirium associated with sedation was the most common type of
24 delirium in ICU, but also the most strongly associated with long-term cognitive impairment
25 [30]. Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term
26 outcomes has been defined as one of the top trials to perform in the next years by a
27 multinational, interprofessional board [31].
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32 Potential benefits of isoflurane use in ICU are the absence of accumulation or tachyphylaxis,
33 the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the
34 wake up speed and the analgesia effect [18, 20, 21, 32]. The duration of use of isoflurane is
35 long and range up to 96 hours in the study by Sackey et al. [33], up to 348 hours in the study
36 by L'Her et al. [18], up to 323 hours in the study by Krannich et al. [34]. Despite these extended
37 times, the duration of mechanical ventilation and length of stay in the intensive care unit are
38 shorter in the study by Krannich et al., extubations are made earlier in the study by Jerath et
39 al., response to simple orders and the extubation are obtained earlier in the study by Sackey
40 et al.[33–35]. RCTs examining volatile anesthetics effects and safety aspects in ICU are
41 currently recruiting (NCT01983800). Inhaled sedation has shown decrease of epithelial injury
42 and inflammation in ARDS [20]. Those results should however be confirmed in a randomized
43 clinical trial (NCT04235608). Safety use for the staff in charge of the patient has been
44 established [22, 23]. Recommendations for use have been issued [36]. Inhaled volatile
45 anesthetics to conserve intravenous sedatives agents have proven to be effective during the
46 COVID-19 pandemic [37, 38, NCT04383730]. In addition, their potential neuroprotective effect
47 would make it an anesthetic of choice in the prevention of ICU delirium [39, 40]. Schoen et al.
48 report that sevoflurane improved short-term post-operative cognitive ability in patients
49 undergoing circulatory assisted heart surgery compared to propofol [41]. Dabrowski et al.
50 have confirmed in patients undergoing bypass surgery that sevoflurane and isoflurane
51 attenuate levels of MMP-9, GFAP, specific biochemical markers of brain injury [42].
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3 All of these results stress the importance of carrying out this study whose hypothesis is that
4 inhaled sedation strategy would decrease delirium occurrence. The use of isoflurane
5 preferentially over sevoflurane is justified by the absence of wake-up gain by the use of
6 sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or
7 pharmacodynamic differences between the molecules during their use in general anesthesia
8 and a more pronounced bronchodilator effect of isoflurane[43–45]. Sevoflurane induced
9 diabetes insipidus is of concern too [46].

10
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14 The INASED study is the first randomised, controlled and open-label trial adequately powered
15 to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are
16 as broad as possible. This strategy maximises recruitment rates and improves the
17 generalisation of results. All patients will be treated using the ABCDEF bundle which implies
18 less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting
19 depth of sedation, type of sedative drug, and duration of use. It is not possible to blind local
20 investigators to allocation treatment. However withdrawing of sedation, SBT, extubation will
21 follow a nurse-driven protocol. Blinding of outcome data assessment is ensured as the
22 cognitive function is evaluated by a research assistant that will not be aware of patient
23 assignment group.

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

37
38 The trial has already achieved many milestones. The study is funded by Sedana Medical and
39 promoted by the University Hospital of Brest. Research ethics committee approval was
40 obtained in april 2020. It is registered with the American registry of trials ([https://](https://clinicaltrials.gov/)
41 clinicaltrials.gov/; NCT04341350). Starting point of the study was August 2020. 12 patients
42 have been included.
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20 **Contributors**

21
22 PB and ELH designed the study and wrote the manuscript together. EN provided substantial
23 contributions to the conception and design of the study, wrote the statistical analysis plan and
24 estimated the sample size. PYE, SE, AWT, CG, GG, FR, OH, SJ contributed for drafting the work,
25 revising it critically for important intellectual content and approved the final version of the
26 manuscript. All authors gave their agreement to be accountable for all aspects of the work,
27 and ensure the accuracy and integrity of any part of the work.
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34 **Funding**

35
36 The study is funded by Sedana Medical which did not interfere with the design of the trial and
37 have no other involvement in the study, data analysis, the writing of the manuscript, or in the
38 decision to submit the manuscript. The study is promoted by the University Hospital of Brest.
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44 **Disclaimer**

45
46 The firm Sedana provides therapy equipment and monitoring to all the participating centres
47 but has no other involvement in the study.
48
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54 **Competing interests**

55
56 PB reports financial support (travel expense coverage to attend scientific meetings) from
57 Sedana Medical.
58
59
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3 SE declares receiving consulting fees, unrestricted research grants and equipment research
4 support from Aerogen Ltd, unrestricted research grant from Fisher & Paykel, unrestricted
5 research grant from Hamilton medical, consulting fees from La Diffusion Technique Française.
6
7

8 AWT reports financial support (payment for lectures and travel expense coverage to attend
9 scientific meetings) from Fisher & Paykel, Covidien, Maquet - Getinge and GE Healthcare.
10

11 SJ reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius Medical and
12 Fisher & Paykel.
13
14

15 ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to
16 automated oxygen administration. He is also a consultant for Sedana Medical, GE Healthcare
17 and Smiths Medical.
18
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22

23 **Ethic approval**

24
25 The study has been approved by the CPP Nord-Ouest 1 with the registration number
26 19.12.20.72129.
27
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30

31 **Provenance and peer review**

32
33 Not commissioned; externally peer reviewed.
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38 **Data sharing statement**

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

47
48 This is an open access article distributed in accordance with the Creative Commons Attribution
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52 indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.
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59 **Figure legend:**

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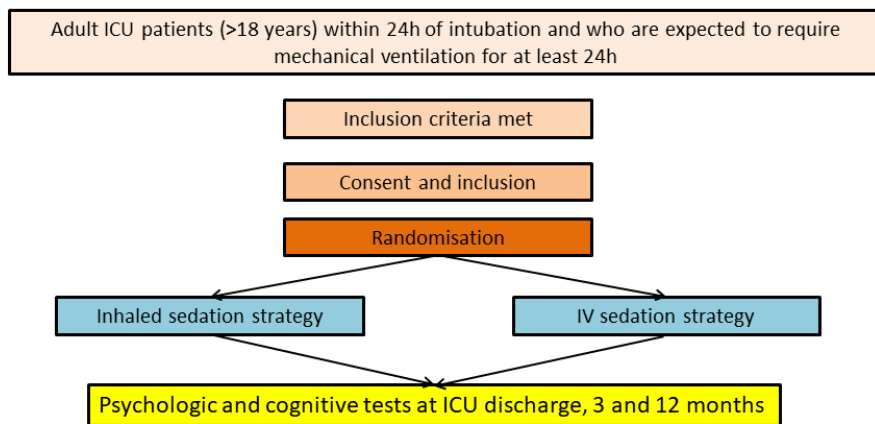
References

1. Devlin JW, Skrobik Y, Gélinas C, *et al.* Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018;46:e825–e873.
2. Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. *Crit Care* 2009;13:R204.
3. Devlin JW. The pharmacology of oversedation in mechanically ventilated adults. *Curr Opin Crit Care* 2008;14:403–407.
4. De Jonghe B, Bastuji-Garin S, Fangio P, *et al.* Sedation algorithm in critically ill patients without acute brain injury. *Crit Care Med* 2005;33:120–127
5. Arias-Rivera S, Sánchez-Sánchez M del M, Santos-Díaz R, *et al.* Effect of a nursing-implemented sedation protocol on weaning outcome. *Crit Care Med* 2008;36:2054–2060.
6. Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008 371:126–134.
7. Pandharipande PP, Girard TD, Jackson JC, *et al.* Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
8. Mehta S, Cook D, Devlin JW, *et al.* Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557–566.
9. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med* 2007;33:1506–1518.
10. Wade DM, Howell DC, Weinman JA, *et al.* Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16:R192.
11. Wolters AE, Peelen LM, Welling MC, *et al.* Long-Term Mental Health Problems After Delirium in the ICU. *Crit Care Med* 2016;44:1808–1813.
12. Vasilevskis EE, Chandrasekhar R, Holtze CH, *et al.* The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient. *Med Care* 2018;56:890–897.
13. Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des* 2004;10:3639–3649.
14. Hemphill S, McMenemy L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth* 2019;122:448–459.

- 1
2
3 15. Pandharipande PP, Pun BT, Herr DL, *et al.* Effect of sedation with dexmedetomidine vs
4 lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS
5 randomized controlled trial. *JAMA* 2007;298:2644–2653.
6
7
- 8 16. Ruokonen E, Parviainen I, Jakob SM, *et al.* Dexmedetomidine versus propofol/midazolam
9 for long-term sedation during mechanical ventilation. *Intensive Care Med* 2009;35:282–
10 290.
11
- 12 17. Shehabi Y, Howe BD, Bellomo R, *et al.* Early Sedation with Dexmedetomidine in Critically
13 Ill Patients. *N Engl J Med* 2019;380:2506–2517.
14
- 15 18. L'her E, Dy L, Pili R, *et al.* Feasibility and potential cost/benefit of routine isoflurane
16 sedation using an anesthetic-conserving device: a prospective observational study.
17 *Respir Care* 2008;53:1295–1303
18
- 19 19. Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic Agents
20 Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated
21 Critical Care Patients: A Meta-analysis and Systematic Review of Prospective Trials.
22 *Anesth Analg* 2016.
23
- 24 20. Jabaudon M, Boucher P, Imhoff E, *et al.* Sevoflurane for Sedation in Acute Respiratory
25 Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med*
26 2017;195:792–800.
27
- 28 21. Mesnil M, Capdevila X, Bringuier S, *et al.* Long-term sedation in intensive care unit: a
29 randomized comparison between inhaled sevoflurane and intravenous propofol or
30 midazolam. *Intensive Care Med* 2011;37:933–941.
31
- 32 22. Sackey PV, Martling C-R, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane
33 consumption during intensive care unit sedation with the Anesthetic Conserving Device.
34 *Crit Care Med* 2005;33:585–590
35
- 36 23. Herzog-Niescery J, Vogelsang H, Gude P, *et al.* The impact of the anesthetic conserving
37 device on occupational exposure to isoflurane among intensive care healthcare
38 professionals. *Minerva Anestesiol* 2018;84:25–32.
39
- 40 24. Sessler CN, Gosnell MS, Grap MJ, *et al.* The Richmond Agitation-Sedation Scale: validity
41 and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*
42 2002;166:1338–1344.
43
- 44 25. Pun BT, Balas MC, Barnes-Daly MA, *et al.* Caring for Critically Ill Patients with the ABCDEF
45 Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med*
46 2019;47:3–14.
47
- 48 26. Tonnelier J-M, Prat G, Le Gal G, *et al.* Impact of a nurses' protocol-directed weaning
49 procedure on outcomes in patients undergoing mechanical ventilation for longer than 48
50 hours: a prospective cohort study with a matched historical control group. *Crit Care*
51 2005;9:R83-89.
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 - 47
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 - 59
 - 60
27. Ely EW, Inouye SK, Bernard GR, *et al.* Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–2710.
28. Olsen HT, Nedergaard HK, Strøm T, *et al.* Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. *N Engl J Med* 2020;382:1103–1111.
29. Patel SB, Poston JT, Pohlman A, *et al.* Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014;189:658–665.
30. Girard TD, Thompson JL, Pandharipande PP, *et al.* Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med* 2018;6:213–222.
31. Pandharipande PP, Ely EW, Arora RC, *et al.* The intensive care delirium research agenda: a multinational, interprofessional perspective. *Intensive Care Med* 2017;43:1329–1339.
32. Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic Agents Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical Care Patients: A Meta-analysis and Systematic Review of Prospective Trials. *Anesth Analg* 2017;124:1190–1199.
33. Sackey PV, Martling C-R, Carlswärd C, *et al.* Short- and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam--a pilot study. *Crit Care Med* 2008;36:801–806.
34. Krannich A, Leithner C, Engels M, *et al.* Isoflurane Sedation on the ICU in Cardiac Arrest Patients Treated With Targeted Temperature Management: An Observational Propensity-Matched Study. *Crit Care Med* 2017;45:e384–e390.
35. Jerath A, Beattie SW, Chandy T, *et al.* Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial. *Crit Care Med* 2015;43:1062–1069.
36. Herzog-Niescery J, Seipp H-M, Weber TP, Bellgardt M. Inhaled anesthetic agent sedation in the ICU and trace gas concentrations: a review. *J Clin Monit Comput* 2018;32:667–675.
37. Jerath A, Ferguson ND, Cuthbertson B. Inhalational volatile-based sedation for COVID-19 pneumonia and ARDS. *Intensive Care Med* 2020;46:1563–1566.
38. Ferrière N, Bodenes L, Bailly P, L’Her E. Shortage of anesthetics: Think of inhaled sedation! *J Crit Care* 2020; S0883-9441(20)30686-9.
39. Chen F, Long Z, Yin J, *et al.* Isoflurane Post-Treatment Improves Outcome after an Embolic Stroke in Rabbits. *PLoS ONE* 2015;10:e0143931.
40. Wang Y-Z, Li T-T, Cao H-L, Yang W-C. Recent advances in the neuroprotective effects of medical gases. *Med Gas Res* 2019;9:80–87.

- 1
2
3 41. Schoen J, Husemann L, Tiemeyer C, *et al.* Cognitive function after sevoflurane- vs
4 propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial.
5 Br J Anaesth 2011;106:840–850.
6
7
8 42. Dabrowski W, Rzecki Z, Czajkowski M, *et al.* Volatile anesthetics reduce biochemical
9 markers of brain injury and brain magnesium disorders in patients undergoing coronary
10 artery bypass graft surgery. J Cardiothorac Vasc Anesth 2012;26:395–402.
11
12 43. Nyktari V, Papaioannou A, Volakakis N, *et al.* Respiratory resistance during anaesthesia
13 with isoflurane, sevoflurane, and desflurane: a randomized clinical trial. Br J Anaesth
14 2011;107:454–461.
15
16 44. Freiermuth D, Mets B, Bolliger D, *et al.* Sevoflurane and Isoflurane-Pharmacokinetics,
17 Hemodynamic Stability, and Cardioprotective Effects During Cardiopulmonary Bypass. J
18 Cardiothorac Vasc Anesth 2016;30:1494–1501.
19
20 45. Zorrilla-Vaca A, Núñez-Patiño RA, Torres V, Salazar-Gomez Y. The Impact of Volatile
21 Anesthetic Choice on Postoperative Outcomes of Cardiac Surgery: A Meta-Analysis.
22 Biomed Res Int 2017:7073401.
23
24 46. L’Heudé M, Poignant S, Elaroussi D, *et al.* Nephrogenic diabetes insipidus associated with
25 prolonged sedation with sevoflurane in the intensive care unit. Br J Anaesth
26 2019;122:e73–e75.
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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

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3 patients. Patients will be assigned to the IV sedation group or the inhaled sedation group, with
4 a 1:1 ratio.
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9 **Methods: participants, interventions and outcomes**

10 Study setting

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12 The INASED study will take place in 10 ICUs in France.
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15 Inclusion criteria

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

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

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40 Patients that are eligible for inclusion will be randomized and assigned to one of the two
41 following groups (Figure 1): (1) The patients assigned to control group will receive continuous
42 infusion of IV propofol (2) The patients assigned to interventional group will receive
43 continuously inhaled isoflurane with use of AnaConDa (Sedana Medical, Uppsala, Sweden).
44 Sedation and pain management in both arms will be guided using an explicit bedside nurse
45 driven sedation-analgesia algorithm. Sedation in both arms will be titrated every 2 hours to
46 target a Richmond Agitation Sedation Scale of (-2;1) (or as clinically indicated) until extubation
47 or tracheostomy [19]. Supplemental sedatives can be used, always at the minimum effective
48 dose, to optimize sedation and achieve the level of sedation specified by the treating clinician
49 at any time when allocated treatment alone is insufficient to provide patient comfort and
50 safety, provide rescue sedation for immediate control of sudden breakthrough agitation at
51 any time. Benzodiazepines will not be administered to any patient, unless deemed mandatory
52 by the treating clinician for conditions such as convulsions, palliation, procedural anesthesia,
53 concomitant neuromuscular blockade or refractory agitation. Patients will be reviewed daily
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3 for assessment of withdrawing sedation to assist ventilator weaning (resolving the underlying
4 pathology that led to mechanical ventilation; $FiO_2 < 50\%$; PEEP 5 to 8 cm H₂O; hemodynamic
5 stability with mean arterial pressure > 60 mmHg, which maybe assisted with stable doses of
6 vasoactive drug support) and extubated according to predefined criteria. Pain scores will be
7 monitored every 2 hours in both groups using the Behavioral Pain Scale (BPS), the Face Legs
8 Activity Cry Consolability or the VICOMORE and/or numerical pain score. Pain treatment is
9 based on the ABCDEF bundle [20], which uses the nurse driven analgesia protocol of each
10 ward involved in the study with a pain assessment score (BPS, VICOMORE, FLACC), local or
11 regional anesthesia, non-opioid adjuncts (acetaminophen, NSAIDs, nefopam), opioids (per os
12 opioids, bolus of sufentanyl followed by continuous infusion if necessary, continuous infusion
13 of remifentanyl). We decided to avoid morphine use for analgesia-based sedation because of
14 its long half-life of action and its accumulation [21]. In both groups, light sedation is
15 encouraged (RASS -2; 1). Whatever the treatment arm allocated, ABCDEF bundle will be used
16 [20].

23 Control group: IV sedation

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

31 Interventional group: inhaled sedation

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

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3 Readmission to ICU

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5 Discharge destination

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7 Post-hospital outcomes

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

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

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16 1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60
17 minutes medical consultation (those tests were also used in the Spice functional
18 and neuro-psychological outcomes SPICEFANS substudy [25]).
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20 2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety and
21 Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental
22 activities of daily living) performed by a clinical research associate.
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28 Sample size

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

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

51 Allocation and sequence intervention

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

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3 Benzodiazepine use is to be avoided within the ICU [1]. If propofol has a more favorable
4 pharmacokinetics than benzodiazepine, its prolonged exposure can lead to hypotension,
5 respiratory depression, hypertriglyceridaemia, pancreatitis and to the often lethal propofol
6 infusion syndrome [26, 27].
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10 Dexmedetomidine (alpha 2 adrenergic receptor agonist) seems to reduce the delirium
11 duration, the coma duration and even mortality in septic patients [28, 29]. However,
12 dexmedetomidine is often insufficient to deeply sedate [29]. Since the publication of these
13 guidelines, the SPICE study, a recent multicenter trial enrolling 4000 patients and comparing
14 dexmedetomidine as the sole or primary sedative to usual sedation care (propofol,
15 midazolam, or other sedatives) failed to show a mortality reduction at day 90, showed that
16 sedation targets were difficult to obtain with dexmedetomidine as the sole agent of sedation
17 and that adverse effects were multiplied by ten [25].
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22 The NONSEDA study (comparing a no sedation group versus a light sedation group [RASS-2;-
23 3]) enrolled 710 patients. Mortality at 90 days did not differ significantly between those
24 assigned to a plan of no sedation and those assigned to a plan of light sedation. 14% of
25 screened patients declined to participate and about one third patient should have been
26 sedated during the first 24 hours in the no sedation group [30].
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30 Delirium during sedation administration is frequent. Rapidly improving cognitive state
31 concerns only a minority of delirium sedated patients (14%). Majority of delirium under
32 sedation patient has a worse long-term prognosis [31]. These results have been confirmed in
33 a large study showing that delirium associated with sedation was the most common type of
34 delirium in ICU, but also the most strongly associated with long-term cognitive impairment
35 [32]. Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term
36 outcomes has been defined as one of the top trials to perform in the next years by a
37 multinational, interprofessional board [33].
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42 Potential benefits of isoflurane use in ICU are the absence of accumulation or tachyphylaxis,
43 the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the
44 wake up speed and the analgesia effect [13, 15, 16, 34]. The duration of use of isoflurane is
45 long and range up to 96 hours in the study by Sackey et al. [35], up to 348 hours in the study
46 by L'Her et al. [13], up to 323 hours in the study by Krannich et al. [36]. Despite these extended
47 times, the duration of mechanical ventilation and length of stay in the intensive care unit are
48 shorter in the study by Krannich et al., extubations were performed earlier in the study by
49 Jerath et al., response to simple orders and the extubation are obtained earlier in the study
50 by Sackey et al. [35–37]. RCTs examining volatile anesthetics effects and safety aspects in ICU
51 are currently recruiting (NCT01983800) or have been published demonstrating the safety and
52 acceptability in limited experience ICUs [38]. Inhaled sedation has shown decrease of
53 epithelial injury and inflammation in ARDS [15]. Those results should however be confirmed
54 in a randomized clinical trial (NCT04235608). Safety use for the staff in charge of the patient
55 has been established [17, 18]. Recommendations for use have been issued [39]. Inhaled
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3 volatile anesthetics to conserve intravenous sedatives agents have proven to be effective
4 during the COVID-19 pandemic [40, 41, NCT04383730]. In addition, their potential
5 neuroprotective effect would make it an anesthetic of choice in the prevention of ICU delirium
6 [42, 43]. Schoen et al. report that sevoflurane improved short-term post-operative cognitive
7 ability in patients undergoing circulatory assisted heart surgery compared to propofol [44].
8 Dabrowski et al. have confirmed in patients undergoing bypass surgery that sevoflurane and
9 isoflurane attenuate levels of MMP-9, GFAP, specific biochemical markers of brain injury [45].

10
11 All of these results stress the importance of carrying out this study whose hypothesis is that
12 inhaled sedation strategy would decrease delirium occurrence. The use of isoflurane
13 preferentially over sevoflurane is justified by the absence of wake-up gain by the use of
14 sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or
15 pharmacodynamic differences between the molecules during their use in general anesthesia
16 and a more pronounced bronchodilator effect of isoflurane [46–48]. Sevoflurane induced
17 diabetes insipidus is of concern in context of long-term sedation [49].

18
19 The INASED study is the first randomized, controlled and open-label trial adequately powered
20 to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are
21 as broad as possible. This strategy maximizes recruitment rates and improves the
22 generalization of results. All patients will be treated using the ABCDEF bundle which implies
23 less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting
24 depth of sedation, type of sedative drug, and duration of use [20]. It is not possible to blind
25 local investigators to allocation treatment. However withdrawing of sedation, SBT, extubation
26 will follow a nurse-driven protocol. Blinding of outcome data assessment is ensured as the
27 cognitive function is evaluated by a research assistant that will not be aware of patient
28 assignment group.

29
30 Given the current data and potential of isoflurane sedation to improve patient outcomes,
31 INASED is a well-designed, adequately powered RCT within a homogeneous population to
32 truly understand the potential clinical effects of this sedation modality.

33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 **Trial status**

48
49 The trial has already achieved many milestones. The study is funded by Sedana Medical and
50 promoted by the University Hospital of Brest. Research Ethics Committee approval was
51 obtained in April 2020. It is registered with the American registry of trials ([https://](https://clinicaltrials.gov/)
52 clinicaltrials.gov/; NCT04341350). Starting point of the study was August 2020. 18 patients
53 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

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Competing interests

PB reports financial support (travel expense 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 from Hamilton medical, consulting fees from La Diffusion Technique Française.

AWT reports financial support (payment for lectures and travel expense 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

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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.

References

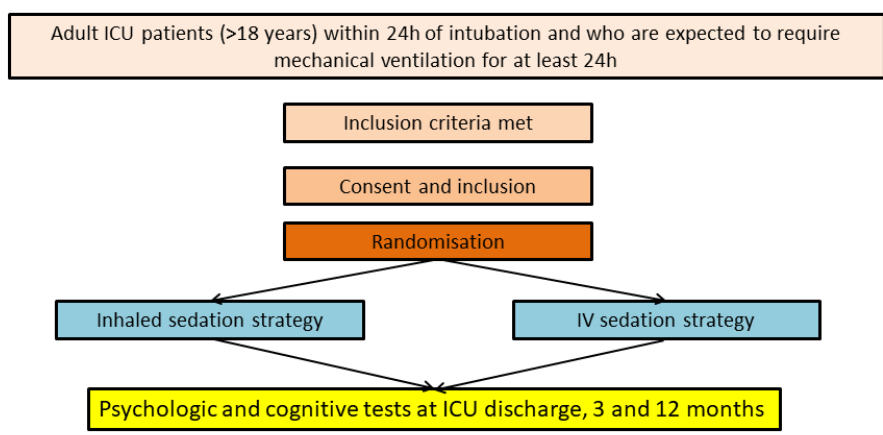
1. Devlin JW, Skrobik Y, Gélinas C, *et al.* Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018;46:e825–e873.
2. Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. *Crit Care* 2009;13:R204.
3. Devlin JW. The pharmacology of oversedation in mechanically ventilated adults. *Curr Opin Crit Care* 2008;14:403–407.
4. De Jonghe B, Bastuji-Garin S, Fangio P, *et al.* Sedation algorithm in critically ill patients without acute brain injury. *Crit Care Med* 2005;33:120–127
5. Arias-Rivera S, Sánchez-Sánchez M del M, Santos-Díaz R, *et al.* Effect of a nursing-implemented sedation protocol on weaning outcome. *Crit Care Med* 2008;36:2054–2060.
6. Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
7. Mehta S, Cook D, Devlin JW, *et al.* Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557–566.
8. Pandharipande PP, Girard TD, Jackson JC, *et al.* Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
9. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med* 2007;33:1506–1518.
10. Wade DM, Howell DC, Weinman JA, *et al.* Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16:R192.
11. Wolters AE, Peelen LM, Welling MC, *et al.* Long-Term Mental Health Problems After Delirium in the ICU. *Crit Care Med* 2016;44:1808–1813.
12. Vasilevskis EE, Chandrasekhar R, Holtze CH, *et al.* The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient. *Med Care* 2018;56:890–897.
13. L'her E, Dy L, Pili R, *et al.* Feasibility and potential cost/benefit of routine isoflurane sedation using an anesthetic-conserving device: a prospective observational study. *Respir Care* 2005;53:1295–1303
14. Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic Agents Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical Care Patients: A Meta-analysis and Systematic Review of Prospective Trials. *Anesth Analg* 2017; 124(4):1190-1199
15. Jabaudon M, Boucher P, Imhoff E, *et al.* Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med* 2017;195:792–800.

16. Mesnil M, Capdevila X, Bringuier S, *et al.* Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011;37:933–941.
17. Sackey PV, Martling C-R, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device. *Crit Care Med* 2005;33:585–590
18. Herzog-Niescery J, Vogelsang H, Gude P, *et al.* The impact of the anesthetic conserving device on occupational exposure to isoflurane among intensive care healthcare professionals. *Minerva Anesthesiol* 2018;84:25–32.
19. Sessler CN, Gosnell MS, Grap MJ, *et al.* The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–1344.
20. Pun BT, Balas MC, Barnes-Daly MA, *et al.* Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med* 2019;47:3–14.
21. Devlin JW, Roberts RJ. Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. *Anesthesiol Clin* 2011;29:567–585.
22. Kermad A, Speltz J, Daume P, *et al.* Reflection efficiencies of AnaConDa-S and AnaConDa-100 for isoflurane under dry laboratory and simulated clinical conditions: a bench study using a test lung. *Expert Rev Med Devices*. doi: 10.1080/17434440.2021.1865151. Online ahead of print.
23. Tonnelier J-M, Prat G, Le Gal G, *et al.* Impact of a nurses' protocol-directed weaning procedure on outcomes in patients undergoing mechanical ventilation for longer than 48 hours: a prospective cohort study with a matched historical control group. *Crit Care* 2005;9:R83-89.
24. Ely EW, Inouye SK, Bernard GR, *et al.* Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–2710.
25. Shehabi Y, Howe BD, Bellomo R, *et al.* Early Sedation with Dexmedetomidine in Critically Ill Patients. *N Engl J Med* 2019;380:2506–2517.
26. Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des* 2004;10:3639–3649.
27. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth* 2019;122:448–459.
28. Pandharipande PP, Pun BT, Herr DL, *et al.* Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298:2644–2653.
29. Ruokonen E, Parviainen I, Jakob SM, *et al.* Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. *Intensive Care Med* 2009;35:282–290.
30. Olsen HT, Nedergaard HK, Strøm T, *et al.* Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. *N Engl J Med* 2020;382:1103–1111.

- 1
- 2
- 3 31. Patel SB, Poston JT, Pohlman A, *et al.* Rapidly reversible, sedation-related delirium versus
- 4 persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014;189:658–665.
- 5
- 6 32. Girard TD, Thompson JL, Pandharipande PP, *et al.* Clinical phenotypes of delirium during critical
- 7 illness and severity of subsequent long-term cognitive impairment: a prospective cohort study.
- 8 *Lancet Respir Med* 2018;6:213–222.
- 9
- 10 33. Pandharipande PP, Ely EW, Arora RC, *et al.* The intensive care delirium research agenda: a
- 11 multinational, interprofessional perspective. *Intensive Care Med* 2017;43:1329–1339.
- 12
- 13 34. Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic Agents
- 14 Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical Care
- 15 Patients: A Meta-analysis and Systematic Review of Prospective Trials. *Anesth Analg*
- 16 2017;124:1190–1199.
- 17
- 18 35. Sackey PV, Martling C-R, Carlswärd C, *et al.* Short- and long-term follow-up of intensive care unit
- 19 patients after sedation with isoflurane and midazolam—a pilot study. *Crit Care Med* 2008;36:801–
- 20 806.
- 21
- 22 36. Krannich A, Leithner C, Engels M, *et al.* Isoflurane Sedation on the ICU in Cardiac Arrest Patients
- 23 Treated With Targeted Temperature Management: An Observational Propensity-Matched Study.
- 24 *Crit Care Med* 2017;45:e384–e390.
- 25
- 26 37. Jerath A, Beattie SW, Chandy T, *et al.* Volatile-based short-term sedation in cardiac surgical
- 27 patients: a prospective randomized controlled trial. *Crit Care Med* 2015;43:1062–1069.
- 28
- 29 38. Jerath A, Wong K, Wasowicz M, *et al.* Use of Inhaled Volatile Anesthetics for Longer Term Critical
- 30 Care Sedation: A Pilot Randomized Controlled Trial. *Critical Care Explorations* 2020;2:e0281.
- 31
- 32 39. Herzog-Niescery J, Seipp H-M, Weber TP, Bellgardt M. Inhaled anesthetic agent sedation in the
- 33 ICU and trace gas concentrations: a review. *J Clin Monit Comput* 2018;32:667–675.
- 34
- 35 40. Jerath A, Ferguson ND, Cuthbertson B. Inhalational volatile-based sedation for COVID-19
- 36 pneumonia and ARDS. *Intensive Care Med* 2020;46:1563–1566.
- 37
- 38 41. Ferrière N, Bodenes L, Bailly P, L’Her E. Shortage of anesthetics: Think of inhaled sedation! *J Crit*
- 39 *Care* 2020; :S0883-9441(20)30686-9
- 40
- 41 42. Chen F, Long Z, Yin J, *et al.* Isoflurane Post-Treatment Improves Outcome after an Embolic Stroke
- 42 in Rabbits. *PLoS ONE* 2015;10:e0143931.
- 43
- 44 43. Wang Y-Z, Li T-T, Cao H-L, Yang W-C. Recent advances in the neuroprotective effects of medical
- 45 gases. *Med Gas Res* 2019;9:80–87.
- 46
- 47 44. Schoen J, Husemann L, Tiemeyer C, *et al.* Cognitive function after sevoflurane- vs propofol-based
- 48 anaesthesia for on-pump cardiac surgery: a randomized controlled trial. *Br J Anaesth*
- 49 2011;106:840–850.
- 50
- 51 45. Dabrowski W, Rzecki Z, Czajkowski M, *et al.* Volatile anesthetics reduce biochemical markers of
- 52 brain injury and brain magnesium disorders in patients undergoing coronary artery bypass graft
- 53 surgery. *J Cardiothorac Vasc Anesth* 2012;26:395–402.
- 54
- 55
- 56
- 57
- 58
- 59
- 60

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2
3 46. Nyktari V, Papaioannou A, Volakakis N, *et al.* Respiratory resistance during anaesthesia with
4 isoflurane, sevoflurane, and desflurane: a randomized clinical trial. *Br J Anaesth* 2011;107:454–
5 461.
6
7 47. Freiermuth D, Mets B, Bolliger D, *et al.* Sevoflurane and Isoflurane-Pharmacokinetics,
8 Hemodynamic Stability, and Cardioprotective Effects During Cardiopulmonary Bypass. *J*
9 *Cardiothorac Vasc Anesth* 2016;30:1494–1501. <https://doi.org/10.1053/j.jvca.2016.07.011>
10
11 48. Zorrilla-Vaca A, Núñez-Patiño RA, Torres V, Salazar-Gomez Y. The Impact of Volatile Anesthetic
12 Choice on Postoperative Outcomes of Cardiac Surgery: A Meta-Analysis. *Biomed Res Int*
13 2017:7073401.
14
15 49. L'Heudé M, Poignant S, Elaroussi D, *et al.* Nephrogenic diabetes insipidus associated with
16 prolonged sedation with sevoflurane in the intensive care unit. *Br J Anaesth* 2019;122:e73–e75.
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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

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3 This study is an investigator-initiated, prospective, multicenter, two-arm, randomized, control,
4 open trial comparing inhaled sedation strategy versus intra-venous (IV) sedation strategy in
5 mechanically ventilated patients in ICU. Two hundred and fifty patients will be randomly
6 assigned to the IV sedation group or inhaled sedation group, with a 1:1 ratio in two groups
7 according to the sedation strategy. The primary outcome is the occurrence of delirium
8 assessed using twice a day confusion assessment method for the ICU (CAM-ICU). Secondary
9 outcomes include cognitive and functional outcomes at 3 and 12 months.
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13 14 Ethics and dissemination

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16 The study has been approved by the Regional Ethics Committee (CPP Ouest) and national
17 authorities (ANSM). The results will be submitted for publication in peer-reviewed journals.
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19 20 Trial registration number

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22 NCT04341350
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29 30 **Strengths and limitations of this study**

31 The INASED study is a multicenter, randomized, controlled and open-label trial, comparing
32 two sedation strategies.
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34 The primary outcome is the occurrence of delirium up until ICU discharge.
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36 Neurocognitive evaluation will be performed for at least 3-months after ICU discharge, which
37 will enable investigators to evaluate patients' outcome on a strong indicator.
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40 The main limitation of the study is that considering the characteristics of the two strategies
41 under evaluation, a double-blind trial is not possible.
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44 However, blinding of outcome data assessment is ensured as the cognitive function is
45 evaluated by a research assistant that will not be aware of patient assignment group.
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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

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3 patients. Patients will be assigned to the IV sedation group or the inhaled sedation group, with
4 a 1:1 ratio.
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9 **Methods: participants, interventions and outcomes**

10 Study setting

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12 The INASED study will take place in 10 ICUs in France.
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15 Inclusion criteria

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

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26 Age less than 18 years; patient that has been intubated for more than 24 hours in the ICU;
27 admission for a cardiac arrest, a traumatic brain injury, and/or a stroke; patient that is unable
28 to complete the neuropsychological test due to aphasia, deafness, blindness or dementia;
29 contraindication to isoflurane (personal or familial history of malignant hyperthermia; liver
30 failure with prothrombin < 30%; acute or chronic neuromuscular disease); occurrence of a
31 severe ARDS (P/F ratio<100), a PaCO₂>50mmHg at the time of randomization; death is
32 deemed to be imminent or inevitable during the ICU admission; pregnancy or breastfeeding
33 woman; patient under guardianship or curatorship.
34
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38 Intervention

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40 As in the VALTS trial, two sedation strategy will be compared: one with volatile agent
41 (isoflurane), the other with IV sedative (propofol) [19]. Patients that are eligible for inclusion
42 will be randomized and assigned to one of the two following groups (Fig. 1): (1) The patients
43 assigned to control group will receive continuous infusion of IV propofol (2) The patients
44 assigned to interventional group will receive continuously inhaled isoflurane with use of
45 AnaConDa (Sedana Medical, Uppsala, Sweden). Sedation and pain management in both arms
46 will be guided using a standardized nurse-driven bedside protocol. Sedation in both arms will
47 be titrated every hour to reach a Richmond Agitation Sedation Scale of (-2;1) (or as clinically
48 indicated) until extubation [20]. Supplemental sedatives can be used, always at the minimum
49 effective dose, to optimize sedation and achieve the level of sedation specified by the treating
50 clinician at any time when allocated treatment alone is insufficient to provide patient comfort
51 and safety, provide rescue sedation for immediate control of sudden breakthrough agitation
52 at any time. Benzodiazepines will not be administered to any patient, unless deemed
53 mandatory by the treating clinician for conditions such as convulsions, palliation, procedural
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3 anesthesia, concomitant neuromuscular blockade or refractory agitation. Patients will be
4 reviewed daily for assessment of withdrawing sedation to assist ventilator weaning (resolving
5 the underlying pathology that led to mechanical ventilation; $FiO_2 < 50\%$; PEEP 5 to 8 cm H₂O;
6 hemodynamic stability with mean arterial pressure > 60 mmHg, which maybe assisted with
7 stable doses of vasoactive drug support) and extubated according to predefined criteria. Pain
8 scores will be monitored every 2 hours in both groups using the Behavioral Pain Scale (BPS),
9 the Face Legs Activity Cry Consolability or the VICOMORE and/or numerical pain score. Pain
10 treatment is based on the ABCDEF bundle [21]. It uses the nurse driven analgesia protocol of
11 each ward involved in the study. It uses a pain assessment score (BPS, VICOMORE, FLACC),
12 local or regional anesthesia, non-opioid adjuncts (acetaminophen, NSAIDs, nefopam), opioids
13 (per os opioids, bolus of sufentanyl followed by continuous infusion if necessary, continuous
14 infusion of remifentanyl). We decided to avoid morphine use for analgesia-based sedation
15 because of its long half-life of action and its accumulation [22]. In both groups, light sedation
16 is encouraged (RASS -2; 1). Whatever the treatment arm allocated, ABCDEF bundle will be
17 used [21].

24 25 Control group: IV sedation

26
27 The patients assigned to the control group will receive continuously IV propofol. Sedation and
28 pain management will be guided using an explicit bedside nurse driven sedation opioid
29 analgesia algorithm.

32 33 Interventional group: inhaled sedation

34
35 Isoflurane will be infused into the AnaConDa device (Sedana Medical, Uppsala, Sweden),
36 which is placed between the endotracheal tube and the ventilator breathing circuit. Isoflurane
37 is placed in a standard syringe pump. The AnaConDa is placed in the breathing circuit between
38 the Y-piece and the ET-tube. Liquid isoflurane is delivered from the syringe through the
39 dedicated line into the AnaConDa where it is vaporized within the device. In order to limit the
40 dead space, INASED study will only use 50mL AnaConDa S filters. The gas monitor samples the
41 gas from the AnaConDa port and displays the exhaled anesthetic concentration in Fet% or
42 MAC values (which indicates the concentration of the drug). Due to AnaConDa's design, most
43 of the exhaled anesthetic agent is adsorbed and reflected to the patient upon inspiration [23].
44 Thus, AnaConDa recycles more than 90 % of the expired volatile agent, which facilitates low
45 infusion rates. The residual anesthetic agent passes through the ventilator and exits through
46 the exhaust where it is captured in the FlurAbsorb. The AnaConDa is changed every 24 h.
47 When patients are being prepared for extubation, Isoflurane will be discontinued, and the
48 AnaConDa device will be removed from the breathing circuit to facilitate rapid drug
49 elimination. Gas-scavenging is performed with a commercially available canister connected to
50 the ventilator output. The canister contains 500g of activated charcoal and removes isoflurane
51 from the expired air up to a weight increase of 150 g, which provides 24 hours with the
52 AnaConDa.
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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

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3 The primary outcome is the occurrence of delirium (yes / no) up until ICU discharge assessed
4 using the confusion assessment method for the ICU (CAM-ICU). As delirium is fluctuating,
5 CAM-ICU is to be evaluated twice a day, first time in the morning during first daily medical
6 examination, second time in the evening at the beginning of the night shift. We decided not
7 to evaluate delirium during the night in order to avoid sleep disorders within our patients and
8 to follow recommendation of the ABCDEF bundle [21].
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10

11 Secondary outcomes

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14 Secondary outcome variables include the following:

15 ICU outcomes:

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19 Number of days with vasopressors or inotropic agents

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22 Number of days with sedation

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25 Cumulative dose and duration of anesthetics drugs

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28 Maximum dose of vasopressors or inotropic agents

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31 Ventilation free days at 28 days following randomization

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34 Proportion of RASS measurements in target range

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36
37 Incidence and duration of delirium (delirium free days at 28 days). Additionally, we
38 consider a positive CAM-ICU assessment to be hyperactive delirium if the
39 corresponding RASS is >0 and hypoactive delirium if the corresponding RASS is <0

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41
42 Number of days until RASS 0; -1 is reach

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45 Mortality at ICU discharge, at 28 days

46
47
48 Length of ICU stay

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

53
54
55 Self or hetero-aggressive act

56 Hospital outcome

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59 Mortality at hospital discharge

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62 Length of hospital stay

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65 Readmission to ICU

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67
68 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

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

15
16 Patient characteristics, severity scores (Acute Physiology and Chronic Health Evaluation score,
17 SOFA score), hemodynamics, vasoactive drug support, ventilation mechanics, laboratory
18 findings, clinical ICU complications, length of stay, and mortality will be recorded. Delirium will
19 be assessed twice daily using the Confusion Assessment Method (CAM-ICU)[27]. All these
20 parameters will be collected each day from day 1 to ICU discharge.

21
22 Cognitive function and functional outcome will be evaluated at discharge, 3- and 12 months
23 using two kinds of scores:

24
25 1- CANTAB test, combining 6 cognitive evaluations with an iPad during a 45-60
26 minutes medical consultation (those tests were also used in the Spice functional and neuro-
27 psychological outcomes SPICEFANS substudy [25].

28
29 2- PCLS (Posttraumatic stress disorder Checklist Scale), HADS (Hospital Anxiety
30 and Depression scale), SF36 (medical outcome study short form 36), IADL (instrumental
31 activities of daily living) performed by a clinical research associate.

32 33 34 35 36 37 38 39 40 41 42 43 44 45 **Statistical methods**

46
47 All the analyses will be performed by an independent statistician, following a predefined
48 statistical analysis plan. The analysis will be performed on an intention-to-treat basis, after a
49 blind review of the data and final database lock. All the analyses will be conducted using SAS
50 V.9.3 statistical software (SAS Institute, Cary, North Carolina, USA). A two-tailed p value equal
51 or less than 0.05 will be considered as statistically significant. All tests, except for the primary
52 outcome, will be exploratory.

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56 Descriptive analysis of patient groups at baseline
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3 Wrongly included subjects as well as those lost to follow-up will be described. Deviations from
4 the protocol will be described. The baseline characteristics of the study participants will be
5 described according to their randomization group.
6
7

8 Analysis pertaining to the main criteria of evaluation 9

10 The frequency of delirium occurrence will be compared between the two groups using a Chi-
11 square test or an exact Fisher test if required. The probability of delirium occurrence will then
12 be modeled (secondary analysis) using a multivariate logistic regression.
13
14

15 Analysis pertaining to the secondary criteria of evaluation 16

17 Secondary criteria of evaluation will be compared between the two treatment groups by
18 means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous
19 quantitative variables and by means of the χ^2 test (or Fisher's exact test) for qualitative
20 variables. Linear models and logistics models will be used to compare the two groups in
21 multivariate analyses.
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23

24
25 Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional
26 hazards model.
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29 Predetermined subgroup analysis 30

31 Duration of delirium will be compared between the two groups among patients who suffered
32 from delirium, using the Student's t-test or the Mann-Whitney U test if required.
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35 Data monitoring 36

37 An investigator at each center will be responsible for daily patient screening, enrolling patients
38 in the study, ensuring adherence to the protocol and completing the e-CRF. Research
39 assistants will regularly monitor all the centers on site to check adherence to the protocol and
40 the accuracy of the data recorded.
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46 **Ethics and dissemination** 47

48 Consent or assent 49

50 The patient will be included after having provided a written informed consent to the
51 investigator according to the decision of the central Ethics Committee. If the patient is not
52 able to understand the information given, he/she can be included if the same procedure is
53 completed with a next of kin. After the patient's recovery, he/she will be asked if he/she
54 agrees to continue the trial. Her/his consent will again be necessary for the continuation of
55 the study.
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59 Confidentiality 60

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3 Data will be handled according to French law. All original records will be archived at trial sites
4 for 15 years. The clean database file will be anonymized and kept for 15 years.
5

6 Declaration of interest

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8
9 The study is promoted by the University Hospital of Brest. Sedana Medical funded the
10 promoter for study monitoring and will provide sedation equipment and monitoring for all the
11 participating centers, but will have no other involvement in the study, data analysis, the
12 writing of the manuscript, or in the decision to submit the manuscript.
13
14

15 Access to data

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18 All investigators will have access to the final data set. Participant-level data sets will be made
19 accessible on a controlled access basis.
20

21 Dissemination policy

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

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32 Patients and public were not involved in the study.
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37 Discussion

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39 International guidelines on sedation and delirium in ICU have been developed and formulated
40 by national and international Societies [1]. Concerning sedation, four messages are important:
41

42 using light sedation versus deep sedation, however there is no consensus on the
43 definition of light, moderate, and deep sedation,
44

45 using a daily sedative interruption protocol or a nurse-driven sedation protocol,
46

47 using propofol or dexmedetomidine over benzodiazepines even if there is no
48 difference between propofol and benzodiazepine use for delirium prevention and even if the
49 pooled analysis of all evaluated studies in these guidelines did not show a significant benefit
50 of dexmedetomidine compared with a benzodiazepine infusion for duration of mechanical
51 ventilation extubation, ICU length of stay and the risk for delirium,
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54

55 monitor sedation.
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58 Benzodiazepine use is to be avoided within the ICU [1]. If propofol has a more favorable
59 pharmacokinetics than benzodiazepine, its prolonged exposure can lead to hypotension,
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3 respiratory depression, hypertriglyceridaemia, pancreatitis and to the often lethal propofol
4 infusion syndrome [28, 29].
5

6
7 Dexmedetomidine (alpha 2 adrenergic receptor agonist) seems to reduce the delirium
8 duration, the coma duration and even mortality in septic patients [30, 31]. However,
9 dexmedetomidine is often insufficient to deeply sedate [31]. Since the publication of these
10 guidelines, the SPICE study, a recent multicenter trial enrolling 4000 patients and comparing
11 dexmedetomidine as the sole or primary sedative to usual sedation care (propofol,
12 midazolam, or other sedatives) failed to show a mortality reduction at day 90, showed that
13 sedation targets were difficult to obtain with dexmedetomidine as the sole agent of sedation
14 and that adverse effects were multiplied by ten [25].
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19 The NONSEDA study (comparing a no sedation group versus a light sedation group [RASS-2;-
20 3]) enrolled 710 patients. Mortality at 90 days did not differ significantly between those
21 assigned to a plan of no sedation and those assigned to a plan of light sedation. 14% of
22 screened patients declined to participate and about one third patient should have been
23 sedated during the first 24 hours in the no sedation group [32].
24
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26
27 Delirium during sedation administration is frequent. Rapidly improving cognitive state
28 concerns only a minority of delirium sedated patients (14%). Majority of delirium under
29 sedation patient has a worse long-term prognosis [33]. These results have been confirmed in
30 a large study showing that delirium associated with sedation was the most common type of
31 delirium in ICU, but also the most strongly associated with long-term cognitive impairment
32 [34]. Moreover, safety and efficacy of alternate sedation paradigms on delirium and long-term
33 outcomes has been defined as one of the top trials to perform in the next years by a
34 multinational, interprofessional board [35].
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39 Potential benefits of isoflurane use in ICU are the absence of accumulation or tachyphylaxis,
40 the wide therapeutic range, the small inter-individual variation, the rapidity of efficacy, the
41 wake up speed and the analgesia effect The duration of use of isoflurane is long and range up
42 to 96 hours in the study by Sackey et al. [36], up to 348 hours in the study by L'Her et al. [13],
43 up to 323 hours in the study by Krannich et al. [37]. Despite these extended times, the duration
44 of mechanical ventilation and length of stay in the intensive care unit are shorter in the study
45 by Krannich et al., extubations were performed earlier in the study by Jerath et al., response
46 to simple orders and the extubation are obtained earlier in the study by Sackey et al.[36–38].
47 RCTs examining volatile anesthetics effects and safety aspects in ICU are currently recruiting
48 (NCT01983800) or have been published demonstrating the safety and acceptability in ICUs
49 with limited experience of using volatile anesthetics-based sedation [39]. Inhaled sedation
50 has shown decrease of epithelial injury and inflammation in ARDS [14]. Those results should
51 however be confirmed in a randomized clinical trial (NCT04235608). Safety use for the staff in
52 charge of the patient has been established [17, 18]. Recommendations for use have been
53 issued [40]. Inhaled volatile anesthetics to conserve intravenous sedatives agents have proven
54 to be effective during the COVID-19 pandemic [41, 42, NCT04383730]. In addition, their
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3 potential neuroprotective effect would make it an anesthetic of choice in the prevention of
4 ICU delirium [43, 44]. Schoen et al. report that sevoflurane improved short-term post-
5 operative cognitive ability in patients undergoing circulatory assisted heart surgery compared
6 to propofol [45]. Dabrowski et al. have confirmed in patients undergoing bypass surgery that
7 sevoflurane and isoflurane attenuate levels of MMP-9, GFAP, specific biochemical markers of
8 brain injury [46].
9

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11
12 All of these results stress the importance of carrying out this study whose hypothesis is that
13 inhaled sedation strategy would decrease delirium occurrence. The use of isoflurane
14 preferentially over sevoflurane is justified by the absence of wake-up gain by the use of
15 sevoflurane versus isoflurane in general anesthesia, the absence of clear hemodynamic or
16 pharmacodynamic differences between the molecules during their use in general anesthesia
17 and a more pronounced bronchodilator effect of isoflurane[47–49]. Sevoflurane induced
18 diabetes insipidus is of concern in context of long-term sedation [50].
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23 The INASED study is the first randomized, controlled and open-label trial adequately powered
24 to determine whether inhaled sedation strategy in ICU reduces delirium. Inclusion criteria are
25 as broad as possible. This strategy maximizes recruitment rates and improves the
26 generalization of results. All patients will be treated using the ABCDEF bundle which implies
27 less variation in study quality, analgesic regimens, use of daily sedation breaks, reporting
28 depth of sedation, type of sedative drug, and duration of use [21]. It is not possible to blind
29 local investigators to allocation treatment. However withdrawing of sedation, SBT, extubation
30 will follow a nurse-driven protocol. Blinding of outcome data assessment is ensured as the
31 cognitive function is evaluated by a research assistant that will not be aware of patient
32 assignment group.
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38 Given the current data and potential of isoflurane sedation to improve patient outcomes,
39 INASED is a well-designed, adequately powered RCT within a homogeneous population to
40 truly understand the potential clinical effects of this sedation modality.
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44

45 **Trial status**

46
47 The study is funded by Sedana Medical and promoted by the University Hospital of Brest.
48 Research Ethics Committee approval was obtained in April 2020. It is registered with the
49 American registry of trials ([https:// clinicaltrials.gov/](https://clinicaltrials.gov/); NCT04341350). Starting point of the
50 study was August 2020. 20 patients have been included.
51
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55 **Contributors**

56
57
58 PB and ELH designed the study and wrote the manuscript together. EN provided substantial
59 contributions to the conception and design of the study, wrote the statistical analysis plan and
60

1
2
3 estimated the sample size. PYE, SE, AWT, CG, GG, FR, OH, SJ contributed for drafting the work,
4 revising it critically for important intellectual content and approved the final version of the
5 manuscript. All authors gave their agreement to be accountable for all aspects of the work,
6 and ensure the accuracy and integrity of any part of the work.
7
8
9

10 11 12 **Funding**

13
14 The study is funded by Sedana Medical which did not interfere with the design of the trial and
15 have no other involvement in the study, data analysis, the writing of the manuscript, or in the
16 decision to submit the manuscript. The study is promoted by the University Hospital of Brest.
17
18
19

20 21 22 **Disclaimer**

23 The firm Sedana provides therapy equipment and monitoring to all the participating centers
24 but has no other involvement in the study.
25
26
27

28 29 30 **Competing interests**

31 PB reports financial support (travel expense coverage to attend scientific meetings) from
32 Sedana Medical.
33

34
35 SE declares receiving consulting fees, unrestricted research grants and equipment research
36 support from Aerogen Ltd, unrestricted research grant from Fisher & Paykel, unrestricted
37 research grant from Hamilton medical, consulting fees from La Diffusion Technique Française.
38

39
40 AWT reports financial support (payment for lectures and travel expense coverage to attend
41 scientific meetings) from Fisher & Paykel, Covidien, Maquet - Getinge and GE Healthcare.
42

43
44 SJ reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius Medical and
45 Fisher & Paykel.
46

47
48 ELH is cofounder and shareholder of Oxynov Inc., a R and D Canadian company dedicated to
49 automated oxygen administration. He is also a consultant for Sedana Medical, GE Healthcare
50 and Smiths Medical.
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54 55 56 57 **Ethic approval**

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3 The study has been approved by the CPP Nord-Ouest 1 with the registration number
4 19.12.20.72129.
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9 **Provenance and peer review**

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11 Not commissioned; externally peer reviewed.
12
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15 **Data sharing statement**

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

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26 This is an open access article distributed in accordance with the Creative Commons Attribution
27 Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build
28 upon this work non-commercially, and license their derivative works on different terms,
29 provided the original work is properly cited, appropriate credit is given, any changes made
30 indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.
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37 **Figure legend:**

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

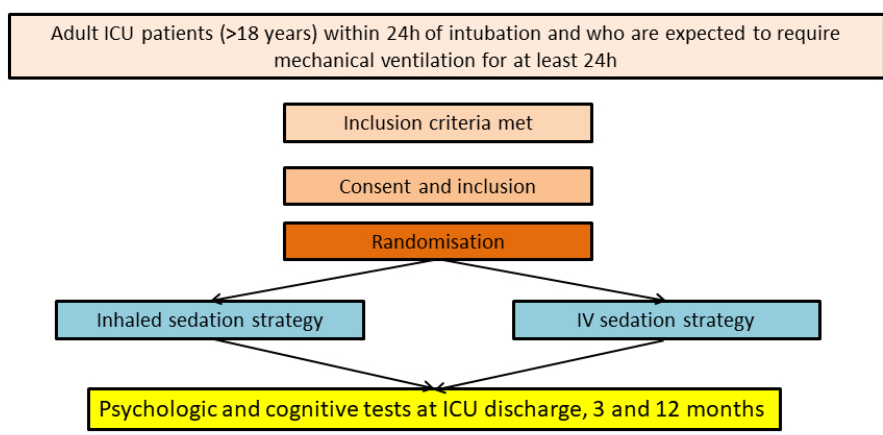
1. Devlin JW, Skrobik Y, Gélinas C, *et al.* Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018;46:e825–e873. 9
2. Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. *Crit Care* 2009;13:R204.
3. Devlin JW. The pharmacology of oversedation in mechanically ventilated adults. *Curr Opin Crit Care* 2008;14:403–407.
4. De Jonghe B, Bastuji-Garin S, Fangio P, *et al.* Sedation algorithm in critically ill patients without acute brain injury. *Crit Care Med* 2005;33:120–127.
5. Arias-Rivera S, Sánchez-Sánchez M del M, Santos-Díaz R, *et al.* Effect of a nursing-implemented sedation protocol on weaning outcome. *Crit Care Med* 2008;36:2054–2060.
6. Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.
7. Pandharipande PP, Girard TD, Jackson JC, *et al.* Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
8. Mehta S, Cook D, Devlin JW, *et al.* Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557–566.
9. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med* 2007;33:1506–1518.
10. Wade DM, Howell DC, Weinman JA, *et al.* Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16:R192.
11. Wolters AE, Peelen LM, Welling MC, *et al.* Long-Term Mental Health Problems After Delirium in the ICU. *Crit Care Med* 2016;44:1808–1813.
12. Vasilevskis EE, Chandrasekhar R, Holtze CH, *et al.* The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient. *Med Care* 2018;56:890–897.
13. L'her E, Dy L, Pili R, *et al.* Feasibility and potential cost/benefit of routine isoflurane sedation using an anesthetic-conserving device: a prospective observational study. *Respir Care* 2008;53:1295–1303
14. Jabaudon M, Boucher P, Imhoff E, *et al.* Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med* 2017;195:792–800.
15. Mesnil M, Capdevila X, Bringuier S, *et al.* Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011;37:933–941.
16. Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic Agents Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical Care

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2
3 Patients: A Meta-analysis and Systematic Review of Prospective Trials. *Anesth Analg*.
4 2017;124(4):1190-1199.
5
6
7 17. Sackey PV, Martling C-R, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane
8 consumption during intensive care unit sedation with the Anesthetic Conserving Device. *Crit Care*
9 *Med* 2005;33:585–590
10
11 18. Herzog-Niescery J, Vogelsang H, Gude P, *et al*. The impact of the anesthetic conserving device on
12 occupational exposure to isoflurane among intensive care healthcare professionals. *Minerva*
13 *Anesthesiol* 2018;84:25–32.
14
15 19. Jerath A, Ferguson ND, Steel A, *et al*. The use of volatile anesthetic agents for long-term critical
16 care sedation (VALTS): study protocol for a pilot randomized controlled trial. *Trials* 2015;16:560.
17
18 20. Sessler CN, Gosnell MS, Grap MJ, *et al*. The Richmond Agitation-Sedation Scale: validity and
19 reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–1344.
20
21 21. Pun BT, Balas MC, Barnes-Daly MA, *et al*. Caring for Critically Ill Patients with the ABCDEF Bundle:
22 Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Crit Care Med* 2019;47:3–14.
23
24 22. Devlin JW, Roberts RJ. Pharmacology of commonly used analgesics and sedatives in the ICU:
25 benzodiazepines, propofol, and opioids. *Anesthesiol Clin* 2011;29:567–585.
26
27 23. Kermad A, Speltz J, Daume P, *et al*. Reflection efficiencies of AnaConDa-S and AnaConDa-100 for
28 isoflurane under dry laboratory and simulated clinical conditions: a bench study using a test lung.
29 *Expert Rev Med Devices* 2020;1-7.
30
31 24. Tonnelier J-M, Prat G, Le Gal G, *et al*. Impact of a nurses' protocol-directed weaning procedure
32 on outcomes in patients undergoing mechanical ventilation for longer than 48 hours: a
33 prospective cohort study with a matched historical control group. *Crit Care* 2005;9:R83-89.
34
35 25. Shehabi Y, Howe BD, Bellomo R, *et al*. Early Sedation with Dexmedetomidine in Critically Ill
36 Patients. *N Engl J Med* 2019;380:2506–2517.
37
38 26. W Thille A, Muller G, Gacouin A, *et al*. High-flow nasal cannula oxygen therapy alone or with non-
39 invasive ventilation during the weaning period after extubation in ICU: the prospective
40 randomised controlled HIGH-WEAN protocol. *BMJ Open* 2018; 8(9):e023772.
41
42 27. Ely EW, Inouye SK, Bernard GR, *et al*. Delirium in mechanically ventilated patients: validity and
43 reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*
44 2001;286:2703–2710.
45
46 28. Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des* 2004;10:3639–
47 3649.
48
49 29. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured
50 literature review and analysis of published case reports. *Br J Anaesth* 2019;122:448–459.
51
52 30. Pandharipande PP, Pun BT, Herr DL, *et al*. Effect of sedation with dexmedetomidine vs lorazepam
53 on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized
54 controlled trial. *JAMA* 2007;298:2644–2653.
55
56
57
58
59
60

- 1
- 2
- 3
- 4 31. Ruokonen E, Parviainen I, Jakob SM, *et al.* Dexmedetomidine versus propofol/midazolam for
- 5 long-term sedation during mechanical ventilation. *Intensive Care Med* 2009;35:282–290.
- 6
- 7 32. Olsen HT, Nedergaard HK, Strøm T, *et al.* Nonsedation or Light Sedation in Critically Ill,
- 8 Mechanically Ventilated Patients. *N Engl J Med* 2020;382:1103–1111.
- 9
- 10 33. Patel SB, Poston JT, Pohlman A, *et al.* Rapidly reversible, sedation-related delirium versus
- 11 persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014;189:658–665.
- 12
- 13 34. Girard TD, Thompson JL, Pandharipande PP, *et al.* Clinical phenotypes of delirium during critical
- 14 illness and severity of subsequent long-term cognitive impairment: a prospective cohort study.
- 15 *Lancet Respir Med* 2018;6:213–222.
- 16
- 17 35. Pandharipande PP, Ely EW, Arora RC, *et al.* The intensive care delirium research agenda: a
- 18 multinational, interprofessional perspective. *Intensive Care Med* 2017;43:1329–1339.
- 19
- 20 36. Sackey PV, Martling C-R, Carlswärd C, *et al.* Short- and long-term follow-up of intensive care unit
- 21 patients after sedation with isoflurane and midazolam—a pilot study. *Crit Care Med* 2008;36:801–
- 22 806.
- 23
- 24 37. Krannich A, Leithner C, Engels M, *et al.* Isoflurane Sedation on the ICU in Cardiac Arrest Patients
- 25 Treated With Targeted Temperature Management: An Observational Propensity-Matched Study.
- 26 *Crit Care Med* 2017;45:e384–e390.
- 27
- 28 38. Jerath A, Beattie SW, Chandy T, *et al.* Volatile-based short-term sedation in cardiac surgical
- 29 patients: a prospective randomized controlled trial. *Crit Care Med* 2015;43:1062–1069.
- 30
- 31 39. Jerath A, Wong K, Wasowicz M *et al.* Use of Inhaled Volatile Anesthetics for Longer Term Critical
- 32 Care sedation: a pilot randomized controlled trial. *Critical Care Explorations* 2020;2:e0281.
- 33
- 34 40. Herzog-Niescery J, Seipp H-M, Weber TP, Bellgardt M. Inhaled anesthetic agent sedation in the
- 35 ICU and trace gas concentrations: a review. *J Clin Monit Comput* 2018;32:667–675.
- 36
- 37 41. Jerath A, Ferguson ND, Cuthbertson B. Inhalational volatile-based sedation for COVID-19
- 38 pneumonia and ARDS. *Intensive Care Med* 2020;46:1563–1566.
- 39
- 40 42. Ferrière N, Bodenes L, Bailly P, L’Her E. Shortage of anesthetics: Think of inhaled sedation! *J Crit*
- 41 *Care* 2020; S0883-9441(20)30686-9.
- 42
- 43 43. Chen F, Long Z, Yin J, *et al.* Isoflurane Post-Treatment Improves Outcome after an Embolic Stroke
- 44 in Rabbits. *PLoS ONE* 2015;10:e0143931.
- 45
- 46 44. Wang Y-Z, Li T-T, Cao H-L, Yang W-C. Recent advances in the neuroprotective effects of medical
- 47 gases. *Med Gas Res* 2019;9:80–87.
- 48
- 49 45. Schoen J, Husemann L, Tiemeyer C, *et al.* Cognitive function after sevoflurane- vs propofol-based
- 50 anaesthesia for on-pump cardiac surgery: a randomized controlled trial. *Br J Anaesth*
- 51 2011;106:840–850.
- 52
- 53 46. Dabrowski W, Rzecki Z, Czajkowski M, *et al.* Volatile anesthetics reduce biochemical markers of
- 54 brain injury and brain magnesium disorders in patients undergoing coronary artery bypass graft
- 55 surgery. *J Cardiothorac Vasc Anesth* 2012;26:395–402.
- 56
- 57
- 58
- 59
- 60

- 1
2
3 47. Nyktari V, Papaioannou A, Volakakis N, *et al.* Respiratory resistance during anaesthesia with
4 isoflurane, sevoflurane, and desflurane: a randomized clinical trial. *Br J Anaesth* 2011;107:454–
5 461.
6
7 48. Freiermuth D, Mets B, Bolliger D, *et al.* Sevoflurane and Isoflurane-Pharmacokinetics,
8 Hemodynamic Stability, and Cardioprotective Effects During Cardiopulmonary Bypass. *J*
9 *Cardiothorac Vasc Anesth* 2016;30:1494–1501.
10
11 49. Zorrilla-Vaca A, Núñez-Patiño RA, Torres V, Salazar-Gomez Y. The Impact of Volatile Anesthetic
12 Choice on Postoperative Outcomes of Cardiac Surgery: A Meta-Analysis. *Biomed Res Int*
13 2017:7073401.
14
15 50. L’Heudé M, Poignant S, Elaroussi D, *et al.* Nephrogenic diabetes insipidus associated with
16 prolonged sedation with sevoflurane in the intensive care unit. *Br J Anaesth* 2019;122:e73–e75.
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