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Level of sedation in critically ill adult patients: a protocol for a systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Introduction It is standard of care to provide sedation to critically ill patients to reduce anxiety, discomfort and promote tolerance of mechanical ventilation. Given that sedatives can have differing effects based on a variety of patient and pharmacological characteristics, treatment approaches are largely based on targeting the level of sedation. The benefits of differing levels of sedation must be balanced against potential adverse effects including haemodynamic instability, causing delirium, delaying awakening and prolonging the time of mechanical ventilation and intensive care stay. This systematic review with meta-analysis aims to investigate the current evidence and compare the effects of differing sedation levels in adult critically ill patients.

Methods and analyses We will conduct a systematic review based on searches of preidentified major medical databases (eg, MEDLINE, EMBASE, CENTRAL) and clinical trial registries from their inception onwards to identify trials meeting inclusion criteria. We will include randomised clinical trials comparing any degree of sedation with no sedation and lighter sedation with deeper sedation for critically ill patients admitted to the intensive care unit. We will include aggregate data meta-analyses and trial sequential analyses. Risk of bias will be assessed with domains based on the Cochrane risk of bias tool. An eight-step procedure will be used to assess if the thresholds for clinical significance are crossed, and the certainty of the evidence will be assessed using Grades of Recommendations, Assessment, Development and Evaluation.

Ethics and dissemination No formal approval or review of ethics is required as individual patient data will not be included. This systematic review has the potential to highlight (1) whether one should believe sedation to be beneficial, harmful or neither in critically ill adults; (2) the existing knowledge gaps and (3) whether the recommendations from guidelines and daily clinical practice are supported by current evidence. These results will be disseminated through publication in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Methodology based on the Cochrane Handbook, Grades of Recommendations, Assessment, Development and Evaluation and trial sequential analyses.
⇒ Broad inclusion criteria including all randomised clinical trials comparing any degree of sedation with no sedation and lighter sedation with deeper sedation in critically ill adults regardless of underlying conditions.
⇒ Broad search strategy including 10 databases and two clinical trial registries.
⇒ Risk of statistical and clinical heterogeneity due to various types of sedative drugs and participants included regardless of underlying condition.
⇒ Risk of type 1 error due to large number of comparisons, which will be considered when interpreting the review results.

INTRODUCTION

Description of the patient population

Critically ill patients by virtue of their disease are at risk of significant morbidity and mortality. More than 4 million patients in the USA are admitted to the intensive care units (ICUs) with critical illness each year and require specialised staff and technical equipment, with high cost for society.[1] Moreover, patients surviving critical illness face a range of physical and functional deficits that may prevail after intensive care discharge.[2–4]

Description of the intervention

It has been standard of care for many decades to provide sedation to patients in need of mechanical ventilation to provide comfort during therapy.[5 6] Approximately 85% of all critically ill patients are sedated during an intensive care stay.[7 8] General indications for sedation are to reduce anxiety, discomfort, ventilatory intolerance and to promote

patient-ventilator synchrony. Patients with more advanced respiratory compromise may require deeper sedation and neuromuscular blockade to allow for better compliance with the ventilator. However, sedation may also compromise haemodynamics, cause delirium, prolong the duration of mechanical ventilation and intensive care stay, cause long-term cognitive impairment and increase the risk of death.[6 9–15] These outcomes are more likely to be affected by the level of sedation rather than the dose of sedatives administered, because the required dose of sedatives needed to reach the target sedation level varies between patients according to patient and disease characteristics and the pharmacological properties of different medications.

Critically ill patients may experience pain due to procedures, tests, prolonged immobilisation and daily care associated with intensive care. It is important to treat pain for patient comfort but also to minimise the risk of delirium and agitation during intensive care stay and post-traumatic stress disorder after intensive care discharge.[1 15–17]

Excess sedation in critically ill patients may lead to adverse events, such as unstable haemodynamics, ventilator associated pneumonia, delayed awakening, prolonged duration of mechanical ventilation, intensive care stay and postintensive care syndrome.[7] To minimise potential harms, protocolised assessment and monitoring of sedation depth is recommended by guidelines.[18] Sedation depth is most effectively monitored using clinical sedation assessment. Richmond Agitation and Sedation Scale (RASS) and Sedation-Agitation Scale are two well-established, validated and reliable sedation scales.[19 20]

Sedation with daily interruption of sedatives is one method used to target lighter sedation to allow for patient awakening and neurological assessment.[10 21 22] Guidelines prefer propofol or dexmedetomidine over benzodiazepines to facilitate titration to lighter sedation and to reduce delirium.[21] Volatile agents, such as sevoflurane and isoflurane, are an alternative route to the intravenous infusion and have shown less accumulation, reduced time of mechanical ventilation and intensive care stay and may have cardioprotective effects.[23–25] Acquisition of equipment required to deliver volatile agents, lack of familiarity, and perceived comparative cost, have limited widespread uptake. Optimal sedation and analgesia treatment regimens are crucial to avoid oversedation and undersedation in critically ill patients.[26 27] The level of sedation is anticipated to affect clinically important outcomes and the use of different sedative drugs do not alter this effect.[14 28 29] Additionally, patients' underlying illness may drive the sedation approach, with differing trade-offs of risks and benefits.

Haemodynamically unstable patients

Haemodynamic instabilities are common in critically ill patients. Sedation using either benzodiazepines and propofol impacts in a dose-dependent fashion haemodynamics causing systemic vasodilation resulting in hypotension.[10] Dexmedetomidine is a selective alpha-2 receptor agonist with sedative and anxiolytic effects, with minimal effect on respiration. Dexmedetomidine also alters haemodynamics causing transient hypertension, hypotension and bradycardia.[30 31]

Neurocritical care patients

Patients suffering from acute brain injury due to severe haemorrhagic or ischaemic stroke, global ischaemia, subarachnoid bleeding, trauma or seizures might differ from general critically ill patients in their requirement for, and adverse effects from, sedation.[32] Sedation is considered part of the treatment of elevated intracranial pressure for example in patients with brain injury.[33 34] Sedation reduces metabolism and thus reduces oxygen consumption and carbon dioxide production, thereby theoretically protecting patients with brain injury from development of oedema or ischaemia that could cause increased intracranial pressure and secondary brain injury. Clinical studies have not yet been demonstrated these improved outcomes.[35–38] Nonetheless, many clinicians consider sedation has specific indications for patients with acute brain injury caused by ischaemic or haemorrhagic stroke, subarachnoid haemorrhage, cardiac arrest, trauma and in treatment of seizures in patients with status epilepticus.[32] After acute brain injury, cerebral autoregulation of blood flow and oxygen supply may be impaired, and patients may be more susceptible to hyperperfusion or hypoperfusion based on blood pressure or metabolic demand.[36] Seizures are common after acute brain injury and increase cerebral metabolic demand and could result in secondary neurological injury. Some sedatives, including benzodiazepines and propofol, suppress clinical seizures and have been proposed as seizure prophylactics. It remains unknown if they affect mortality.[39 40]

Cardiac arrest patients

Patients resuscitated from cardiac arrest may have varying extent of brain injury, seizures, organ failure and haemodynamic instability.[41 42] Haemodynamical instability is common after return of spontaneous circulation, potentially causing inadequate circulation of blood to vital organs, most importantly the heart and brain. Patients remaining comatose after resuscitation are recommended to be treated with targeted temperature management (TTM) to mitigate brain injury.[41 42] The implementation of TTM in early 2000' has led to routine provision of sedation in these patients. However, this may change in future practice since recent trials have shown no improvement in outcome in patients treated with hypothermia compared with normothermia.[43] Regardless of temperature chosen, shivering, a response to external interventions that decrease body temperature, increases metabolism and oxygen consumption, is an important complication of induced hypothermia.[44] One specific sedation indication in patients treated with TTM is to reduce shivering either without or in conjunction with neuromuscular blockade. Other benefits of sedation in

this population are a potential reduction in the risk of seizures, which can occur after cardiac arrest, and treatment in patients with increased intracranial pressure caused by cerebral oedema.[33 34 39 40 45] TTM alters the pharmacodynamics of sedative and analgesic drugs and may impact drug metabolism, both need to be considered when administering sedation to these patients.[46–50] Possible drug accumulation is of great importance in cardiac arrest patients since it may confound neurological prognostication, resulting in either the devastating consequence of premature withdrawal of life-sustaining therapies,[46 49–51] or (likely more common) persistence with treatment that is ultimately futile. Short-acting sedatives and analgesics are recommended to minimise these risks, although these recommendations are difficult to apply to this patient population due the complexity of haemodynamic instability and severity of brain injury.

Why is this review important?

The benefits of sedatives in critical care patients must be balanced against the potential harms of affecting haemodynamics, causing delirium and prolonging the time of mechanical ventilation and intensive care stay, which may affect outcome. It is important to consider intensive care that preserves the function of the brain and neuromuscular system, from the perspective of life altering disabilities and impairments after intensive care. Additional understanding of optimal sedation is warranted.[52] Moreover, treating patients at an optimal sedation level may not only improve outcome but may also optimise resource utilisation.[53] Previous systematic reviews and meta-analyses have assessed the effects of different sedation depths in critically ill adult patients:

- Long *et al* compared the effects of lighter sedation versus deeper sedation. The primary outcome was occurrence of delirium and secondary outcomes were agitation-related adverse events and mortality in mechanically ventilated adult patients.[54] Ten randomised clinical trials, four before-and-after controlled trials, two prospective and two retrospective studies were assessed. Meta-analyses showed that the deeper sedation group, as compared with the lighter sedation group, had a significantly higher risk of death (OR 1.82, 95% CI 1.23 to 2.69, p=0.003). Meta-analysis showed no significant difference in the occurrence of delirium in deeper sedation compared with patients with lighter sedation (OR 1.00, 95% CI 0.64 to 1.58, p=0.993). Long *et al* assessed the risk of bias in the included trials using the Cochrane handbook and the Newcastle-Ottawa Scale, a systematic search was conducted, and Grades of Recommendations, Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence.[55 56] The groups were defined based on sedation scales defined by the individual study. The major limitation of this review was that patients with brain injury, alcohol withdrawal syndrome and speech disorder were excluded.
- Aitken *et al* also compared the effect of lighter sedation versus deeper sedation on the duration of mechanical ventilation and intensive care mortality in adult patients receiving mechanical ventilation in the ICU.[57] Eight randomised controlled trials and 12 cohort studies, with a total of 7865 patients, were analysed. Meta-analysis of the included randomised trials showed no evidence of a difference in intensive care mortality (risk ratio, RR 0.82 (95% CI 0.58 to 1.17)) or in duration of mechanical ventilation but found a significantly shorter time of mechanical ventilation in patients treated with lighter sedation in the cohort studies (MD: −1.52 days (95% CI −2.71 to −0.34)). Aitken *et al*[57] assessed the risk of bias in the included trials using the Cochrane handbook and ROBINS-I, a systematic search was conducted and GRADE was used to assess the certainty of the evidence.[58 59]
- Stephens *et al* compared the effects of lighter sedation vs deeper sedation within the first 48 hours of initiating mechanical ventilation in adult patients.[60] To be included, studies had to report some objective measurement of sedation depth like RASS or GCS. Studies of patients mechanically ventilated in the operating room and then admitted to an ICU were included, and studies mainly focusing on perioperative outcomes were excluded. Two randomised clinical trials and seven observational studies, totally comprising 4521 patients, were included, but no separate analyses including only randomised trials were presented. The review authors found significantly lower mortality rate in patients treated with lighter sedation compared with deeper sedation (OR 0.34 (95% CI 0.21 to0.54), p<0.001). Stephens *et al*[60] assessed the risk of bias in the included trials using the Cochrane Collaboration tools and Newcastle-Ottawa Scale handbook, a systematic search was conducted but the GRADE was not used to assess the certainty of the evidence.[55 61] Another limitation of this review was that the studies enrolling patients after 48 hours of initiation of mechanical ventilation were excluded, and thus, 15 relevant studies were not included.

The previously conducted meta-analyses because of the findings of above-described analyses are inconclusive and have several limitations. None of the trials have taken into account both risks of random errors and systematic errors.[62] Consequently, there is no clear consensus on the impact of sedation on mortality and other clinically important outcomes in critically ill patients.

This systematic review and meta-analysis aim to compare the effects of the level of sedation in adult critically ill patients, to investigate the current evidence. We plan to compare (1) no sedation vs any degree of sedation and (2) lighter sedation versus deeper sedation. Moreover, because of the clinical heterogeneity of critically ill, we want to investigate the effect of the level of sedation in patients with acute brain injury, postcardiac arrest and

haemodynamically unstable patients in subgroup analyses, where sedation might have specific effects.

METHODS

Methods and analysis

This systematic review protocol has been developed based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines for reporting systematic reviews evaluating healthcare interventions.[63] This study will be registered on International Prospective Register of Systematic Reviews. The planned start date of this study is September 2022 and planned end date is February 2023.

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespectively of design, setting, blinding, publication status, language, publication year and reporting of outcomes.

Types of participants

We will include adult patients admitted to an ICU (as defined by trialists), irrespectively of sex and comorbidities. Trials that only include a subset of eligible participants will be included if: (1) separate data on the eligible participants are available or (2) more than 90% are eligible.

Types of interventions

We will assess two types of comparisons:

- Any degree of sedation (as defined by trialists) compared with no sedation.
- Light sedation (as defined by trialists) compared with deep sedation (as defined by trialists). Studies comparing any intervention with one group receiving lighter sedation than the other group, were eligible for inclusion. Studies not eligible if no separation of sedation depth could be identified.

The results of these two comparisons will be presented separately.

We will accept any type of cointerventions when such cointerventions are intended to be delivered similarly to the experimental and control group.

Outcome measures

Primary outcomes

- All-cause mortality at longest follow-up (dichotomous outcome).

Secondary outcomes

- Serious adverse event at any time point (dichotomous outcome).
- Poor neurological outcome at longest follow-up (dichotomous outcome) (as defined by trialists).
- Delirium at any point in the ICU admission (dichotomous outcome) (as defined by trialists).

We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability. As we expect the reporting of serious adverse events to be very heterogeneous and not strictly according to the 'International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice' (ICH-GCP) recommendations in many trials, we will include the event as a serious adverse event if the trialists either: (1) use the term 'serious adverse event' but not refer to ICH-GCP or (2) report the proportion of participants with an event we consider fulfil the ICH-GCP definition. If several of such events are reported, we will choose the highest proportion reported in each trial. We will second analyse each component of serious adverse events separately.

Exploratory outcomes

- Duration of mechanical ventilation (continuous scale) (as defined by trialists).
- Quality of life (any valid continuous scale).
- Post-traumatic stress disorder (dichotomous outcome).
- Mean arterial blood pressure (continuous scale).
- Body core temperature (continuous scale).
- Intracranial pressure (continuous scale).
- Duration of delirium/proportion of time spent in delirium (continuous scale).

Search methods for identification of studies

Electronic searches

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (Ovid, from 1946 and onwards).
- Embase (Ovid, from 1980 and onwards).
- LILACS (Bireme, 1982 and onwards).
- BIOSIS (Thomson Reuters, 1926 and onwards).
- CINAHL.
- Scopus.
- Web of Science Core Collection.

A preliminary search strategy for MEDLINE (Ovid) is given in online supplemental material 1. We will adapt the preliminary search strategy for MEDLINE (Ovid) for use in these databases. We will apply the Cochrane sensitivity-maximising randomised clinical trial filter to MEDLINE (Ovid) and adaptations of it to all the other databases, except CENTRAL. A medical librarian will conduct the electronic search.

Searching other resources

We will search the reference lists of included randomised clinical trials, previous systematic reviews and other types of reviews for any unidentified randomised clinical trials. We will also contact authors of included randomised clinical trials for further information by email. Further, we will search for ongoing and unidentified randomised clinical trials on:

- ClinicalTrials.gov (www.clinicaltrials.gov).

- The WHO International Clinical Trials Registry. Platform search portal (http://apps.who.int/trialsearch/).
- Google Scholar (https://scholar.google.com/).
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/).

We will also include unpublished and grey literature trials if we identify these and assess relevant retraction statements and errata for included studies.

Data collection and analyses

We will perform the review following the recommendations of Cochrane. The analyses will be performed using the R statistical software (V.4.0.3, R Foundation for Statistical Computing, Vienna, Austria).

Selection of studies

Two review authors AC and JHo will independently screen titles and abstracts for inclusion of all potentially eligible trials. We will code the studies 'retrieve', defined as (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (JJ or NN). We will retrieve all relevant full-text study reports/publications and two review authors AC and JHä will independently screen the full-text and identify trials for inclusion. We will report reasons for exclusion of the ineligible studies. We will identify and exclude duplicated and collated multiple reports of the same trial so that each trial rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

We will use a data collection tool for study characteristics and outcome data, which has been piloted on at least one study in the review. Two authors will extract and validate data independently from the included trials. Any disagreement concerning the extracted data will be discussed between the two authors. If no agreement can be reached, a third author (NN or JJ) will resolve the issue. We will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication. We will extract data on trial, participants', and intervention characteristics and outcomes (see online supplemental table 1).

Assessment of risk of bias in the included studies

Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 2 as recommended in The Cochrane Handbook of Systematic Reviews of Interventions (see online supplemental material 2).

Measures of treatment effect

Dichotomous outcomes

We will calculate RRs with 95% CI for dichotomous outcomes, as well as the TSA-adjusted CIs (see paragraph Trial sequential analysis below). We will calculate the absolute risk reduction or absolute risk increase and number needed to treat, or number needed to harm if the outcome result shows a beneficial or harmful effect, respectively. If we observe problems with single zero events when meta-analysing data, we will use reciprocal zero cell correction. If we observe problems with double zero events, we will analyse data using beta-binominal regression.

Continuous outcomes

We will calculate the mean differences and if necessary, as a hypothesis generating analysis, the standardised mean difference with 95% CI for continuous outcomes, as well as the TSA-adjusted CIs (see paragraph Trial sequential analysis below).

Unit of analysis issues

We will only include randomised clinical trials. For trials using cross-over design, only data from the first period will be included. For trials where multiple trial intervention groups are reported, we will only include the relevant groups. If two comparisons from the same trial are combined in the same meta-analysis, we will halve the control group to avoid double counting. We will not include cluster randomised trials, as these have a high risk of biased results due to confounding.

Dealing with missing data

We will, as first option, contact all trial authors to obtain any relevant missing information and data.

Dichotomous outcomes

We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph Sensitivty analysis below), we will impute data.

Continuous outcomes

We will primarily analyse scores assessed at single time points. If only change from baseline scores are reported, we will analyse the results together with follow-up scores.[58] If SDs are not reported, we will calculate the SDs using trial data for example, calculate SD based on CIs or SE, if possible.[58] We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis, but we will impute in two of our sensitivity analyses (see paragraph Sensitivity analysis below).

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess for signs of heterogeneity. We will second assess the presence of statistical heterogeneity by the χ^2 test (threshold

p<0.10) and measure the quantities of heterogeneity by the I^2 statistic. We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided.

Assessment of reporting biases

We will use a funnel plot to assess reporting bias in the meta-analyses including 10 or more trials. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (ie, a funnel plot assesses bias due to small sample size, and asymmetry of a funnel plot is not necessarily caused by reporting bias. From this information, we assess possible reporting bias). For dichotomous outcomes, we will test asymmetry with the Harbord test if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test and the adjusted rank correlation.

Data synthesis

Meta-analysis and assessment of significance

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions, Keus *et al* and the eight-step assessment suggested by Jakobsen *et al* for better validation of meta-analytical results in systematic reviews. We will use the statistical software Review Manager V.5.338 provided by Cochrane and R statistical software (V.4.0.3) to analyse data. We will assess our intervention effects with both random-effects meta-analyses and fixed-effect meta-analyses and report the more conservative result as (highest p value) as our primary result and the less conservative results as a sensitivity analysis. If there is substantial discrepancy between the results of the two methods, we will report both results and discuss what caused the difference. We will adjust our thresholds for statistical significance due to problems with multiplicity (family-wise error rate), by dividing the prespecified p value threshold with the value halfway between 1 (no adjustment) and the number of primary and secondary outcome comparisons (Bonferroni adjustment). We will assess a total of two primary and three secondary outcomes and we will, therefore, consider a p value of 0.02 or less as the threshold for statistical significance.[62] If quantitative synthesis is not appropriate, we will report the results in a narrative way.

Trial sequential analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data. Therefore, TSA can be applied to control these risks (http://www.ctu.dk/tsa/).[62] Similar to a sample size calculation in a randomised clinical trial, TSA estimates the diversity-adjusted required information size (DARIS) (ie, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random errors. The DARIS considers the anticipated intervention effect, the variance of the anticipated difference in intervention effects, the acceptable risk of falsely rejecting the null hypothesis (alpha), the acceptable risk of falsely confirming the null hypothesis (beta). We searched for suitable empirical data to determine and predefine the anticipated intervention effects. However, no suitable data could be found. Instead, we pragmatically hypothesised the anticipated intervention effects:

- When analysing dichotomous outcomes, we will pragmatically anticipate an intervention effect equal to aRR reduction (RRR) of 25%, as recommended by the GRADE guidelines when previous evidence do not provide other preliminary estimations.[58] Additionally, we will use trial sequential analyses to define the lowest intervention effects threshold we can confirm or reject.
- When analysing quality of life, we will pragmatically anticipate an intervention effect equal to the mean difference of the observed SD/2.

TSA enables testing for significance to be conducted each time a new trial is included in the meta-analysis. Based on the DARIS, trial sequential monitoring boundaries are constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the DARIS. Firm evidence for benefit or harm may be established if a trial sequential monitoring boundary (ie, upper boundary of benefit or lower boundary of harm) is crossed before reaching the DARIS, in which case further trials may turn out to be superfluous. In contrast, if a boundary is not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z-score crosses the trial sequential boundaries for futility. The TSA programme is also able to calculate TSA-adjusted CIs, which we will report in addition to the unadjusted naïve 95% CI. TSA-adjusted CI compared with unadjusted naive 95% CI gives a more correct estimation of the true CI, as it is adjusted for lack of information. If the TSA cannot be conducted because of too little information, we will conduct a more lenient analysis by increasing the anticipated intervention effect (in these cases, the TSA-adjusted CI is overly optimistic). For dichotomous outcomes, we will estimate the DARIS based on an anticipated intervention effect (our anticipated intervention effect for each dichotomous outcome is stated above), the observed proportion of participants with an outcome in the control group, an alpha of 2.0% for our primary and secondary outcomes and 5.0% for our exploratory outcomes (see the 'Meta-analysis and assessment of significance' section), a beta of 10% and a diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will estimate the DARIS based on a minimal clinically important difference of SD/2, the SD observed in the control group, an alpha of 2.0% for our primary and secondary outcomes and 5.0% for our exploratory outcomes (see the 'Meta-analysis and assessment of significance' section), a beta

of 10% and a diversity as suggested by the trials in the meta-analysis. We will document difficult decisions in the review and sensitivity analyses will assess the impact of these decisions on the findings of the review.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses on all our outcomes (see online supplemental table 2). We will use the formal test for subgroup differences in Review Manager. Other post hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis in which we exclude trials with overall 'high risk of bias'. To assess the potential impact of the missing data for dichotomous outcomes, we will perform two sensitivity analyses, 'best-worst- case' scenario and 'worst-best- case' scenario, when assessing each dichotomous outcome (all-cause mortality, serious adverse events and non-serious adverse events) (see online supplemental table 3).

To assess the potential impact of the missing data for continuous outcomes, we will perform two sensitivity analyses, 'best-worst-case' scenario and 'worst-best-case' scenario, when assessing each continuous outcome (quality of life and time of mechanical ventilation) (see online supplemental table 3).

To assess the potential impact of missing SDs for continuous outcomes, we will perform sensitivity analysis. Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. We will present results of this scenario in our review.

Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.

Summary of findings

We will use the GRADE system to assess the certainty of the body of evidence associated with each of our outcomes constructing 'Summary of Findings' (SoF) tables using the GRADEpro software.[58] The GRADE approach appraises the certainty of the body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We will assess the GRADE levels of evidence as high, moderate, low and very low and downgrade the evidence by one or two levels depending on the following certainty measures: within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias. We will use TSA to assess 'imprecision'. We will use methods and recommendations described in chapter 8 (section 8.5) and chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions.[58] We will justify all decisions to downgrade the certainty of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary. We will include all trials in our analyses and conduct a sensitivity analysis excluding trials at high risk of bias. If the results are similar, we will base our SoF table and conclusions on the overall analysis. If they differ, we will base our SoF table and conclusions on trials at low risk of bias.

Differences between the protocol and the review

We will conduct the review according to this protocol and report any deviations from it in the 'differences between protocol and review' section of the systematic review.

Patient and public involvement

We conducted this protocol for a systematic review without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this protocol for readability or accuracy.

DISCUSSION

This protocol aims to assess the effects of the level of sedation on critically ill patients regardless of underlying condition to assess the beneficial and harmful effects of sedation. The primary outcomes will be all-cause mortality and secondary outcomes will be serious adverse events, poor neurological outcome and delirium.

This protocol has number of strengths. The predefined methodology is based on the PRISMA-P guidelines for reporting systematic reviews evaluating healthcare interventions, GRADE, TSA and the eight-step assessment suggested by Jakobsen *et al* for better validation of meta-analytical results in systematic reviews.[58 62 63] Hence, this protocol considers both risks of random errors and risks of systematic errors.

Our protocol also has several limitations. The primary limitation is that we will include various types of sedative drugs, and it is possible that different sedatives have different effects on the outcomes. Another limitation is that we will include various types of participants regardless of their underlying condition, and it is possible that sedation affect participants differently depending on their condition. To minimise these limitations, we have planned to assess carefully clinical and statistical heterogeneity including several subgroup analyses, but it must be recognised that these subgroup analyses presumably will be underpowered. We will carefully take this into account when interpreting our results. Another limitation is the large number of comparisons, which increases the risk of family-wise error. To minimise this limitation, we have adjusted our thresholds for significance according to the total number of our primary and secondary outcomes. Nevertheless, we have not adjusted our thresholds for significance according to the large number of subgroup

analyses. The substantial risks of type I errors will also be considered when interpreting our result

Ethics and dissemination

No formal approval or review of ethics is required for this systematic review as individual patient data will not be included. The results of this systematic review will be disseminated through publication in a leading peer-reviewed journal.

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Supplement table 1. Table of data that will be extracted from the included trials.

Trial characteristics
Bias risks components
Trial design (parallel, factorial or crossover)
Trial period
Number of trial sites
Name of countries in which the trial was conducted
Number of intervention arms
Length of follow-up and
Inclusion and exclusion criteria
Patients' characteristics and diagnosis
Number of randomized participants
Number of analyzed participants
Number of participants lost to follow-up
Mean age
Age range
Sex ratio
Specific inclusion criteria based on the condition of the adult (eg, neurological injury, cardiac arrest, hemodynamically unstable, infection, trauma, respiratory failure, or other organ failure)
Experimental intervention characteristics
Type of sedative drug
Dose of sedation
Duration of sedation
Mode of administration
Routines of sedation interruption and cessation
Control intervention characteristics
Type of control intervention
Dose of intervention

Duration of intervention *Mode of administration* *Defined target sedation depth*
Co-intervention characteristics *Type of co-intervention* *Dose of co-intervention* *Duration of co-intervention* *Mode of administration*
Outcomes *Primary and secondary outcomes specified and collected* *Time points reported* *Differences in planned and reported outcomes*
Notes (if available) *Type of depth of sedation measuring scales* *Funding of the trial and* *Notable conflicts of interest of trial authors*

Supplement table 2. Subgroups analyses.

Comparison of the effects between trials with different types of sedation interventions
Trials including volatile sedation
Trials including dexmedetomidine
Trials including propofol
Comparison of the effects between critically ill based on the cause of admission
Trials including patients with non-traumatic brain injury or
Trials including patients with traumatic brain injury or
Trials including patients with post cardiac arrest care or
Trials including patients with hemodynamic instability
Comparison of the effects between trials with different maximal follow-ups
Up to 90 days or
90 days and above
Comparison of the effect between trials with different control interventions
Placebo-controlled trials
No control intervention
Comparison of the effects between industry funded trials or trials with unknown funding compared to non-industry funded trials
Industry funded trials or unknown funding
Non-industry funded trials

Supplement table 3. Describes sensitivity analyses of how the patients with lost to follow-up will be treated in the analyses of different scenarios for dichotomous and continuous outcomes, respectively.

Dichotomous outcomes
'Best-worst- case' scenario
Experimental group *Have survived, had no serious adverse event, and had no non-serious event*
Control group *Have not survived, had a serious event, and had a non-serious adverse event*
'Worst-best- case' scenario
Experimental group *Have not survived, had a serious event, and had a non-serious adverse event*
Control group *Have survived, had no serious adverse event, and had no non-serious event*
Continuous outcomes
'Best-worst- case' scenario
Experimental group will have a beneficial outcome *The group mean plus one SD of the group mean*
Control group will have harmful outcome *The group mean minus one SD of the group mean*
'Worst-best- case' scenario
Experimental group will have a beneficial outcome *The group mean plus one SD of the group mean*
Control group will have harmful outcome *The group mean minus one SD of the group mean*

[1]Search strategies for
Level of sedation in critically ill adult patients
(A Ceric)
Preliminary searches prepared 21 January 2022

Cochrane Central Register of Controlled Trials (latest issue) in the Cochrane Library (*in 2022, Issue 1: 3354 hits*)

#1 MeSH descriptor: [Critical Illness] explode all trees
#2 MeSH descriptor: [Critical Care] explode all trees
#3 MeSH descriptor: [Intensive Care Units] explode all trees
#4 ((critical* and (care* or ill*)) or intensive care or ICU or respirat* or ventilat*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Conscious Sedation] explode all trees
#7 MeSH descriptor: [Deep Sedation] explode all trees
#8 MeSH descriptor: [Hypnotics and Sedatives] explode all trees
#9 MeSH descriptor: [Benzodiazepines] explode all trees
#10 MeSH descriptor: [Propofol] explode all trees
#11 MeSH descriptor: [Dexmedetomidine] explode all trees
#12 (sedati* or benzodiazepin* or midazolam or propofol or dexmedetomidin* or lorazepam)
#13 #6 or #7 or #8 or #9 or #10 or #11 or #12
#14 #5 and #13
#15 (adult* or aged or elder* or middle next age* or old next age):ti,ab
#16 #14 and #15

MEDLINE Ovid (1946 to the date of the search) (*on 21 January 2022: 3310 hits*)

1. exp Critical Illness/
2. exp Critical Care/
3. exp Intensive Care Units/
4. ((critical* and (care* or ill*)) or intensive care or ICU or respirat* or ventilat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. exp Conscious Sedation/
7. exp Deep Sedation/
8. exp "Hypnotics and Sedatives"/
9. exp Benzodiazepines/
10. exp Propofol/
11. exp Dexmedetomidine/
12. (sedati* or benzodiazepin* or midazolam or propofol or dexmedetomidin* or lorazepam).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 5 and 13
15. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. 14 and (15 or 16)
18. limit 17 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

Embase Ovid (1974 to the date of the search) (*on 21 January 2022: 8782 hits*)

1. exp critical illness/
2. exp critically ill patient/
3. exp intensive care/
4. exp intensive care unit/

5. ((critical* and (care* or ill*)) or intensive care or ICU or respirat* or ventilat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
6. 1 or 2 or 3 or 4 or 5
7. exp sedation/
8. exp hypnotic sedative agent/
9. exp benzodiazepine derivative/
10. exp propofol/
11. (sedati* or benzodiazepin* or midazolam or propofol or dexmedetomidin* or lorazepam).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.nr.
15. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
16. 13 and (14 or 15)
17. limit 16 to (adult <18 to 64 years> or aged <65+ years>)

LILACS (Bireme; 1982 to the date of the search) (*on 21 January 2022: 125 hits*)
((critical$ and (care$ or ill$)) or intensive care or ICU or respirat$ or ventilat$) [Words] and (sedati$ or benzodiazepin$ or midazolam or propofol or dexmedetomidin$ or lorazepam) [Words] and (random$ or blind$ or placebo$) [Words]

Science Citation Index Expanded (1900 to the date of the search) and Conference Proceedings Citation Index – Science (1990 to the date of the search) (Web of Science) (*on 21 January 2022: 2037 hits*)
#7 #5 AND #6
#6 TI=(adult* or aged or elder* or middle next age* or old next age) or AB=(adult* or aged or elder* or middle next age* or old next age)
#5 #3 AND #4
#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)
#3 #2 AND #1
#2 TS=(sedati* or benzodiazepin* or midazolam or propofol or dexmedetomidin* or lorazepam)
#1 TS=((critical* and (care* or ill*)) or intensive care or ICU or respirat* or ventilat*)

1. Higgins JPT TJ, Chandler J.: **Cochrane Handbook for systematic reviews of interventions version 6.1**. *Cochrane* 2020.

Supplement material

Bias arising from the randomization process

This domain encompasses allocation sequence generation and concealment as well as baseline differences between the trial arms.

Low risk of bias

Allocation was adequately concealed, AND there are no baseline imbalances across intervention groups at baseline appear to be compatible with chance, AND an adequate (random or otherwise unpredictable) method was used to generate allocation sequence, OR there is no information about the method used to generate the allocation sequence

Some concerns

Allocation was adequately concealed, AND there is a problem with the method of sequence generation, OR baseline imbalances suggest a problem with the randomization process, OR no information is provided about concealment of allocation, AND baseline imbalances across intervention groups appear to be compatible with chance, OR no information to answer any of the signaling questions

High risk of bias

Allocation sequence was not concealed, OR no information is provided about concealment of allocation sequence, AND baseline imbalances suggest a problem with the randomization process.

Bias due to deviation from intended interventions

Low risk of bias

Participants, treatment providers, and study personnel were unaware of intervention groups during the trial, OR participants, treating providers, or personnel were aware of intervention groups during the trial but any deviations from intended intervention reflected usual practice, OR participants, treating providers or personnel were aware of intervention groups during the trial but any deviations from intended intervention were unlikely to impact on the

outcome, AND no participants were analyzed in the wrong intervention groups (that is, on the basis of intervention actually received rather than of randomized allocation).

Some concerns

Participants, treatment providers, or study personnel were aware of intervention groups and there is no information on whether there were deviations from usual practice that were likely to impact on the outcome and were imbalanced between intervention groups, OR some participants were analyzed in the wrong intervention groups (on the basis of intervention actually received rather than of randomized allocation) but there was little potential for a substantial impact on the estimated effect of intervention.

High risk of bias

Participants, carers, or personnel were aware of intervention groups, and there were deviations from intended interventions that were unbalanced between the intervention groups and likely to have affected the outcome, OR some participants were analyzed in the wrong intervention groups (on the basis of intervention actually received rather than of randomized allocation), and there was potential for a substantial impact on the estimated effect of intervention.

Bias due to missing outcome data

Low risk of bias

No missing data OR non-differential missing data (similar proportion of and similar reasons for missing data in compared groups) OR evidence of robustness of effect estimate to missing data (based on adequate statistical methods for handling missing data and sensitivity analysis)

Some concerns

An unclear degree of missing data or unclear information on proportion and reasons for missingness in compared groups AND there is no evidence that the effect estimate is robust to missing data.

High risk of bias

A high degree of missing data AND differential missing data (different proportion of or different reasons for missing data in compared groups) AND there is no evidence that the effect estimate is robust to missing data.

Bias in measurement of outcomes

Low risk of bias

The outcome assessors were unaware of the intervention received by study participants, OR the outcome assessors were aware of the intervention received by study participants, but the assessment of the outcome was unlikely to be influenced by knowledge of the intervention received.

Some concerns

There is no information available to determine whether the assessment of the outcome is likely to be influenced by knowledge of the intervention received.

High risk of bias

The assessment of the outcome was likely to be influenced by knowledge of the intervention received by study participants. Bias arising from selective reporting of results.

Bias arising from selective reporting of results

Low risk of bias

Reported outcome data are unlikely to have been selected, based on the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain, and reported outcome data are unlikely to have been selected, based on the results, from multiple analyses of the data.

Some concerns

There is insufficient information available to exclude the possibility that reported outcome data were selected, based on the results, from multiple outcome measures (e.g., scales, definitions, time points) within the outcome domain, or from multiple analyses of the data. Given that analysis intentions are often unavailable or not reported with sufficient detail, we anticipate that this will be the default judgment for most trials.

High risk of bias

Reported outcome data are likely to have been selected, based on the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain, or from multiple analyses of the data (or both).

Overall assessment of risk of bias

Low risk of bias

The study is judged to be at low risk of bias for all domains for this result.

High risk of bias

The study is judged to be at high risk of bias or to be at some concerns in at least one domain for this result. Our subgroup analysis will compare the intervention effect of trials at low risk of bias with trials at high risk of bias, that is one or more domains at some concern or high risk of bias. We will assess the domains “missing outcome data”, “risk of bias in measurement of the outcome”, and “risk of bias in selection of the reported result” for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.