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Feasibility and effects of using ketamine sedation for patients on the Intensive Care Unit.

Submission date
06/08/2024

Recruitment status
Recruiting

Registration date
17/10/2024

Overall study status
Ongoing

Last Edited
10/02/2025

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Around half of patients needing ICU require breathing support on a ventilator. Most patients need a combination of painkiller (analgesics) and sleep-inducing (sedatives) drugs to allow this to happen.
A side effect of sedative drugs currently used is an inability to maintain blood pressure adequately. Potentially, this can mean other organs (such as the heart, liver, kidneys, and brain) may be affected. Low blood pressure can cause increased mortality (risk of dying) and increased length of time in ICU.
ICU can also be an unpleasant experience for patients. Hallucinations (seeing or hearing things that aren't real), delirium (severe confusion), depression, and post-traumatic stress disorder (PTSD) in survivors is common, and it's widely accepted that traditional sedative medications put patients at higher risk of these occurring.
Ketamine is a sleep-inducing and pain-relieving drug that has been used safely for over 50 years to produce anaesthesia (sleep) for surgery. Recent studies using ketamine as a sedative in intensive care show it does not significantly reduce blood pressure compared to current sedatives, whilst being similar in terms of overall safety.
Early studies show that ketamine sedation may have potential patient benefits, such as: maintained blood pressure, less delirium, better sedation, and reduced pain.
More recently it has been discovered that ketamine is a strong and quick-acting anti-depressant. This has not been investigated in ICU patients, but there is potential that it could reduce or prevent depression and PTSD following ICU admission.
Ketamine is not currently used as part of routine practice in ICU due to gaps in the evidence, however, further investigation is needed. This study aims to test initial feasibility of using ketamine sedation through a single-arm, prospective cohort study, helping refine study designs, identify key clinical and patient-centre outcomes, and identify barriers to implementation.

Who can participate?
Adults over 18 years old requiring sedation and mechanical ventilation on ICU

What does the study involve?
When patients start on the breathing machine (ventilator) in ICU, the majority will start on a sedative called propofol and a painkiller called alfentanil, this is what we call 'standard care'.

Once enrolled to the study, participants will change over to ketamine sedation. In this crossover period they will be receive both Propofol and ketamine so that the change is more gradual. They will continue to receive additional painkillers (alfentanil).
During the study we will monitor at participant progress by assessing their sedation level and comfort, monitoring for side-effects, as well as all the observations that would usually occur. There will not be any specialist tests performed beyond what is normally carried out in ICU, nor will any additional blood or DNA samples be taken or stored.
Data will be collected at several points: at the start (after determining eligibility and enrolling), daily while the patient is receiving the treatment, at ICU discharge, and 90 days later. This will include collecting routine data as well as questionnaires regarding their recovery, mood, feelings of anxiety and depression, and experiences on and since ICU, which is something we aim to do with most of our patients even if they are not enrolled in a study.

What are the possible benefits and risks of participating?
Benefits:
The study is aimed at improving the treatment for critically unwell patients admitted to ICU as well as improving their experience of ICU. Participation in the study could help shape the future of intensive care by helping identify ways to improve outcomes for patients requiring ventilator support. There is not necessarily a direct benefit in taking part at this stage.
Risks:
The medicines used in this study, like all medicines, have side effects. Common side-effects associated with ketamine include hallucinations, abnormal dreams, confusion, nausea and vomiting, rashes, abnormal eye or limb movements. These are minor but can occur between 1-10% of the time. Rarely participants may experience more serious side-effects such as allergic reactions, or abnormal heart rhythms though these are rare and approximately occur around 0.1-0.01% of the time.
The occurrence of all side-effects will be carefully monitored and recorded during the study. Ketamine and propofol have been used in medical practice for over 30 years. The nursing and medical staff are well trained in identifying and managing these side effects as well as the risks associated with sedating medicines in general. They are able to reduce or stop the medicines as necessary. We anticipate ketamine to not be any higher risk than other sedation medicines currently used.
As with any research study, there is a risk that confidential identifiable data may be disclosed though every precaution will be taken to try to prevent this happening.
Administering the IMP (ketamine) poses no additional burden to standard practice as participants will receive the same number of infusions, via the same route, for the same indication, that will be titrated and weaned as would occur in standard practice. They will continue to receive additional pain relief (alfentanil) the help ensure comfort, as would occur in standard practice.
Although currently not commonly used in ICU for primary sedation, safety profiles reported in recent studies of ketamine show it is at least as safe as other more common sedatives, with lower or similar rates of adverse events compared to standard of care.

Where is the study run from?
Leeds Teaching Hospitals NHS Trust (UK)

When is the study starting and how long is it expected to run for?
August 2024 to September 2026

Who is funding the study?
Leeds Teaching Hospitals NHS Trust (UK)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007276

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
2022-CT02, IRAS 1007276

Study information

Scientific Title
The Sedative and Haemodynamic Effects of Continuous Ketamine Infusions on Intensive Care Unit Patients (SHOCK-ICU): Investigating key outcomes, resource utilisation, and staff decision-making.
Workstream 2: Feasibility Study

Acronym
SHOCK-ICU: Feasibility Study

Study objectives
The primary objective is to establish the feasibility of using continuous ketamine infusions for sedation to inform a subsequent randomised controlled trial.
Given the complexity of the clinical setting, patient population, and ICU sedation, it is essential to develop an understanding of how this intervention may be implemented in a future larger study. Feasibility data will help distinguish between intervention failure and implementation failure; this includes:
1. Establishing the extent to which the intervention is implemented as intended (implementation fidelity)
2. Exploring feasibility of using proposed clinical markers of efficacy and patient reported outcomes (data completeness / ability to collect data)
3. Exploring clinical staff experience and reported barriers and facilitators to implementation (organisational, logistical, cultural)
4. Monitoring protocol deviations in order to affect changes prior to further studies

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/10/2024, Cambridgeshire and Hertfordshire Research Ethics Committee (2 Redman Place, London, EC20 1JQ, United Kingdom; +44 (0)2071048096; cambsandherts.rec@hra.nhs.uk), ref: 24/EE/0186

Study design
Interventional feasibility study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Intensive care patients requiring sedation in order to facilitate mechanical ventilation

Interventions
Single arm, non-randomised, open-label study of continuous intravenous ketamine infusions. The use of continuous ketamine infusions will follow the regimens used in recent trials and will be calculated on a weight based (mg/kg/h) basis and titrated to effect. A review of the literature revealed an overall average sedation dose of 1.05mg/kg/h, or 2.03mg/kg/h when used as primary sedation.
Dosing will be based on actual body weight, unless the participant has a BMI >40Kg/M2, in which case an adjusted body weight (ABW) will be used in keeping with recommendations from recent evidence on dosing of ketamine in obese patients.
If an accurate actual weight is not available, then an estimated weight may be used until an actual weight is recorded to reflect standard practice for weight-based dosing on ICU. In this instance, an actual weight should be recorded at the earliest clinically appropriate timepoint.

1000mg of ketamine (2x500mg vials) will be diluted with 80mls of 0.9% sodium chloride, providing an intervention concentration of 10mg/1ml. This concentration is within the accepted concentration range for use on ICU according to the UK Clinical Pharmacy Association (UKCPA) minimum volume for infusion guide and Medusa-NHS injectable Medicines guide, both of which state a maximum preparation of 50mg/ml for use in ICU.

Infusions will be titrated up or down (usually in increments or decrements of 10-50% from current rate) between a maximum dose of 2.7mg/kg/h and a minimum of 0mg/kg/h, according to participant's sedation level, agitation, and response to IMP, replicating current practice. Boluses of 1ml (10mg) may be delivered via the infusion pump in order to maintain participant or staff safety where up titration of sedation may not have desired effect within the necessary timeframe.

Data will be collected at baseline (after eligibility and enrolment), daily whilst receiving IMP, ICU discharge, and at 90 days.

Intervention Type
Drug

Pharmaceutical study type(s)
The aim of this project is to generate feasibility data and to highlight potentially important clinical and patient centred outcomes that may become key endpoints in subsequent trials

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ketamine

Primary outcome measure
Study process measurements:
1. Recruitment and refusal rates (Frequencies and percentages) - Continuously during study period and at the end of the study period
2. Withdrawal and follow-up rates (Frequencies and percentages) - Continuously during study period and at the end of the study period
3. Withdrawal and refusal reasons (Frequencies and percentages) - Continuously during study period and at the end of the study period

Ability to collect data measurements:
4. Standard of care data completeness for proposed clinical efficacy markers (Frequencies and percentages) - At the end of the study period
5. Ability to collect PROMs at ICU discharge and 90-day follow-up (Frequencies and percentages) - At the end of the study period
6. Ability to collect health economic data during study period (Frequencies and percentages) - At the end of the study period

Staff feedback measurements:
7. Feedback on ability to provide intervention and care for study participants (Anonymous categorical data via Google forms) - At the end of the study period

Reliability measurements:
8. Correct / accurate recording and formatting of representative sample of CRFs (Frequencies and percentages) - At the end of the study period
9. Completeness of representative sample of CRFs (Frequencies and percentages) - At the end of the study period

Level of safety and adverse event measurements:
10. Incidence of AEs /SAEs, ARs, SUSARs (Numerical and categorical data) - Continuously from enrolment until ICU discharge

Exploratory assessment of clinical efficacy measurements:
11. Ability to collect proposed clinical efficacy measurements (Frequencies and percentages) - At the end of the study period
12. Ability to collect exploratory outcome measurements (Frequencies and percentages) - At the end of the study period

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
02/08/2024

Completion date
30/09/2026

Eligibility

Key inclusion criteria
1. Requiring mechanical ventilation on ICU
2. Aged 18 years or older
3. Within 48hrs of starting mechanical ventilation
4. Requiring sedation
5. Expected to require more than 48hrs of mechanical ventilation
6. Expected to require a further 24hrs of mechanical ventilation at time of eligibility

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
30

Key exclusion criteria
1. Acute brain injury (hypoxic, traumatic, ischaemic, haemorrhagic) at time of screening
2. Acute central nervous system infection (including meningitis and encephalitis) at time of screening
3. Acute liver failure (Hyper-acute, acute, or sub-acute liver failure as defined by O'Grady et al33*) at time of screening
4. Acute liver injury (ALT >400iu/L ± INR>1.5 in absence of other causes)** at time of screening
5. Acute myocardial infarction or known severe coronary or myocardial disease at time of screening
6. Allergy to ketamine or any of its formulation excipients, or allergy to alfentanil
7. Continuous neuromuscular paralysis at time of screening
8. Decision to provide only palliative or end-of-life care by clinical team at time of screening
9. Drug induced / malignant hyperpyrexia at time of screening
10. Enrolled in another CTIMP or any ICU study at time of screening
11. Home ventilation (including overnight non-invasive ventilation / CPAP)
12. Liver transplant recipient at any point in participant's medical history
13. Long-term medical condition resulting in the participant lacking capacity prior to current illness, and who is not expected to ever regain capacity to provide consent to participate after cessation of sedation
14. Neuromuscular junction disorder as admitting or contributing diagnosis (e.g. Guillain-Barre, myasthenia gravis etc.) at time of screening
15. Patient not expected to survive >24 hours at time of screening
16. Patient known to be taking / prescribed ergometrine or memantine (severe interaction with IMP)
17. Post cardiac arrest where there is clinical concern of acute hypoxic brain injury at time of screening
18. Pregnancy***, up to 6 weeks post-partum (following delivery), suspected eclampsia / pre-eclampsia, or breast feeding / expressing milk
19. Previously enrolled into SHOCK-ICU
20. Psychosis or any mental health illness requiring treatment at time of screening
21. Raised intra-ocular pressure (suspected, confirmed, or history of****)
22. Severe hypertension (systolic blood pressure >180mmHg) at time of screening
23. Tachyarrhythmia (ventricular and supraventricular) at time of screening excluding atrial fibrillation with rapid ventricular response or sinus tachycardia in the context of a precipitating cause e.g. sepsis
24. Transferred from another ICU in which MV occurred for >6 hours
25. Prisoner or detained in police custody prior to admission

* O’Grady jaundice to encephalopathy time intervals: Hyper-acute = <7 days, acute = 8-28 days, sub-acute = 5-12 weeks.33
**These tests should be performed and recorded in the medical notes as part of the standard of care for ICU patients. Any potential participants in this category without liver function tests from the previous 7 days at the time of eligibility screening will be excluded from participation.
*** Any woman of childbearing potential (as defined by Clinical Trials Facilitation and Coordination Group34 i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation includes hysterectomy, bilateral salpingectomy and bilateral oophorectomy) lacking capacity with a possibility of being pregnant should have a pregnancy test performed and recorded in the medical notes as part of the standard of care for ICU patients. Any potential participants in this category without a valid negative pregnancy test at the time of eligibility screening will be excluded from participation.
**** It is not a requirement to measure intraocular pressure specifically (beyond any clinical reason to outside of the study). Any patient with a documented history of raised intra-ocular pressure or on long-term treatment will be excluded.

Date of first enrolment
24/01/2025

Date of final enrolment
01/09/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leeds Teaching Hospitals NHS Trust (LTHT)
J54 Intensive Care Unit
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

Website
https://www.leedsth.nhs.uk/research/

ROR
https://ror.org/00v4dac24

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Leeds Teaching Hospitals NHS Trust

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Submission to regulatory authorities
Other
Anonymous data collected or generated by the study may be transferred to external organisations including the University of Leeds to be used for further research and or analysis in accordance with the UK Policy Framework for Health and Social Care Research.

Intention to publish date
30/09/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the trial contact. Anonymous data collected or generated by the study may be transferred to external organisations to be used for further research and or analysis in accordance with the UK Policy Framework for Health and Social Care Research. No personal or

identifiable data will be shared.
Archiving will be authorised by the Sponsor following submission of the End of Trial report. Long-term storage and archiving will occur in accordance with MHRA guidance. Essential documentation will be archived using the LTHT approved external archiving service. Documentation will be retained for at least 25 years after completion or discontinuation of the study.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.1	11/07/2024	10/02/2025	No	No