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Early sedation with dexmedetomidine vs. placebo in older ventilated critically ill patients

Submission date
13/02/2024

Recruitment status
Recruiting

Registration date
10/04/2024

Overall study status
Ongoing

Last Edited
15/05/2024

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Most ICU patients who need a breathing machine (ventilator) to help them breathe require sedation with one or more sedative (calming) drugs, given as continuous drip into a vein. Currently, there is no agreement amongst doctors around the world about the best choice of sedative drug or the best way to manage sedation. Many of the commonly used sedative drugs have side effects and are thought to be associated with longer time on the ventilator, longer stay in the ICU, leading to delirium (a confused state often including hallucinations) and decreased mental awareness after recovery from critical illness. Dexmedetomidine is a commonly used sedative drugs that can be used alone or in combination, to keep ICU patients comfortable while on a ventilator. The purpose of this study is to evaluate dexmedetomidine, which might improve survival and recovery for older patients who require sedation in ICU.

Who can participate?
Patients will be able to participate in this trial if they are aged 65 or older and they require mechanical ventilation for more than 24 hours.

What does the study involve?
This is a type of study called a randomised controlled trial.
Hospitals with intensive care units that treat these patients will be involved in this trial. Half of the patients will be given DEX and the other half will be given a placebo (which looks the same as DEX but does not have any active ingredient). Results will be compared between the two groups. We will find out whether DEX is better than placebo by measuring outcomes such as whether the patient lives, whether they experience delirium (which means they have confused thinking and a lack of awareness of their surroundings), how long they are ventilated for, and whether they experience injury to their kidneys.
The trial is set to start in 2024 in the United Kingdom and is anticipated to conclude by the end of 2026. Participants in the trial will be contacted for an assessment at 90 days and six months after enrolment to see how well they have recovered.

What are the possible benefits and risks of participating?
Patients participating in this trial are heavily dependent on medical care. Therefore, they would receive sedative medications including study medication to facilitate safety, pain relief, comfort,

and necessary therapeutic procedures. In addition, these patients would be allowed to be visited by their families and close relatives to facilitate their comfort.

These patients are usually monitored minute by minute in intensive care environments and cared for by highly specialised and trained intensive care practitioners and bedside carers. Common risks involved in the trial includes low or high blood pressure, and drop in heart rate. These variations in blood pressure and heart rate are continuously monitored by intensive care staff who are trained to promptly treat these conditions appropriately.

Other risks involved are no different from those experienced in the routine care of critically ill patients in the intensive care unit. All data collected from participants will be de-identified, stored in a password-protected and encrypted database accessible exclusively to authorised trial personnel, ensuring minimal risk of privacy breaches. Monash University has approved a data protection assessment to safeguard participant confidentiality.

The drug (DEX) used in the study are used within standard clinical practice within critical care units internationally. The sedative drugs used are to reduce discomfort and distress associated with ventilation, the patient will not be distressed by receiving the study intervention or standard care. The assessments needed for the study are the same as would be in standard clinical practice. There should be very little burden on the patient for participating in the study, the phone calls at 6 months should only be a mild inconvenience.

Where is the study run from?
Monash Medical Centre (Australia)

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

Who is funding the study?
National Health and Medical Research Council (Australia)

Who is the main contact?
Prof Yahya Shehabi, yahya.shehabi@monashhealth.org
Dr Matt Wise, mattwise@doctors.org.uk

Contact information

Type(s)
Principal Investigator

Contact name
Prof Yahya Shehabi

Contact details
Level 5, E Block, Monash Medical Centre 246 Clayton Road
Clayton
Australia
3168
+61 (419)296 986
Yahya.Shehabi@monash.edu

Type(s)
Public, Scientific

Contact name
Dr Matt Wise

Contact details
Critical Care Medicine, University Hospital of Wales, Heath Park Way
Cardiff
United Kingdom
CF14 4XW
+44 29 2074 7747
Mattwise@doctors.org.uk

Additional identifiers

EudraCT/CTIS number
2022-501157-36

IRAS number
1008709

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
YS004, IRAS 1008709

Study information

Scientific Title
Sedation Practice in Intensive Care Evaluation-SPICE IV. Early Sedation with Dexmedetomidine vs. Placebo in Older Ventilated Critically Ill Patients. A Prospective, Multi-Centre, Double-Blind, Randomized, Controlled Trial

Acronym
SPICE IV

Study objectives
Primary objective:
To evaluate mortality and other key clinical outcomes in older patients (65 years and older) receiving early sedation with dexmedetomidine as the primary sedative agent. The primary outcome measure is 90-day all-cause mortality.

Secondary objective:
To assess the effect of dexmedetomidine on ventilator free days, coma and delirium free days, major adverse kidney events (MAKE-28) at day 28, duration of ventilation, and hospital stay in survivors.

Ethics approval required

Ethics approval required

Ethics approval(s)
Approved 09/04/2024, Wales REC 3 (HCRW, Castlebridge 4, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922941107; Wales.REC3@wales.nhs.uk), ref: 24/WA/0065

Study design
Interventional double blind randomized parallel group placebo controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Critically ill patients who are 65 years of age and older, and expected to be ventilated for more than 24 hours in an intensive care unit and are dependent on high level medical care including vasopressors, and sedative agents.

Interventions
Intravenous infusion of dexmedetomidine or saline as placebo will be started shortly after randomisation, at a recommended dose equivalent to 1 mcg/kg/h without a loading dose. The infusion will be adjusted between 0 and 1 mcg/kg/hr to achieve target sedation assessed by the Richmond Agitation Sedation Scale (RASS). The default target is RASS score of -1 to+1. The infusion would continue in intensive care until sedation is no longer required or to a max of 28-days whichever comes first. All study participants will receive standard routine care. The need for ongoing sedation will be determined by the attending clinician based on frequent clinical assessment.
Adherence to the intervention will be monitored by onsite research support staff and the study PI at individual sites. In addition, monitoring through study website via built in queries will be regularly conducted.

The comparator is placebo in the form of equivalent volume of normal saline will be used.
As the study design is double-blind, staff, including clinicians and bedside carers will be blinded to the intervention. The study algorithm prescribes a sedation target for participants. Therefore, additional supplemental sedatives would be added, as per usual or routine care in ICU, to achieve desired sedation target.

Intervention Type
Drug

Pharmaceutical study type(s)

Pharmacoeconomic, Therapy

Phase
Phase IV

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

Primary outcome measure
90-day all-cause mortality measured using phone follow-up by the sites research support staff at 90-days following randomisation

Secondary outcome measures
1. Number of days alive and free of coma and delirium at 28 days collected through medical records and direct patient assessment for delirium, coma at 28 days following randomisation
2. Number of days alive and ventilator free at 28 days collected directly from medical records and entered into study database at 28 days following randomisation
3. Major Adverse Kidney Events at 28 days (Mortality + Acute Kidney Injury > stage II, defined by Kidney Disease Improving Global Outcome (KDIGO) definition) collected directly from medical records and entered into study database at 28 days following randomisation
4. Duration of mechanical ventilation in survivors collected directly from medical records and entered into study database at ICU discharge
5. Hospital length of stay in survivors collected directly from medical records and entered into study database at Hospital discharge

Overall study start date
08/02/2024

Completion date
29/12/2026

Eligibility

Key inclusion criteria
1. Age ≥ 65 years
2. Intubated and receiving invasive mechanical ventilation in an intensive care unit
3. The treating clinicians believe that the patient will remain intubated and ventilated until the day after tomorrow (unlikely to be extubated next day)
4. The patient requires immediate ongoing sedative medication for comfort, safety and to facilitate the delivery of life support measures.

Participant type(s)
Patient

Age group
Senior

Lower age limit
65 Years

Sex
Both

Target number of participants
3,500

Key exclusion criteria
1. Has been intubated (excluding time spent intubated within an operating theatre or transport) for greater than 12 hours, with an additional 6 hours grace period, a total of 18 hours, in an intensive care unit
2. Proven or suspected acute primary brain lesion such as traumatic brain injury, intracranial haemorrhage, stroke, or hypoxic brain injury
3. Proven or suspected spinal cord injury or other pathology that may result in permanent or prolonged weakness
4. Admission with a suspected or proven drug overdose or burns.
5. Administration of ongoing neuromuscular blockade
6. Mean arterial blood (MAP) pressure that is less than 50 mmHg despite adequate resuscitation and vasopressor therapy at time of randomization
7. Heart rate less than 55 beats per minute unless the patient is being treated with a betablocker or a high grade atrio-ventricular block in the absence of a functioning pacemaker
8. Known sensitivity to dexmedetomidine
9. Acute fulminant hepatic failure
10. Death is deemed to be imminent or inevitable during this admission and either the attending physician, patient or substitute decision maker is not committed to active treatment
11. Patient has an underlying disease that makes survival to 90 days unlikely
12. Previously enrolled in the SPICE IV study

Date of first enrolment
31/12/2023

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
Brazil

Canada

England

Ireland

Kuwait

Malaysia

Netherlands

New Zealand

Northern Ireland

Saudi Arabia

Switzerland

Taiwan

United Kingdom

Wales

Study participating centre
Cardiff and Vale University Health Board
University Hospital of Wales (UHW)
Heath Park
Cardiff
Cardiff
United Kingdom
CF14 4XW

Study participating centre
St George's University Hospitals
Critical Care Department
Blackshaw road
London
United Kingdom
SW17 0QT

Study participating centre
Liverpool University Hospitals NHS Foundation Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Royal Victoria Hospital
274 Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
Kings College Hospital
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Imperial College London
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Manchester Royal Royal Infirmary
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Hampshire Hospitals NHS Foundation Trust
Romsey Road
Winchester
United Kingdom
SO22 5DG

Study participating centre
University Hospital Southampton
Southampton University Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
University Hospitals Bristol NHS Trust
Bristol Royal Infirmary
Upper Maudlin Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
The Royal London Hospital
80 Newark Street
London
United Kingdom
E1 2ES

Sponsor information

Organisation
Cardiff and Vale University Health Board

Sponsor details
Cardiff Joint Research Office
Cardiff
Wales
United Kingdom

CF14 4XW
+44 2921 02921846327
Research.Development@wales.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.cardiffandvaleuhb.wales.nhs.uk/home

ROR
https://ror.org/0489f6q08

Funder(s)

Funder type
Research council

Funder Name
National Health and Medical Research Council

Alternative Name(s)
NHMRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Australia

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Submission to regulatory authorities

Intention to publish date
29/12/2027

Individual participant data (IPD) sharing plan

1. Any research access to or use of shared SPICE IV data or information must be in accordance with the consent obtained, which includes consent to future use of data
2. Independent applications for the secondary use of data from the SPICE IV trial should be sent to the Chief Principal Investigator or his delegate from Monash University School of Clinical Sciences for review by the SPICE IV management committee. Applicants should be aware of the following:
a. Data sharing requests can be received 6 months after publication and for up to 36 months after publication
b. Applications should include a defined protocol and analysis plan
c. All applications will be evaluated on a case-by-case basis and according to established principles, including the current NHMRC's 'National Statement on Ethical Conduct in Human Research 2007 (updated 2018)'
d. Only data underlying the published tables, figures and the supplementary material may be available for sharing
e. Only data where direct and indirect identifiers are removed will be shared
f. Applicants must provide a data management plan in accordance with the current NHRMC's 'National Statement on Ethical Conduct in Human Research 2007 (updated 2018) and include details on banking or sharing of the data or information, and, in particular, of any confidentiality agreements or other conditions on the identifiability or re-use of the data or information.
g. The decision will be communicated within 6 weeks of application
3. Data sharing applications for the purpose of any forms of meta-analysis and/or systematic reviews, are expected to be collaborative in nature with a defined dataset. Such applications can be submitted to the Chief Principal Investigator or his delegate from Monash University School of Clinical Sciences and are not restricted to any time frame.

IPD sharing plan summary

Available on request