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A study investigating sedation using a special sleeping monitor on patients with severe lung conditions whose blood is oxygenated externally by a machine

Submission date
08/02/2023

Recruitment status
Recruiting

Registration date
23/03/2023

Overall study status
Ongoing

Last Edited
21/01/2025

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Extracorporeal membrane oxygenation (ECMO) supports patients with heart and lung failure with their blood getting oxygenated outside their body in a unique device. These patients are put to sleep. Managing sedation, an artificial sleep, is challenging. Critical care staff use sedation scores, which are subjective and not sensitive enough in a deep sleep. The bispectral index (BIS) monitor, a special monitor sensing the brain's electrical waves, is used in operating theatres and some intensive care units to monitor sedation; however, the value of this monitor in ECMO care has not been investigated. Its use is simple, and BIS-guided sedation may reduce sedative drug requirements; hence, it has potential benefits.
To date, this study will be the first to investigate the role of BIS monitoring in ECMO care. Unlike previous studies, this study will measure ECMO sedation in numbers to help manage optimal drug therapy. The study will provide data to inform the design of a large-scale clinical study and investigate safety aspects. If BIS monitoring is deemed feasible for ECMO, clinicians will have evidence to use it in ECMO.

Who can participate?
Patients aged over 18 years who are admitted for venovenous ECMO to treat their severe respiratory failure requiring sedation

What does the study involve?
The study is observational. The Richmond Agitation Sedation Scale (RASS) score will routinely determine the participants' target level of sedation according to standard practice. The proposed study investigates whether BIS monitoring is possible and feasible during venovenous (VV)-ECMO; hence, it may reduce the sedative drug requirement and avoid oversedation. For 48 hours, one group of participants will be observed as having BIS monitoring with a standard sedation score, and another group will not have BIS monitoring. Sedative drug requirements will be assessed in the groups to identify differences, proving the feasibility of the study.

What are the possible benefits and risks of participating?
This study investigates the feasibility of routine clinical practice in a special patient population. Processed EEG sedation monitoring has not been investigated with scientific scrutiny during VV-ECMO treatment. According to standard clinical practice, the target RASS scores provide a safety net for sedation management. The BIS monitoring may offer beneficial fine-tuning in deep sedation, where the sedation scores do not perform well. The researchers expect improved sedation practice with BIS monitoring; however, safety and event records will be established to reveal potential adverse effects. This study's expected benefit is demonstrating the feasibility of BIS monitoring during ECMO care, observing drug titration, and collecting data to design a larger-scale clinical study to quantify potential benefits.
The BIS electrodes may cause skin irritation like other electrodes (ECG). The likelihood is very small; however, standard NHS treatment will be provided if it occurs, and the electrodes will be removed.

Where is the study run from?
Wythenshawe Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2020 to January 2026

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Dr Lajos Szentgyorgyi, l.szentgyorgyi@nhs.net

Contact information

Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
305985

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 305985, CPMS 54233

Study information

Scientific Title
A prospective parallel group feasibility study of the use of electroencephalogram-based sedation depth monitoring in adults receiving venovenous extracorporeal membrane oxygenation

Acronym
PRO-BIS on ECMO

Study objectives
Feasibility studies are not hypothesis-driven.

Rationale:
The research question is whether it is feasible to use bispectral index (BIS) monitoring on adult venovenous extracorporeal membrane oxygenation (VV-ECMO) patients.
The study investigates the feasibility of using BIS monitoring on VV-ECMO patients.
If the study demonstrates reduced sedative requirement, titration of the sedatives according to BIS values safely achieving the same target sedation scores, the feasibility of this method will be established, and further clinical aspects can be investigated in subsequent research.
In a review, Hajat et al. suggested that "BIS monitoring seems advisable in the ICU to avoid awareness during invasive and stimulating procedures, particularly when neuromuscular blockade (NMB) is employed" (Hajat et al., 2017). Because ECMO is a very invasive procedure, patients are often paralysed, fulfilling these criteria for BIS monitoring.
So far, no published literature has focused on BIS or any other EEG-based sedation monitoring in adult ECMO care. Although some scanty retrospective studies mentioned using BIS monitoring in ECMO sedation, they did not investigate its role with scientific scrutiny. Therefore, prospective work has yet to be done to evaluate the value of this quantifiable parameter, the BIS number, in relation to ECMO sedation. The proof of the concept of a prospective clinical study or trial would be a feasibility study. Therefore, the researcher intends to evaluate BIS monitoring feasibility as an adjunct to routine sedation management in the ECMO practice.

The rationale for the feasibility design
Sedation and continuous ECMO care are labour-intensive, complex procedures requiring a team effort. Sedation monitoring and management rely on nursing attention provided by multiple teams over long courses of ECMO runs. It is unknown whether sedatives can be titrated during ECMO care, which is not comparable to traditional critical care. In the initial phases, almost general anaesthetic equivalent sedation is provided by intensive care nurses rather than anaesthetic doctors. The success of an ECMO sedation study depends on nursing compliance with sedation and study protocols. The feasibility of compliance is unknown as this has not been done in the participating department; also, there has not been any similar BIS monitoring ECMO

study published in the literature. The nurse training and BIS user experience will also be crucial for this study.
Multiple sedative agents are utilised, and care personnel have some degree of freedom to vary these drugs. It is also unknown how much sedative drug reduction is possible and whether data can be collected as planned. Protocol violations may happen because of clinical or training issues. The pharmacokinetic variations during ECMO, the extracorporeal circulation, the higher incidence of neurological injury and potential relative hypoxia may change the expected BIS response to the sedative agents. The BIS value correlation with the Richmond Agitation Sedation Scale (RASS) score is also uncertain in this setting.
The dropout rate is also unknown due to ECMO's relatively high morbidity, and mortality, and willingness to participate needs to be established. Therefore, a feasibility study is the most appropriate design for addressing these unknown factors and informing a future clinical trial design.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 06/12/2022, University of Salford Academic ethics approval panel (Doctoral & Research Support Research & Enterprise, Room 827, Maxwell Building, University of Salford, Manchester, M5 4WT, UK; +44 (0)161 295 2280; ethics@salford.ac.uk), ref: HSR2223-001
2. Approved 17/11/2022, North West - Greater Manchester South Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8143; gmsouth.rec@hra.nhs.uk), ref: ETH2122-0186, 22/NW/0316

Study design
Prospective parallel-group feasibility study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Emergency VV-ECMO admissions

Interventions
Thirty consecutive VV-ECMO patients will be included in the study. Due to the observational study design, the researcher will alternate the BIS monitor allocation instead of randomisation. Hence, 15 patients will be monitored using BIS monitors and the RASS score in an alternating

fashion, and 15 will not be monitored with the BIS monitor; only the RASS score will guide the sedation.

Sedation management using the RASS score only:
According to the standard departmental practice, all 30 patients' RASS scores will be determined hourly by the nursing staff and documented in the electronic patient record (Epic HIVE). They titrate the sedative drugs according to the planned level of sedation to achieve the appropriate RASS score for the clinical condition and treatment plan. The nurses follow the stepwise departmental sedation protocol. The monitoring system is connected to an electronic patient record (Epic HIVE), continuously recording the monitored physiological parameters.

BIS monitoring process:
BIS-trained nurses, medical staff or the researcher, will commence BIS monitoring after identifying the patients and potential contraindications.
The BIS monitoring of the alternating fifteen patients starts when they arrive in their bed space after their ECMO retrieval. BIS electrodes will be placed onto the patients' forehead; simultaneously with other monitors and electrodes (ECG, blood pressure, saturation probes, and other ECMO-related monitors). The BIS electrodes will be changed to a new electrode every 24 hours as per the manufacturer's recommendations.
The primary place of electrode applications will be the forehead. Alternative applications are described in the literature, but the need for these is improbable in the ECMO practice at Wythenshawe Hospital. Hence, those patients should need alternative electrode positions will be excluded from this study. The left and right-sided forehead positions will alternate 24 hourly.
The BIS monitors will feed real-time data to the electronic patient records (Epic HIVE) and record the BIS parameters into their internal memory.
The sedation level for each patient is routinely determined using a target RASS score. The target ranges between -5 to -3. All BIS-monitored patients will be sedated to achieve their target RASS.
According to the stepwise departmental sedation protocol, the person managing the sedation will titrate the sedative medications to achieve the BIS number of 60 or less but keep it strictly above 40 achieving the target RASS score. The RASS score will also be recorded hourly as a daily clinical routine to set sedation targets.

Intervention Type
Other

Primary outcome measure
Sedative drug titration according to the BIS values will demonstrate the feasibility of BIS monitoring. To demonstrate sedative drug titration, sedative drug requirements (propofol, opioids, clonidine/dexmedetomidine, midazolam, and neuromuscular blocking agent doses measured in the appropriate equivalents and milligrams) will be recorded using BIS-guided sedation (BIS number is recorded in dimensionless numbers) and only RASS score-guided sedation (recorded in numbers) during the first 48-hour VV-ECMO care. If drug titration occurs, these doses will differ between the two groups, confirming that the nursing staff can use the BIS monitor appropriately. So, they can reliably titrate the drugs according to the departmental sedation protocol to achieve the intended RASS score and BIS values. Hence, the method is feasible for nurse-led sedation, and a larger clinical study is doable. The data will be downloaded or manually transcribed into the eCRF.

Secondary outcome measures
1. Safety and other events (ECMO flow issues, inadvertent device removal, skin irritation, cardiac arrest, mortality during the first 48 hours, ICU mortality, etc) recorded in the eCRF after the 48-

hour data collection period for the monitored and control groups to explore potential unwanted side effects during BIS monitoring
2. Monitored clinical parameters and sedative drug requirements (propofol, opioids, benzodiazepines, clonidine doses in the appropriate equivalents) in the BIS monitored and the control group in the 48-hour data collection period. The proportion of lost data and the causes will be analysed. Although the parameters will be recorded automatically in the electronic patient record (monitoring system), unforeseen technical complications may cause data loss. Certain limitations can be revealed in the case of an incomplete database. On the other hand, the recorded amount of drug doses may allow for calculating reduced drug use; beneficial cost implications could be revealed.
3. The estimated potential recruitment and drop-out rate. Due to the relative uncertainty of the VV-ECMO admission rate (ECMO is an emergency rescue service) and the suitability of these patients (variable survival and neurological morbidity rates), the recruitment and drop-out assessments are crucial for estimating a future prospective clinical study sample size. In addition, the participants or their legal representatives will be asked about their views and willingness to participate in a potentially randomised study. Low acceptance of randomisation might influence the design of a future clinical study.
4. The feedback of medical and nursing staff within 1 week after they finished their shifts with the monitored patients, exploring their satisfaction with BIS monitoring. Staff contribution is essential for any prospective studies because BIS monitoring must be feasible for any ICU staff in any hospital to perform reliably. Therefore, future research must be designed around robust intervention and data collection methods.
5. Correlations between the BIS values and the RASS score during the BIS-monitored 48-hour study period. This correlation may indicate the clinical sensitivity of the device. Similar to general anaesthesia, a positive correlation is expected, confirming the usefulness and sensitivity of BIS monitoring in ECMO sedation. However, there is a need for alternative explanations or a different study design in case of no or negative correlation. BIS values and RASS scores will be downloaded or transcribed from the electronic monitoring systems and recorded in the electronic patient record (HIVE Epic) into the eCRF.

Overall study start date
05/05/2020

Completion date
01/01/2026

Eligibility

Key inclusion criteria
1. Any ethnic background
2. Already sedated or continuous intravenous sedation will be commenced shortly before or parallel with VV-ECMO initiation
3. VV-ECMO treatment

Participant type(s)
Patient

Age group
Adult

Lower age limit

18 Years

Sex
Both

Target number of participants
30

Key exclusion criteria
1. Patients who are younger than 18 years old
2. Patients who are not sedated with intravenous agents during the planned study period
3. Patients with a significant skin lesion or damaged area on the forehead make the BIS electrode placement impossible or risky concerning further skin damage
4. Known allergy to the BIS electrode materials
5. Patients who are sedated with ketamine during the study period. Ketamine may artificially increase BIS number despite an adequate level of sedation. Newer technologies address these issues, but including this patient group is not practical; it would require advanced knowledge in BIS monitoring beyond the daily clinical routine.
6. Those cases will be excluded with a strong suspicion of significant neurological damage diagnosed with a CT scan (This scenario would be an exclusion criterion for ECMO; however, these patients might still have ECMO due to diagnostic difficulties and ambiguities; therefore, they will be monitored during the study period). Unless the ECMO is withdrawn early, these patients will be considered subgroup analysis subjects. The analysis will investigate whether the BIS monitoring would show an early sign of neurological injury. These unfortunate cases will not be included in the planned completed 15 monitored patients. These cases may impact the sample size calculation for a future clinical study.
7. If active treatment is withdrawn earlier than the study period
8. VA-ECMO (the sedation management priorities can differ in VA-ECMO cases because these patients' sedation is often short and frequently awake during their VA-ECMO course)

Date of first enrolment
15/05/2023

Date of final enrolment
30/09/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Wythenshawe Hospital, Manchester University NHS Foundation Trust
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ROR
https://ror.org/01tmqtf75

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
The ISRCTN registration will provide easy access to information about the study for patients, family members, researchers, clinicians and healthcare professionals. The results from this research will be presented at meetings, seminars and symposiums within the University of Salford, Wythenshawe Hospital (Manchester University NHS Foundation Trust) and at relevant

local and national conferences. Papers will also be prepared for publication in appropriate scientific journals. The researcher will also prepare teaching material for the nursing and medical staff to provide continuous professional education utilising the study results and the collected knowledge from the ongoing literature reviews.
The researcher's (CI) PhD thesis at the University of Salford will summarise the study outcomes. The PhD thesis will be accessible from the University of Salford data repository.

Intention to publish date
31/12/2026

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study are not expected to be made available due to confidentiality reasons.
Only the CI (PhD researcher) will have full access to the final dataset and share the relevant encrypted data with the university PhD supervisors and the clinical supervisors. Those data will be shared only that are necessary to complete the scientific calculations, the PhD thesis and associated publications.
All investigators must and will comply with the Data Protection Act 2018 (Data Protection Act, 2018) regarding the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The collected personal data will be kept secure and maintained. This will involve the creation of coded, depersonalised data where an unrelated sequence of characters replaces the participant's identifying information. Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password-protected folders and storage media ("ECMO shared drive" at Wythenshawe Hospital). The access will be limited to the minimum number of individuals necessary for quality control, audit, and analysis. The data will be stored for 5 years after the study's completion.
In potential publications and the final thesis, patients will not be identifiable.
The clinical data custodian is the Manchester University NHS Foundation Trust.
All patient data, including the data downloaded for the study and other general patient data that were not used for the study, will be stored in Wythenshawe Hospital's electronic patient record servers and drives according to NHS standards and managed by the hospital's IT team. The hospital's IT team is responsible for the confidential access and safety of these servers and computer drives. In addition, the researcher and research team are responsible for encrypting the study files and folders on these drives.
All essential documents will be archived for a minimum of 5 years after completing the study. Destruction of essential documents will require authorisation from the Sponsor.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No