Continuous infusion ketamine as analgesia or sedation in mechanically ventilated adults in the intensive care unit: a scoping review

Nicholas David Richards (nicholas.richards5@nhs.net)
Leeds Teaching Hospitals NHS Trust https://orcid.org/0000-0002-3200-7114
Simon Howell
University of Leeds
Mark Bellamy
Leeds Teaching Hospitals NHS Trust
Ruben Mujica-Mota
University of Leeds

Protocol

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Abstract

Introduction

Mechanical ventilation (MV) is a common and often live-saving intervention on the Intensive Care Unit (ICU). In order to facilitate this intervention, the majority of patients require medical sedation. Optimising sedation is one of the fundamentals of ICU care, and inadequate sedation (predominantly too deep) has consistently been associated with worse outcomes for patients.

This article presents the protocol for a scoping review of published literature on the use of ketamine as a sedative to facilitate MV on ICU.

The scoping review has been designed to answer the question '*What is known about the use of ketamine as a continuous infusion to provide sedation in mechanically ventilated adults in the intensive care unit, and what gaps in the evidence exist?'*

Methods

The scoping review protocol has been designed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) checklist and the JBI manual for evidence synthesis. Data will be extracted using a dedicated form, and reviewed by 2 reviewers.

Results

Results will be tabulated and presented along side descriptive summaries. A PRISMA flow diagram will also be generated.

Ethics and Dissemination

This scoping review is designed to map out the literature using existing published articles and does not require ethical approval.

Results will be submitted for publication in relevant peer-reviewed journals and to international meetings as well as disseminated to relevant professional groups.

Background

Mechanical ventilation (MV) is a common intensive care intervention (approximately 20 million patients per annum(1) worldwide). Patients requiring MV experience high mortality and morbidity. MV accounts for much intensive care unit (ICU) resource utilisation(2).

Most patients requiring MV are medically sedated. Optimizing sedation and analgesia is fundamental to the management of critically ill patients. There is a consistent association between deep sedation and negative prognostic markers(3, 4), driving international guidance aimed at improving outcomes(3, 5).

Providing adequate sedation, maintaining comfort, reducing pain, and minimising agitation / delirium have been identified as top priorities for ICU research by both patients and clinicians(6).

Ketamine is an N-methyl D-aspartic acid (NMDA) receptor antagonist that has be used since the 1970s to provide cataleptic, amnesic, analgesic, and dose dependant anaesthetic effects(7).

Ketamine has been particularly successful in military(8) and pre-hospital(9) settings owing to its ability to stimulate the sympathetic nervous system, resulting in increased heart rate and blood pressure(10).

Over this time ketamine has also become increasingly popular as an anaesthetic agent for emergency surgical procedures in hypotensive patients(11, 12).

More diverse effects of ketamine include: providing anti-inflammatory effects in sepsis(13), bronchodilation(14), neuroprotective properties(15, 16), tumour inhibition(17, 18), and antidepressant effects(19).

Although having been around for 50 years, ketamine, particularly as a continuous infusion, has not become a routine sedative option to facilitate MV.

In a survey of ICUs in the UK, propofol in combination with either alfentanil or fentanyl was the most common sedation-analgesia regime used with 92.2% of units using propofol as their first choice agent(20). A third of units reported using other non-ketamine sedative agents either ‘frequently’ or ‘very frequently’, these included benzodiapines e.g. midazolam (29.4%), clonidine (35.3%), and dexmedetomidine (11.8%).

Adverse features of sedatives

Hypotension

Hypotension is a common adverse effect of most sedative agents. It is thought that the predominant mechanism behind this is attenuation of external stimulation, reduced sympathetic tone, and vasodilation(21).

During induction of anaesthesia propofol has been shown to cause a 12% reduction in Mean Arterial Pressure (MAP), a 13% decrease in cardiac output (CO), and an 18% reduction in left ventricular stroke work index.(22)

In the 2009 SEDCOM study comparing dexmedetomidine and midazolam, hypotension occurred in a total of 56% patients and required intervention in 28%(23).

More recently, in 2019, the SPICE 3 study also found a significantly increased incidence of hypotension, bardycardia, and asystole wuth dexmedetomidine(24).

Maintaining patients' blood pressure is a fundamental part of ICU care, and the American College of Critical Care Medicine (ACCM) suggests a MAP of between 60-65mmHg is necessary to perfuse vital organs(25). Hypotension has been consistently linked to poor outcomes, conversely studies have shown that maintaining MAP ≥ 65mmHg in ICU patients with sepsis can reduce the incidence of acute kidney injury (AKI) by 7%, myocardial injury by 4.5%, and overall in-hospital mortality by 11.4%(26).

These findings are in keeping with the consensus guidelines '*Surviving Sepsis'*, which recommend that, following sufficient fluid resuscitation, vasopressor medications should be initiated if MAP is below 65mmHg(27). This is often extended to other causes of hypotension and a target MAP of ≥ 65mmHg is generally considered reasonable.

Whilst hypotension and shock may be a feature of a patient's illness, there may be a subset of patients who suffer exacerbation or perpetuation of hypotension through administration of sedative medications. Through stimulation of the sympathetic nervous system, Ketamine has the ability to induce anaesthesia without significant cardiovascular consequences; we hypothesise that these benefits may extend to sedation on ICU, however it was unclear if there was pre-existing literature to support this.

Delirium

Delirium is common during critical illness and result in higher mortality rates, longer ICU stays, and worse long-term outcomes(28, 29). Research into causative factors has been largely unsuccessful at reducing delirium incidence, however it is widely accepted that sedation particularly using benzodiazepines significantly increases risk(3, 5, 30).

Reluctance to adopt frequent use of ketamine often relates to possible '*emergence reactions*'. Emergence reactions are psychomotor symptoms experienced by some patients when waking from ketamine-induced anaesthesia. The incidence of these reactions vary in the literature from 5–30%.(31)

These reactions, which can vary from mild manifestations such as floating sensations, disorientation, excitement, dysphoria, vivid dreams, and amnesia, up to more marked reactions including frank delirium, hallucinations, and agitation(31–33) are well documented in the context of general anaesthesia, however, to our knowledge have not been examined in the context of critically unwell sedated patients on ICU. As part of this scoping review we aimed to define exactly what is known with regards to delirium and ketamine use in ICU, and what, if any, gaps existed in the literature.

Adverse features of ICU

Depression and PTSD

Major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are common amongst the survivors of ICU, with the prevalence of MDD ranging in the literature from 17–43%(34, 35) and PTSD ranging from 21–35%(34, 36).

Associations between perceived risk factors and PTSD have been extensively examined with varied results(35). Duration of ICU delirium, early post-ICU depressive symptoms, the use of benzodiazepines, and physical and cognitive impairment during recovery and rehabilitation have all been identified as significant risks for developing MDD(36–38).

Ketamine was recently licensed for MDD treatment following reviews that highlighted transient psychotomimetic effects with single-dose administration(39, 40). This warrants further investigation to establish whether any literature exists relating to either depression post-ICU or patient centred outcomes (e.g. QALY or EQ5D) and ketamine sedation on ICU.

Methods

Objectives

The scoping review was designed to answer the question '*What is known about the use of ketamine as a continuous infusion to provide sedation in mechanically ventilated adults in the intensive care unit, and what gaps in the evidence exist?'*

Study outcomes of specific interest include ketamine's efficacy and safety as a continuous infusion to provide sedation in MV patients on ICU, the cardiovascular effects, of ketamine, and also if any literature exists documenting psychological effects including depression and delirium.

Protocol

The scoping review protocol was designed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) checklist(41) and the JBI Manual for Evidence Synthesis(42); Sect. 11.2 Development of a scoping review protocol.

This article outlines the methods and protocol for the scoping review, which is currently in the initial screening phase.

Patient and Public Involvement

It was deemed not applicable to have Patient or Public involvement in the design of this scoping review protocol as it is aimed at reviewing existing published literature.

Eligibility criteria

This scoping review is concerned with the provision of sedation and or analgesia in mechanically ventilated adult intensive care patients.

In order to attempt to answer this question, included studies had to meet the following criteria:

Population:

- Human studies
- Adult patients (≥ 18 years old)
- Mechanically ventilated on ICU

Interventions:

- Administration of continuous ketamine infusions for the purpose of analgesia and or sedation during mechanical ventilation

Comparators:

- Any other sedation regime
- None (e.g. case reports)

Outcomes:

- Any recorded, but of those of particular interest include: haemodynamic measurements, sedation scores, delirium, agitation, adverse side effects, patient centred outcomes (e.g. QALY)

Inclusion criteria:

- Full text reports of mechanically ventilated patients
- Published in English (or translated to English) in a peer-reviewed journal
- Any geographical location

Information sources

This scoping review will consider full text publications from peer-reviewed sources. Both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, and interrupted time-series studies will be considered for inclusion.

In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion. This review will also consider case series, individual case reports and descriptive cross-sectional studies for inclusion.

Systematic reviews and meta-analyses will not be included, but their references will be screened for appropriate studies that meet the inclusion criteria.

Qualitative studies and opinion papers will also not be considered for inclusion in this scoping review.

Search Strategy and Terms

To identify potential articles for inclusion, a three-step approach to literature searches will be undertaken in accordance with JBI methodology for scoping reviews(42):

A preliminary search of PubMed will be conducted using the terms: “(Ketamine) AND (Intensive Care) AND ((Sedation) OR (Analgesia))”.

Following this initial search, a subsequent search will be conducted across all included databases (PubMed, OVID, Scopus, Web of Science) using words contained in the title and abstract of papers retrieved during the preliminary search, and of the index terms used to describe these articles.

Thirdly, the reference list of identified reports and articles will be analysed for additional sources and reports.

Our preliminary search returned 664 articles (24/08/21), which are currently undergoing screening.

Screening of sources

Following the search, all identified citations will be collated and uploaded into EndNote X6, and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria.

Potentially relevant sources will be retrieved in full and then assessed in detail against the inclusion criteria by two or more independent reviewers.

Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional independent reviewer.

The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) flow diagram.

Data charting process

Data will be extracted from all included publications by two independent reviewers using a data extraction tool that has been developed by the reviewers (see appendix 1).

The data extracted will include:

- Author(s)
- Year of publication
- Origin/country of origin (where the source was published or conducted)
- Aims/purpose
- Population and sample size within the source of evidence
- Methodology / methods
- Intervention type, comparator and details of these (e.g. duration of the intervention)

- Outcomes and details of these (e.g. how measured)
- Key findings that relate to the scoping review question

The draft data extraction tool will be piloted during the preliminary search, and will be modified and revised as necessary during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion, or with an additional independent reviewer. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Critical appraisal of sources

Sources will also be critically apprised using the relevant CASP checklists (https://casp-uk.net/casp-tools-checklists/) allowing us to assess the quality of each source and document any biases further highlighting any gaps or inadequacies in the literature.

Presentation Of Results

Results will be presented in table form with frequency counts of concepts, populations, and study characteristics, accompanied by a descriptive summary. If appropriate, graphic representation of these data will also be produced.

Strengths And Limitations

- Developed using the PRISMA-ScR checklist
- No conflicts of interest
- Protocol generation has been reviewed by 3 separate supervising persons
- At time of protocol writing, it is unknown how many sources will need screening.

Abbreviations

ACCM – American College of Critical Care Medicine

AKI – Acute Kidney Injury

CASP – Critical Appraisal Skills Programme

CO – Cardiac Output

EQ5D – EuroQual 5 Dimension

ICU – Intensive Care Unit

MAP – Mean Arterial Pressure

MDD – Major Depressive Disorder

MV – Mechanical Ventilation

NMDA – N-methyl D-aspartic acid

PRISMA-ScR – Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews

PTSD – Post-Traumatic Stress Disorder

QALY – Quality Adjusted Life Years

Declarations

Ethics approval and consent to participate

This scoping review is designed to map out the literature using existing published articles and does not therefore require ethical approval.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the above study will be available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

No additional funding is being sought for any aspect of the scoping review.

Contributors

NDR conceived the idea for the scoping review, developed the research question, and constructed the protocol. SH, MB, and RMM supervised the process above and reviewed the manuscript. All authors have reviewed and approved the final manuscript.

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Not applicable

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Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.pdf
- PRISMAPchecklist.docx