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Use of adjunct continuous ketamine infusion in mechanically ventilated patients

Submission date 03/02/2020	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 05/02/2020	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 01/09/2021	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims
Ketamine is used to produce sedation and relieve pain to minimize discomfort while a breathing tube placed in trachea (windpipe) and a machine (ventilator) used in the ICU. Several publications have shown that a low-dose ketamine in combination to opioids has been used to relieve acute pain after surgery. Ketamine has a favorable characteristics including bronchodilation, increase in blood pressure, does not cause constipation, maintain respiratory reflexes (respiratory spontaneous responses) make it an especially viable alternative for patients with unstable respiratory and hemodynamic function. However, the majority of these trials are conducted in a surgical ICU setting, retrospective in nature or randomized controlled clinical trials focusing on comparison of ketamine to placebo or two study drugs (e.g. ketamine versus opioid), despite the fact that most ICU patients are sedated with a combination of drugs. The aim of this study is to assess weather ketamine can help to shorten the time of being in breathing tube and ventilator (duration of mechanical ventilation).

Who can participate?
ICU (Medical or surgical) patients (> 14 years old) who have been mechanically ventilated within the previous 24 hours and expected to remain intubated for more than 24 hours.

What does the study involve?
Participants will be randomly allocated to receive treatment as usual or a low dose of ketamine whilst under mechanical ventilation.

What are the possible benefits and risks of participating?
Benefit: increased medical attention irrespective of the group the patients are in and this study may help in improvement of knowledge and medical science progress
Risk: administration of sedative agents are standard of practice in the intensive care units to minimize discomfort and remain calm while a breathing tube placed on trachea (windpipe) and a machine (ventilator). The expected adverse effects will not exceed what is encountered in daily practice (e.g. benzodiazepine associated delirium, opioid induced constipation, propofol and dexmedetomidine decrease blood pressure and heart rate, ketamine associated with increase in blood pressure and heart rate, possible delirium). The participants will be closely monitored to minimize any potential safety concerns

Where is the study run from?
King Faisal Specialist Hospital and Research Centre (Saudi Arabia)

When is the study starting and how long is it expected to run for?
September 2019 to December 2020

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
NCT04075006

Protocol serial number
Research Advisory Council (RAC) number 2191 187

Study information

Scientific Title
Adjunct Low-Dose Ketamine Infusion versus Standard of Care in Mechanically Ventilated Critically Ill Patients at a Tertiary Saudi Hospital (ATTAINMENT Trial)

Acronym
ATTAINMENT

Study objectives
Low-dose ketamine infusion will reduce the duration of MV with an acceptable safety profile compared to standard of care.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/07/2019, Research Ethics Committee (REC) and Clinical Research Committee (CRC) at King Faisal Specialist Hospital and Research Center (MBC-03, PO Box 3354, Riyadh 11211, Saudi Arabia; +966114424528; aomar@kfshrc.edu.sa), ref: ACCM/462/40.

Study design
Prospective randomized open-label active controlled parallel group pilot feasibility phase 3 study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mechanically ventilated adult critical illness

Interventions

Current interventions as of 19/03/2020:
Experimental: Ketamine Group
Adjunct low dose continuous infusion ketamine in addition to the standard of care. Ketamine will be given at a fixed infusion rate of 0.12 mg/kg/h (2 µg/kg/min) in the first 24 hours followed by 0.06 mg/kg/h (1 µg/kg/min) in the second 24 hours, then discontinued

No Intervention: Control Group
Standard of care in the ICU including propofol and/or fentanyl and/or midazolam according to KFSHRC sedation and analgesia protocol.

Randomization:
Patients will be randomly assigned to one of two study groups in a 1:1 ratio by a computer generated randomization list created by an independent biostatistician and no stratification will be performed. Our initial screening and eligibility assessment is done by
bedside ICU nurses who are blinded to treatment assignment. To further ensure allocation concealment (masking), access to the randomization will be restricted to a Pharmacist (third party and not part of the study) to whom principal investigators refer at distance to know the assigned treatment (by telephone) The study investigators and study participants during recruitment and consenting process will be blinded to the treatment assignment. Once consenting process complete, principal investigators will contact the Pharmacist (third party) for patient allocation and initiation of the trial intervention. Group allocation will be concealed until after randomization.

Previous interventions:
Experimental: Ketamine Group
Adjunct low dose continuous infusion ketamine in addition to the standard of care. Ketamine will be given at a fixed infusion rate of 0.12 mg/kg/hr (2 µg/kg/min) in the first 24 hours followed by 0.06 mg/kg/hr (1 µg/kg/min) in the second 24 hours, then discontinued

No Intervention: Control Group
Standard of care in the ICU including propofol and/or fentanyl and/or midazolam according to KFSHRC sedation and analgesia protocol.

Randomization will involve reading from a computer-generated randomization list with blocks of size eight to ensure interim balance of treatment assignment. This randomization list is designed by KFSH&RC biostatistical and epidemiology section. The principal investigators will have access to the randomization list. Once a patient is recruited, the principal investigators will refer to the list and assign treatment accordingly.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Duration of Mechanical Ventilation [from Intubation to extubation date and off Mechanical Ventilation or until ICU discharge, death, or 28 days post randomization whichever occurs first]

Key secondary outcome(s))
Current secondary outcome measures as of 19/03/2020:
Using patient records:
1. Cumulative Sedation Dosages within the first 48 h after randomization
2. Dexmedetomidine use within the first 48 h after randomization
3. Richmond Agitation Sedation Score (RASS) within the first 48 h after randomization
4. Pain score measured using the King Faisal Specialist Hospital & Research Centre (KFSHRC) pain scale within the first 48 h after randomization
5. Vasopressor Medication Dosages within the first 48 h after randomization
6. Changes in Mean Arterial Blood Pressure (MAP) and Heart Rate (HR) within the first 48 h after randomization
7. Hospital Length of Stay (LOS) throughout study completion measured at 1 year
8. ICU Length of stay (LOS) throughout study completion measured at 1 year
9. Tracheostomy rate at 28 days after randomization
10. Unplanned extubation at 28 days after randomization
11. Re-intubation rate at 28 days after randomization
12. Incidence of Delirium measured using Confusion Assessment Method in Intensive Care Unit (CAM-ICU) at 48 h after randomization
13. The use of anti-psychotics for confirmed ICU-acquired delirium within 48 h after randomization
14. Use of Physical restraints within 48 h after randomization
15. Frequency of endotracheal tube Suctioning: Proportion of patient with changes in requirements of suctioning frequency of 2 h or less within the first 48 h after randomization
16. Mortality at 28 days after randomization

Previous secondary outcome measures:
Using patient records:
1. Cumulative Sedation Dosages [first 48 hours after randomization]
2. Dexmedetomidine use [first 48 hours after randomization]
3. Richmond Agitation Sedation Score (RASS) [first 48 hours after randomization]
4. Pain score measured using the KFSHRC pain scale [first 48 hours after randomization]
5. Vasopressor Medication Dosages [first 48 hours after randomization]
6. Hospital Length of Stay (LOS) [throughout study completion (1 year)]
7. ICU Length of stay (LOS) [throughout study completion (1 year)]
8. Tracheostomy rate [28 days after randomization]
9. Unplanned extubation [28 days after randomization]
10. Re-intubation rate [28 days after randomization]
11. Incidence of Delirium measured using Confusion Assessment Method in Intensive Care Unit (CAM-ICU) [48 hours after randomization]
12. The use of anti-psychotics for confirmed ICU-acquired delirium [48 hours after randomization]
13. Use of Physical restraints [48 hours after randomization]
14. Mortality [28 days after randomization]

Completion date
31/12/2020

Eligibility

Key inclusion criteria
1. ICU (Medical or surgical) patients (> 14 years old)
2. Mechanically ventilated within the previous 24 hours and expected to remain intubated for

more than 24 hours.
3. Patient requires ongoing sedative medication
4. No objection from the ICU attending MD for enrollment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Total final enrolment
85

Key exclusion criteria
Current participant exclusion criteria as of 19/03/2020:
1. Patients with a history of dementia or psychiatric disorders or on any anti-psychotics or anti-depressants medications at home
2. Pregnancy
3. Expected to need mechanical ventilation less than 24 hours
4. Known hypersensitivity to ketamine
5. Patient on dexmedetomidine as primary sedative agent prior to randomization
6. Patients with cardiogenic shock, heart failure, myocardial infarction
7. History of end-stage liver disease (Child Pugh score C)
8. Proven or suspected primary neurological injury (traumatic brain injury, ischemic stroke, intracranial hemorrhage, spinal cord injury, anoxic brain injury)
9. Patients with persistent heart rate (HR) > 150 bpm or systolic blood pressure (SBP) >180 mmHg
10. Patients who assigned as do-not-resuscitate order (DNR) or expected to die within 24 h
11. Patients on ECMO
12. Patients with status epilepticus patients who are receiving the ketamine infusion for refractory status epilepticus
13. Proven or suspected status asthmaticus
14. Patients with expected targeted RASS of -5 such as patients on continuous infusion neuromuscular blockade

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13. Proven or suspected status asthmaticus

Date of first enrolment
01/09/2019

Date of final enrolment
15/11/2020

Locations

Countries of recruitment
Saudi Arabia

Study participating centre
King Faisal Specialist Hospital and Research Centre
Zahrawi St
Al Maather
Riyadh
Saudi Arabia
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Sponsor information

Organisation
King Faisal Specialist Hospital & Research Centre

ROR
https://ror.org/05n0wgt02

Funder(s)

Funder type
Other

Funder Name

investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. Data will be collected in the KFSH&RC Research Electronic Data Capture (REDCap) platform, Riyadh, Saudi Arabia https://redcap.kfshrc.edu.sa/index.php?user_verify=M7cUjf6KwCb6qHkZLNTr. Each subject will be given a unique subject ID number (database numbers and all identifiers will be removed). A subject ID key will be used to match the subjects' Medical Record Number and will be kept in a password-protected file that is accessible to the principal investigators. Access to REDCap requires authentication (username and password) for secure maintenance of the data. Access to the RedCap data will be limited to the principal investigators and co-investigators involved in data collection only. The database includes multiple logic checks for double entry and range checks for data values.
All collected information will be stored in a secure manner and all patient data will be kept confidential. Data to be collected as follows: age, gender, weight, mode of MV at baseline, percentage of renal replacement therapy at baseline, lactate level at baseline, and severity of illness as estimated by Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE II) score, with higher scores indicating higher severity of illness. Moreover, we will collect ICU type, baseline analgesics, sedatives, vasopressor requirements, and Pre-Deliric Delirium Risk Score, which is a delirium prediction model specifically designed for adult critical care patients 24 hours after ICU admission. It will be used to predict the factors that may influence delirium risk prior to randomization. We will also collect RASS, pain scores, and CAM-ICU scores at baseline, 24 and 48 hours post-randomization. The RASS is a scale used to assess the depth of sedation on a scale of -5 to +4, with a negative value indicating deeper sedation and positive values indicating increased agitation. The CAM-ICU is a valid and reliable delirium assessment tool. Patients with a RASS of -3 or lower will be excluded from CAM-ICU status assessment as they cannot participate in the exam. We will also record the proportion of eligible participants enrolled, rates of recruitment, protocol deviations and adverse events. To ensure consistency in data collection, training sessions will be held by the principal investigators for all research co-investigators involved in data collection prior to study commencement. Additionally, the principal investigators will conduct educational sessions for ICU physicians and ICU nurses, which will include the study protocol, and periodic follow-up educational sessions to provide feedback and ensure optimal compliance with the study protocol.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		30/08/2021	01/09/2021	Yes	No
Protocol article	protocol	20/03/2020	20/04/2020	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes