**KETAMINE IN ACUTE BEHAVIOURAL DISTURBANCE(KIA):**

THE SAFETY AND EFFECTIVENESS OF KETAMINE FOR SEDATION OF PATIENTS WITH ACUTE BEHAVIOURAL DISTURBANCE DURING AEROMEDICAL RETRIEVAL

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**Protocol version:**

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**Disclosures:**

None of the investigators will receive any financial benefit from the outcome of this trial. In particular, none of the investigators have any affiliation with or financial interest in any manufacturers or distributors of ketamine.

**Study registration:**

The study shall be registered with the Australian and New Zealand Clinical Trial Registry.

**Sponsorship and funding:**

No external sponsorship or funding will be sought.

**Milestones:**

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| --- | --- | --- |
|  | Start Date  | Completion Date |
| Literature Review & Protocol Drafting  | 10/06/2016 | 30/06/2016 |
| Ethics/Governance Approvals | 07/2016 | 07/2016 |
| Staff Recruitment | 06/2016 | 06/ 2016 |
| Protocol training, Data Abstraction, Data monitoring AND Data Analysis | 1/08/2016  | 30/09/ 2016 |
| Write-up |  | October 2016 |
| Publication |  | March 2017 |

**Background:**

Acute behavioural disturbance(ABD), also known as Excited Delirium Syndrome(ExDS), is a medical emergency with reported mortality of 8-10%. (1, 2). The management of ABD usually necessitates a judicious combination of de-escalation techniques, physical restraints and sedation (1, 3, 4). Sedation of patients with ABD is usually accomplished with benzodiazepines and antipsychotics, either alone or in combination. (5, 6). The use of these two drug classes can be limited by several factors, primarily respiratory depression with benzodiazepines and a delayed onset of action of up to 20min with antipsychotics (7, 8). In recent years, several small studies have explored the suitability of ketamine as an alternative agent for sedating patients with ABD in the prehospital, retrieval and emergency settings(9-27). Favourable pharmacological properties including rapid onset of action of 2-5min, protection of airway reflexes and maintenance of respiratory drive make ketamine a promising sedative agent in the management of ABD(28). Nevertheless insufficient data about effectiveness and safety of ketamine in the setting of ABD have prevented it from gaining widespread acceptance for this indication (29, 30). Firstly, the effectiveness of ketamine sedation in ABD, as measured by sedation failure rates, has varied between no failures in one retrospective study and 10% in a recent prospective study(11, 19). Furthermore, the reported incidence of endotracheal intubations with ketamine has also varied widely between studies, from no intubations to 39% (11, 17). Interestingly, a large study looking at the incidence of intubations before and after introduction of a ketamine sedation protocol for ABD found a decrease in incidence from 3.5% to 2.3% while a smaller study using a combination of sedatives including ketamine also reported an intubation rate of 3%(20, 27). Finally, there is a lack of clarity about the minimum effective ketamine dose needed to achieve safe sedation of behaviorally disturbed patients with reported dose ranges of 0.5-1mg/kg as the initial intravenous dose followed by 1 - 5.56mg/kg/h intravenous infusion and 2.25- 9.42mg/kg as the total intramuscular dose. (11, 13, 23).

Along with benzodiazepines and antipsychotics, ketamine has been a part of the Standard Operating Procedure(SOP) for management of ABD at Lifeflight Retrieval Medicine( previously known as Careflight Retrieval Medicine, Queensland),Australia for over 3 years and Royal Flying Doctor Service(RFDS), Queensland, Australia for over 9 years (Appendix 1 & Appendix 2). We want to examine the experience at these organizations to address our research question of whether ketamine is a safe and effective alternative agent for sedation of patients with acute behavioural disturbance in the aeromedical retrieval setting. We will be looking at the incidence of intubations as the primary outcome and the incidence of adverse reactions, the median effective dose of ketamine and the proportion of patients adequately sedated with ketamine as the secondary outcomes of our study. Our study hypothesis is that in our aeromedical retrieval setting ketamine reduces the incidence of intubations in patients needing sedation for acute behavioural disturbance compared to the reported incidence of intubations in existing literature(20, 27).

**Recruitment and Consent:**

This will be a retrospective study involving perusal of patient records for data as a result of which there will be no direct contact with study participants obviating the need for participant recruitment and consent.

**Methods:**

Setting:

This will be a retrospective review of clinical records of patients with ABD who were sedated with ketamine during aeromedical retrievals performed by Lifeflight Retrieval Medicine (LRM) and Royal Flying Doctor Service(RFDS) which are responsible for all retrievals in the state of Queensland, Australia. Both organizations employ a flight physician-flight nurse model for long-haul retrievals of patients with ABD while CMS employs a flight physician-flight paramedic model for short-haul retrievals.

Participant selection:

All patients with ABD needing needing aeromedical retrieval will be included as study participants. ABD will be defined as any behaviour that puts the patient or others at immediate risk of serious harm and may include threatening or aggressive behavior, extreme distress and serious self-harm which could cause injury or death.(4) Participants will be excluded from the study if the sedative agent was administered for reasons other than managing ABD and if there is no documentation of administered dose of sedative agent. A convenience sample of patient records will be identified by searching the electronic databases at LRM and RFDS over a 18-month period between January 1,2015 and June 30,2016 using keywords ketamine, droperidol, midazolam, diazepam, olanzapine, sedation, restraint, agitation, aggression, volatile, violence, behavioural disturbance, schizophrenia, psychosis, delirium, mania, psychiatric and mental health.

Data abstraction and analysis:

Ethics approval will be sought from CQU human research ethics committee prior to data abstraction. Data abstraction will be done by study authors whilst adhering to standard chart review guidelines including abstractor training, explicit eligibility criteria, precise definition of variables, standardized abstraction forms, periodic meetings and performance monitoring (31-37). Interrater reliability will be tested by a blinded review of a random sample of 15% of the charts by the principal investigator and will be measured using the κ-statistic. The abstractors will not be blinded to the study hypothesis as they are co-investigators of this study and are closely involved in its design and conduct. The data will be abstracted from the patient records after de-identification using a standardized data abstraction form and procedures manual (Appendix 3 & Appendix 4). Any data conflicts during data abstraction due to ambiguous, conflicting or erroneous data will be resolved by periodic meetings and consensus between the abstractors VG, ML, LB, KH, MW and AP(34, 35).Missing data will be managed by imputation(35).

The collected data will be analyzed using SPSS 22.0 and descriptive and comparative statistics will be calculated. Continuous variables will be tested for normality. Based on the outcome of the test, parametric Student’s T test or non-parametric Mann-Whitney test will be carried out to determine the differences in data. Categorical data will be analyzed using the Chi-squared analysis. P-values and confidence intervals will be used to determine statistical significance. A p value < 0.05 and 95% confidence intervals that do not overlap unity will be considered statistically significant. The results will then be examined by the study investigators to determine the following parameters of safety and effectiveness of ketamine sedation:

1. Incidence of intubations expressed in percentages with 95% confidence intervals.
2. Proportion of patients adequately sedated expressed in percentages with 95% confidence intervals (adequacy defined as depth of sedation assessed by flight physician as sufficient to ensure safe transport of the patient without further ABD)
3. Incidence of adverse reactions expressed in percentages with 95% confidence intervals.
4. Effective ketamine dose expressed as median dose in milligrams per kg per hour with a range.
5. Duration of ketamine administration expressed as median time in minutes with a range.

Data management:

Data will initially be written onto paper data abstraction forms and then entered into SPSS for analysis. Original hard copies of materials will be stored in a secured location for a period of 5 years. All electronic data will be stored securely on password-protected folders on computer hard drives at LRM office in Townsville and RFDS offices in Mt.Isa and Cairns in a locked room with access restricted to study investigators.

**Ethical considerations:**

As this is a retrospective study with no direct contact with study participants, the investigators do not foresee any potential risk of harm, discomfort or inconvenience to study participants.

**Authorship, dissemination and data sharing:**

The study protocol has been developed by the principal investigator, Dr Vinay Gangathimmaiah with advice and recommendations from Dr Minh Le Cong, Dr Luke Burman and Prof.Brian Mcguire.

Following completion of data analysis and interpretation, the study investigators will convene to discuss the authorship of the study report which will then be disseminated through publication in a peer-reviewed journal (anticipated in March 2017) and social media updates on Twitter and Facebook.

De-identified complete data-sets will be available on direct request to the Principal Investigator from 3 years after study publication. All versions of the study protocol will be available through the Australian and New Zealand Clinical Trial Registry.

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