**Reviewer’s report**

**Title:** Study protocol for a randomized, blinded, controlled trial of ketamine for acute painful crisis of sickle cell disease

**Version:** 0 **Date:** 21 Feb 2019

**Reviewer:** Penny Reynolds

**Reviewer's report:**

This is the study protocol for a randomized prospective parallel group trial investigating low dose ketamine compared with standard of care morphine for reducing neuropathic pain associated with sickle cell crisis. According to ICH E9 [1] the statistical analyses and overall protocol with identification of endpoints is planned a priori. Therefore the protocol should be reviewed and approved prior to unblinding of the study, or for open label studies prior to database lock approval. A check of clinicaltrials.gov shows that study start date was January 1, 2018, estimated Primary Completion Date was January 1, 2019 and study completion date Feb 27 2019. What was the current status and recruitment status of the trial at the time of protocol manuscript submission? (p 19 . 'current' status and recruitment, although not date, identified)

Authors: why do so many coauthors have emails that show no affiliated status with the academic centre? Please clarify

Abstract: spell out VOC at first use

"To the best of the author's knowledge, there has been no previous large, prospective, randomized controlled trial investigating the impact of adding low-dose ketamine on improving the quality of analgesia in patients with VOC in SCD patients". Not true, the authors cite a few but a quick check of clinicaltrials.gov entries indicates that there at least two others recruiting and another 6 terminated, withdrawn or inactive (mostly for lack of feasibility and low recruitment)

'Blinding: we aim to blind the participant, health care providers, and the outcome assessors'. Please reword: you intend to blind participants, health care providers, and outcome assessors to treatment allocation.

SPIRIT figure: indicate approximate or actual time periods for each phase (as indicated in the clinicaltrials.gov registry, the study should be nearly completed by now)

The primary hypothesis is that early administration of ketamine should show 'more rapid' reduction of pain compared to standard of care pain relief. The primary outcome is identified as 'improvement' of pain scores using Numerical Pain Rating Score (NPRS) for 6 hours following ED admission.
Efficacy aim is "more effective" pain reduction. Please define what 'more effective' means in practical quantifiable terms e.g. 20% change from baseline.

Safety aims. Avoid use of =, use full sentences. What is the expected incidence of SAE based on past data from this hospital?

Secondary outcomes are length of ED stay, cumulative use of opioid etc.

"rate of hospital admission is not defined. Do you mean patient readmission in a specified time frame, e.g. a week, a month, a year? The clinicaltrials.gov entry is similarly uninformative describing as "Number of patients admitted to the hospital after admission to the ED during the same admission". please clarify.

"Patient and Public involvement: No patients were involved either in the trial design or recruitment or on any part of the study methods" However was there community notification? If not justify, particularly since ketamine is not standard of care. Is it approved for off-label use for neuropathic pain?

4.1. All patients, irrespective of allocation, will receive a standard dose of non-narcotic analgesia..." Define dose, timing of initial administration and frequency of additional supplementation.

"If no pain relief is achieved within 30 minutes after study drug is given,... admission decision shall be taken within a maximum of 180 minutes" what happens to the patients who are recruited but not admitted? Are they included in intention to treat?

4.2. define age eligibility for 'adults' '. In clinicaltrials.gov it is given as 18-60 years

'acute crisis within 7 d' A patient with SCC occurring a week ago is not the same as one with SCC in the last hour. Please clarify why the 7 d window was chosen.

4.8 sample size calculations.

" mean SD of pain NPRS at 1 hour following administration was 6.5 + 3.41565 in the case of morphine administration and that with ketamine administration, it was 1.6667 + 1.52753"

This is very poorly reported and incorrectly estimated. The NPRS is a subjective 10-level ordinal measure of pain intensity. It is nonsensical to report this metric as one would for a continuous variable and with spurious precision (5 decimal points?!). These scores are usually whole numbers with at most half-interval precision. e.g 5.5. You cannot use power estimates for t-tests
that are intended for continuous data. You need to compute power for a two-tailed two-sample comparison of ordinal outcomes under the proportional odds ordinal logistic model.

Generally a change on the NPRS of 20% between two time points of an assessment is regarded as being clinically relevant change. It is not clear that a 1.5 score change is sufficient especially for patients at intermediate levels of pain.

Why is there an anticipated dropout rate of 20%. Is attrition expected to be random, or are there certain groups of patients more liable to show attrition.

What is the randomization algorithm? What is the blocking variable and what block sizes will be used? Is this actually a permuted block design?

"We will randomize patients in a 1:1 trend" This makes no sense. Permuting block sizes makes it more difficult to determine treatment allocation order; the total number of patients will be randomised as 1:1 ratio of test intervention to controls

"The procedure for randomization warrants confidentiality" makes no sense. Are you talking about patient treatment allocation and assessments being blinded and therefore treatment identify being masked?

"When a serious adverse event comes in and if it might be a SUSAR, (Respiratory depression, severe hypotension, laryngeal spasm, severe allergic reaction and cardiac arrest) the blind should be broken only for those patients by the principal investigator"

This should not be the call of the PI alone but of the independent Data Safety Review Committee

How are Protocol deviations handled and flagged?

Please describe processes and procedures for data capture and processing. Specify capture instruments (paper, electronic, remote site, bedside; survey, lab measurements etc), methods for data recording, collation; data screening and clean-up; data security; data archiving; and personnel responsible. How will missing data be accounted for?

Describe Data Monitoring Committee (DMC) data monitoring procedures and frequency of oversight activities for safety or efficacy questions. Provide clarification of names and responsibilities of the involved personnel. To do their job properly they should be independent of the study.

This will include

* Descriptive statistics and methods - e.g. summary statistics of subject data (means, standard deviations, extreme values, counts with corresponding percent, etc.; statistical tests (analysis of variance, t-tests, etc)

* Description of analysis populations - e.g. safety set, intention to treat set, full analysis set, etc.

* Data handling rules - e.g. imputation rules, algorithms for derived variables

* Statistical software to be used.

* It is especially important to define timing, duration and 'landmarks' for baseline measurements. Are the baseline variables defined for all variables with a pretreatment/intervention measurement? e.g. since ED entry is identified as baseline visit what happens if some measurements are not done at this visit?

How will missing data be handled in analyses?

ETHICS APPROVAL AND CONSENT TO PARTICIPATE. Please indicate where signed patient consent forms are archived

AVAILABILITY OF DATA AND MATERIAL

"The IAU Emergency Department Research Administrators will be responsible for the overall management of the study, providing central guidance to protocol adherence".

Not what was asked in this section, and is too vague in any case to be helpful. We need specific information on plans to disseminate research data and results to the research community. Presumably at trial conclusion data will be posted to the clinicaltrials.gov site, as mandated by federal law? Please describe other data sharing plans.

FUNDING. "The study receives no funding from any governmental or commercial agency." How were operating expenses and drug costs covered?
AUTHOR CONTRIBUTION

"The principal investigator will appoint members to a steering committee" identify who is on the steering committee. Is it all listed authors?

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

Quality of figures
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

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Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

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No