Author’s response to reviews

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

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Author’s response to reviews:

TRLS-D-18-00656

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

Oscar Bortolami, Ph.D,

Trials

https://trialsjournal.biomedcentral.com/Editor-in-Chief

Iacopo Cappellini, MD
Penny S Reynolds, PhD

Dear Drs. Bortolami, Cappelini and Reynolds,

Thank you for considering our manuscript “Study protocol for a randomized, blinded, controlled trial of ketamine for acute painful crisis of sickle cell disease” for review and hopefully for publication in Trials Journal.

We would also like to thank the editorial board and the reviewers for their in-depth review and practical feedback, which has strengthened the manuscript. We have addressed all of the comments provided by the reviewers.
Please find attached specific reply to each of the concerns raised by the reviewers along with the revised manuscript.

We would appreciate the opportunity for considering our revised manuscript for publication in The Trials Journal.

Sincerely,

On behalf of all authors

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Editor’s Comments:

1. Associate editor report: Please address referee concerns

2. I am in a slight disagreement with a referee suggestion. I consider the sample size on a continuous outcome an acceptable approximation when used on ordinal outcomes. The robustness of the conventional two-sample t-test and ANCOVA, for three-, four- and five point ordinal scale data using assigned scores has been demonstrated for sample sizes as small as 20 (Heeren1997, Sullivan2003, Walters2004). Given the present scale will be a 10-point scale and sample size is greater than 100, parametric methods may be a suitable approximation. Moreover ANCOVA, in a randomized setting, may outperform non parametric methods (Vickers2005). Nevertheless, as the referee suggest, please use an appropriate number of digits and make explicit it which will be the SD used on your calculation.
For instance, I calculate that 108 subjects per group would be needed to detect a difference of 1.5 points using a SD of 3.4 with power 90% and a two sided alpha of 0.05.

The nominal alpha may be a little bit higher given that an alpha error spending function is used if the calculation is considered at 90% power. Nevertheless, the sample size should provide enough power (i.e. greater than 80%) taking in account the sequential nature of the trial.

Reply:

Thank you for this comment.

The sample size calculations are explained further down in response to reviewer’s comments.

3. Please double check the boundaries that you would use on the interim analysis. For instance, using the gsDesign package on the R statistical software with the following code

```
timing <- c(.25, .5, .75)
x <- gsDesign(k=4, sfu="OF", test.type=2, alpha=0.025, n.fix=220, timing=timing )
```

The following n and p values are returned

<table>
<thead>
<tr>
<th>N</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>113</td>
<td>0.0021</td>
</tr>
<tr>
<td>169</td>
<td>0.0097</td>
</tr>
<tr>
<td>225</td>
<td>0.0215</td>
</tr>
</tbody>
</table>

* p value to be searched with better precision

Can you please state which software was used to calculate the boundaries?

Reply:

Thank you for this observation. The comments on interim analysis was answered and explained further down in response to reviewer’s comments. We used IBM SPSS Statistics V25.
4. I am in a slight disagreement with a referee suggestion. As per SPIRIT guidelines, block sizes should not be made explicit on the protocol.

Reply:

Thanks, we agree with that too.

5. I suggest to have only one primary outcome otherwise it may be questioned how alpha should be allocated between two primary outcomes. Please consider the use of ANCOVA for the pain scale in order to account for the expected correlation between baseline and outcome. This may lead to an increased precision.

Reply:

Thank you. We only have the improvement on NPRS as our primary outcome.

References


Reviewer’ Comments

#1: Dear Authors,

Congrats for the manuscript and the study. It is very well designed and I have no further comments.

Reply: Thank you for considering our manuscript.

Reviewer #2:

1. 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)

Response:

Thank you for your comment. To clarify, the protocol was submitted to the journal early August 2018 where at that time there were only 40% of sample recruited, and to date, data is still blinded waiting for the protocol approval.

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

Response:

Thank you for your comment, all co-author’s emails was changed according to academic affiliations.

3. Abstract: spell out VOC at first use

Response:

Thank you for this comment. Correction was made in the revised manuscript.
4. "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)

Response:

Thank you for this comment. We revised the related paragraph as follows: “To the best of author’s knowledge, no previous (published) large, prospective randomized controlled trials investigating the impact of adding low-dose ketamine on improving the quality of analgesia in patients with VOC in SCD patients”.

As the reviewer mentioned, all registered protocols only but no (large) published data yet to date.

5. 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.

Response:

Thank you for the comment. Statement was changed in the manuscript accordingly.

6. 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)

Response:

Thanks for the comment; the exact time period for each phase were added in the revised manuscript.

7. 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

Response:

Thank you for the comment. More effective pain reduction was identified on the method section as improvement of (NPRS) 1.5 points or more compared to the control arm. Statement changed in the main manuscript.

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

Response:

Thank you for this comment.

Drug related side effects or adverse events were added in detail based on what is known in the literature and observed in regular practice as side effects (dizziness, nausea, vomiting, hypotension, flushing itching, hypoxia, apnea, respiratory depression, paraesthesia, tingling, cardiac arrests and any other observed side effect).

9. 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.

Response:

Thank you for this comment: We clarified this comment in the manuscript as “the rate of hospital admission defined as (Number of patients who needed hospital admission from the ED under the internal medicine team due to refractory painful crises) compared to those who were discharged home from ED in both arms”.

10. "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?
Response:

Thank you for the comment.

The community was not involved in the trial design and no notification was made for the below listed reasons:

1. Ketamine had been used as a pain medication for long time in our ED as off-label indication with observational positive response.

2. Saudi FDA approval was obtained for the use of this medication in the trial as off label indication.

3. Patients were consented for the intervention with all expected drug details explanation.

11. 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

Reply:

Thanks for the comment.

Because it is unethical to let patients wait for the randomization and drug preparation process without any pain management, and because of the pragmatic type of the trial, we allowed for an initial administration of analgesia which is the usual practice in our ED post assessment and within 30 minutes of physician-patient contact with a single dose of either:

Paracetamol 1 gm IV infusion over 30 minutes

Or

NSAIDS (either lornoxicam 8-16 mg IV) or Diclofenac 75 mg IM injection

12. What happens to the patients who are recruited but not admitted? Are they included in intention to treat?

Reply:
Thanks for the comment. All patients were included in the intension to treat analysis whether admitted or not.

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

Reply:

Thank you for this comment. Based on our hospital policy, adult’s age definition is from 18 years and above.

14. 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.

Reply:

Thanks for the comment. This statement was chosen based on previous literature definitions of acute painful SCD crises.

15. 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.

Reply:

Thank you very much for your comment. We apologize for such incorrect presentation. The mean and SD values of pain NPRS were abstracted to one and two decimals, respectively. You can read it now as “A study including 10 SCD patients with VOC pain who received either morphine or ketamine showed that the mean SD of pain NPRS at 1 hour following administration had abnormal distribution (Morphine administration; 6.5 ± 3.42, ketamine administration, 1.7 ± 1.53)”. 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.

Reply:
Thank you very much for your important comment. The main point of criticism by the reviewer is that you calculated it using means when the original scale is ordinal. We do not think that is necessary. Our sample size calculation is in agreement to the study of Nogueira et al (N Engl J Med 2018; 378:11-21). The primary outcome is ordinal (Rankin scale) but they considered the mean similar to what we are doing. They report that "The first primary end point was the mean score for disability on the utility-weighted modified Rankin scale at 90 days. The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability)”. We agree with the reviewer that is not clear enough in the first submitted manuscript. We consulted an experienced statistician at the European Society of Anesthesiology, PROVEnet Investigators. He reproduced the statistical analysis plan. We have clarified that in the amended version as you can read “Difference between the mean score for pain, assessed on an ordinal scale ranging from 0 (no pain) to 10 (maximum pain), every 30 minutes until a maximum of 180 minutes whereupon either a discharge or an admission decision will be made or had already been taken already based on abovementioned predefined criteria or ED physician discretion”. You can read also "The sample size was based on the primary efficacy analysis of the mean score for pain, which was tested at a two-sided significance level of 0.05. Based on the assumptions of a standard deviation of 3.41, a mean difference among the groups of 1.5 in the score and a power of 90%, 220 patients are required. We would need to recruit 240 patients as we used the Lan-DeMets O'Brien Fleming approach for interim analysis using a two-sided, asymmetric, beta-spending with non-binding lower bound at the 0.044 significance level. Additional patients (10%) will be added for a final sample size of 264 patients to compensate for those dropping out during the study."

16. 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.

Reply:

We acknowledge that considering change of 2 points (20%) in the mean NPRS might have clinical importance in like other studies (e.g. Anesth Analg 2015; 121(5): 1383–1388). However, there is no a clear consensus about the most clinically relevant changes in pain scores. Ruchira et al considered detection of 10 mm on the 100-mm pain VAS (Anesth Analg 2017; 124(2): 554–559). Xavier et al calculated the sample size to detect 25 mm changes in the pain VAS (Anesth Analg 2017; 124(1): 336–345). Similarly, Gambling et al described that “From the literature, expected differences in VRPS score ranged from 1 to 2 points on an 11-point scale (0 to 10), with a standard deviation also ranging from 1 to 2” (Anesth Analg 2013; 116(3): 636–643).
17. 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.

Reply:

We apologize for the inaccuracy in describing that. It has been corrected in the amended version of the manuscript as shown in the description of sample size calculation.

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

Reply:

Thank you for this question. We used an online, computer generated sealed envelope program wherein the randomization and treatment allocation was concealed. We randomized patients to one of two treatment groups with block size of 6 and stratified according to gender to ensure that the groups are balanced.

19. "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?

Reply:

Thank you for your comment. We agree to the reviewer’s comment. The statement was deleted from the revised manuscript.

20. "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

Reply:

Thank you for this observation. In the event of an adverse event, we have an independent safety monitoring team mandated to identify, evaluate, minimize and appropriately manage risks. The team consists of qualified independent investigators and clinicians who will unmask treatment allocation and will provide immediate medical care to subjects enrolled in the trial.
21. How is 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.

Reply:

Thank you for your comment. Our Clinical research data manager is tasked to compile and review on a regular basis the accumulating data collected to ensure the continuing safety of current participants and those yet to be enrolled. Once a protocol deviation/ violation is identified, the data manager shall forward the issue to the safety monitoring team to handle the deviation/ violation.

The bedside research nurse upon enrollment collects data on paper case report forms (CRF’s). All enrolled patients will receive a random patient identification code. The paper data shall be forwarded by the research nurse to the data manager at the end of the 180 hours window and shall be transcribed electronically and will be stored digitally, encrypted with a double password, and as a hard copy under lock and key. Access to the data-entry system is managed and protected by a personalized username and is password protected.

Missing data will be accounted by complete case analysis and multiple imputations by data manager, data safety monitoring team and a statistician.

22. Please describe statistical analysis plan.

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?

Reply:

All data analyses will be carried out according to a pre-established analysis plan. We are planning for complete case analysis and multiple imputations for missing data. All data will be analyzed according to the intention-to-treat principle, beginning immediately after randomization.

Demographic and baseline disease characteristics will be summarized with the use of descriptive statistics. Categorical variables will be reported as absolute numbers and percentages. Generalized linear model will be used to compare the two treatment groups. Categorical data and 95% confidence intervals will be calculated by means of the two-by two-table methods with the use of log-normal approximation. Continuous variables will be reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Normality will be evaluated using visual histogram evaluation and a Q-Q plot. Between-group differences will be evaluated using the T test or Wilcoxon signed rank test, in accordance with normality of the distribution.

Sample size calculation was performed using both PS (Power and Sample Size Calculator, Vr3.04, 2009 http://biostat.mc.vanderbilt.edu/PowerSampleSize) and in the R (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

Data analysis will be performed using SPSS (vr 16.0 for Windows, IBM)

Interim Analysis

You can read it now as “An independent safety committee will perform three interim analyses on information time 25% (70 patients), 50% (140 patients) and 75% (210 patients). Data evaluation at each interim analysis will be based on the alpha spending function concept using a Lan-DeMets O'Brien Fleming approach with the use of a two-sided, asymmetric, beta-spending with non-binding lower bound. For the first interim analysis the efficacy-stopping rule would require an extremely low P value (P< 0.000015). For the second interim analysis P< 0.0015 will be taken as efficacy stopping rule. For the third interim analysis P< 0.0081 will be taken as efficacy stopping rule. Investigators will be kept blinded to the interim analysis results.”
23. ETHICS APPROVAL AND CONSENT TO PARTICIPATE. Please indicate where signed patient consent forms are archived

Response:

Thank you for the comment. All signed informed consents would be stored in the Emergency Department Research office. The paper data collection sheets and signed informed consents would be stored in a locked cabinet for safe keeping and made available for trial related monitoring, audits, institutional review board and regulatory inspections when required. Federal regulations require research records to be retained for at least 3 years after the completion of the research (45 CFR 46) and shall be destroyed on a maximum of 5 years after publication.

24. 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.

Response:

Thank you for this comment.

At the time of protocol submission in the journal, data are still blinded and are not publicly available pending approval of the protocol publication. All datasets that will be generated and analyzed in this study will be included in the published article and its supplementary information files.

25. 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.

Response:

Thanks for the comment:

Results will be posted to the clinicaltrials.gov site as stated and as planned, data sharing plan will include posting the results at the official study and department social media accounts (twitter @ketamineScd)
26. FUNDING. "The study receives no funding from any governmental or commercial agency." How were operating expenses and drug costs covered?

Response:

Thanks for the comment.

Clinical research operational and management cost is integrated within the processes of clinical research program in our institution. The drug cost was covered by the hospital as part of supporting research activities in the department. (N.B. both drugs are of reasonable cost)

27. AUTHOR CONTRIBUTION

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

Response:

Thanks for this comment.

All listed authors are part of the steering committee and was involved in all meetings conducted.

The primary investigator, senior investigators, research coordinators, research nurses, and a biostatistician operate the Research Unit at Emergency Medicine Department. At regular face-to-face meetings, we managed protocol implementation, patient enrolment and data validation.

The Steering Committee communicated throughout the trial, overseeing recruitment and any methodological issues that arose.