PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Sub-dissociative intranasal ketamine plus standard pain therapy versus standard pain therapy in the treatment of pediatric sickle cell disease vasoocclusive crises in resource-limited settings: study protocol for a randomized controlled trial
AUTHORS	Young, James; Sawe, Hendry; Mfinanga, Juma; Nshom, Ernest; Helm, Ethan; Moore, C; Runyon, Michael; Reynolds, Stacy

VERSION 1 - REVIEW

REVIEWER	Paul Musey Indiana University School of Medicine, USA
REVIEW RETURNED	27-Apr-2017

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol entitled "Sub-dissociative intranasal ketamine plus standard pain therapy versus standard pain therapy in the treatment of pediatric sickle cell disease vasoocclusive crises in resource-limited settings: study protocol for a randomized controlled trial." I find this to be a well written protocol. There are only several minor clarifications that should be addressed. 1. For the primary safety aim please clarify if the frequencies for comparison are both SAE and AE or just SAEs. It seems that they should be compared separately. 2. For the follow up interviews are there any considerations for subjects without access to a phone or are these subjects excluded from enrollment. 3. What are the cutoff ages of consent vs. assent you are using? 4. In the Trial Status section please clarify when and for how long enrollment was held. Additionally, what was the current enrollment at the time of submission and the anticipated end date? 5. Pregnancy is an exclusion. Is this determined by history or testing?

REVIEWER	Dipesh Uprety, MD Hematology and Medical Oncology Gundersen Health System 1900 South Avenue, Mail Stop EB2-001 La Crosse, WI 54601 USA.
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	This is an interesting and smart study being conducted in sub-Saharan Africa. I would like to congratulate all the team members for initiating such a nice study which is very much relevant in resource limited settings.

	The abstract is well balanced and complete. The research ethics, to my knowledge, is addressed appropriately. Although less likely to happen in children, I think, any one with underlying psychiatric condition, like schizophrenia, should be excluded from the study. This study have clearly defined outcomes. Although the primary efficacy is well defined, I would like to warn investigators about its (FPS-R) wide variability in children. The score can be overestimated in the setting of anxiety, unfamiliar environment and hospital setting. The references are, to my knowledge, up-to-date. I would also recommend to add one of the important mechanism by which ketamine carries analgesic property. Ketamine is a non-competitive antagonist at the NMDA receptor and this property has shown to modulate opioid tolerance and opioid induced hyperalgesia. I think this property of ketamine should not be ignored.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. For the primary safety aim, please clarify if the frequencies for comparison are both SAE and AE or just SAEs. It seems that they should be compared separately.

Yes, we will indeed collect and analyze rates of serious adverse events, adverse events, and side effects. We anticipate that rates of serious adverse events will be quite low given ketamine's safety profile, and had therefore used adverse events as the primary safety aim. However, this has been amended in the text to indicate that we will compare rates of all three. [Page 5, Safety Aim]

2. For the follow up interviews are there any considerations for subjects without access to a phone or are these subjects excluded from enrollment.

This point is well taken, and we will add phone access for follow-up as an exclusion criterion for the study. In our experience, the vast majority of families presenting to both hospitals have cell phone access. In both settings, receiving a phone call does not use cellular credit, whereas placing a call does. As such, families are generally very willing to answer phone calls, as it has no direct financial impact for them. We anticipate a 10% attrition rate for patients unable to be reached by phone. This attrition rate will not impact the safety and efficacy outcomes collected during the hospital stay. [Page 7, Exclusion Criteria]

3. What are the cutoff ages of consent vs. assent you are using?

Consent is obtained from parents/guardians in all encounters. Patients who are eight-years or older are also asked for assent. [Page 8, last sentence of first paragraph]

4. In the Trial Status section please clarify when and for how long enrollment was held. Additionally, what was the current enrollment at the time of submission and the anticipated end date?

Enrollment began first in Cameroon in December 2015, but was temporarily halted due to personnel changes within the pediatrics department. Enrollment resumed in mid-2016. Enrollment began in Tanzania in March of 2017. To date, 19 participants have been enrolled. We anticipate completion of enrollment by December 2017. [Page 14, Trial Status]

5. Pregnancy is an exclusion. Is this determined by history or testing?

As per local practice, pregnancy is determined by history. Should there be overt concern for pregnancy, a urine or blood test may be performed, but that is not mandated by the study protocol.

Reviewer 2

The abstract is well balanced and complete. The research ethics, to my knowledge, is addressed appropriately. (1) Although less likely to happen in children, I think, anyone with underlying psychiatric condition, like schizophrenia, should be excluded from the study.

The incidence of diagnosed psychiatric disease is very low in both settings. However, your point is appreciated. We will add schizophrenia to the exclusions. To this date, no patient has been enrolled with a psychiatric history. [Page 7, Exclusion Criteria]

(2) This study has clearly defined outcomes. Although the primary efficacy is well defined, I would like to warn investigators about its (FPS-R) wide variability in children. The score can be overestimated in the setting of anxiety, unfamiliar environment and hospital setting.
Indeed, we would agree that self-report pain scores are imperfect. However, of the self-report pain scores, the FPS-R has the most data for international use across cultural settings (see references 68-73). We realize that measures may not be completely representative of each patient's true level of pain, but this is the best surrogate marker available. In contrast to elevated scores due to anxiety, unfamiliar environment and hospital settings, the patient populations in both settings are generally quite stoic, and scores may even be artificially low.

(3) The references are, to my knowledge, up-to-date. I would also recommend to add one of the important mechanisms by which ketamine carries analgesic property. Ketamine is a non-competitive antagonist at the NMDA receptor and this property has shown to modulate opioid tolerance and opioid induced hyperalgesia. I think this property of ketamine should not be ignored.
Again, thank you for bringing this up. The specific pharmacology of ketamine and its effects on opioid tolerance and hyperlagesia are indeed important, and have been added to the introduction paragraph discussing ketamine. Although opioids are used in the ED in our clinical setting, they are not prescribed for outpatient management, and are truly a rarity for longitudinal management of sickle cell-related pain. Most pain is managed with oral NSAIDs and paracetamol (acetaminophen). As such, we did not focus on this aspect of ketamine, but agree that is an important topic to include. [Page 4, towards bottom of first complete paragraph]

VERSION 2 – REVIEW

REVIEWER	Paul Musey Indiana University, USA
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	Thank you for the opportunity to review the revised manuscript: "Sub-dissociative intranasal ketamine plus standard pain therapy versus standard pain therapy in the treatment of pediatric sickle cell disease vasoocclusive crises in resource-limited settings: study protocol for a randomized controlled trial". This is a well written manuscript describing this study protocol. After reviewing the authors' responses, I believe this manuscript is ready for publication.

REVIEWER	Dipesh Uprety, MD Gundersen Health System 1900 South Avenue Mail Stop EB2-001 La Crosse WI 54601 USA
REVIEW RETURNED	31-May-2017

GENERAL COMMENTS	No further recommendations