PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Study Protocol of a Randomized Controlled Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected, Isolated Extremity Fractures in the Pediatric Emergency Department</th>
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<tr>
<td>AUTHORS</td>
<td>Reynolds, Stacy; Studnek, Jonathan R.; Bryant, Kathleen; Vanderhave, Kelly; Grossman, Eric; Moore, Charity; Young, James; Hogg, Melanie; Runyon, Michael</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Thomas Kurien</th>
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<td></td>
<td>Academic Division of Trauma and Orthopaedics, Queen's Medical Centre, University of Nottingham, Nottingham, UK, NG7 2UH</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>01-May-2016</td>
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GENERAL COMMENTS

A good paper with a detailed study protocol with a clear research question. The methods are clear with a structured power analysis based on numbers of potential adverse effects of the two treatments. Using validated paediatric pain rating scales for the children the Wong-Baker FACES pain rating scale and the Adult VAS scale is a major strength. The randomisation technique is sound with evidence of allocation concealment, blinding and monitoring. Assessment of the change in pain rating 20 minutes post intervention is entirely appropriate in this study plan. The statistical methods for analysis are well thought out and there is a clear process to analyse the data between the two arms. There are no ethical concerns regarding this study.

However IN fentanyl or IN ketamine are not routinely used in in the emergency department in the United Kingdom for the treatment of suspected paediatric fracture pain, which is a minor concern. Recently a paper by Kurien et al 2016 in the Bone and Joint Journal has shown that intranasal diamorphine is acceptable well tolerated treatment that allows manipulation of the fracture into a satisfactory position in the ED and I believe this paper should be referenced.

Manipulation and reduction of paediatric fractures of the distal radius and forearm using intranasal diamorphine and 50% oxygen and nitrous oxide in the emergency department: a 2.5-year study.


One of the main aims of this study was to reduce the quantity of opioid administered to the children and for that reason IN ketamine needs to be researched further and this study when completed may offer an alternative to emergency department physicians and orthopaedic teams in the UK and worldwide.
I would accept this study protocol to the BMJ given has a clear research question and the protocol is well written.

<table>
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<th>REVIEWER</th>
<th>Sylvie Le May</th>
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<tr>
<td>University</td>
<td>University of Montreal, Canada</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>09-May-2016</td>
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**GENERAL COMMENTS**

This study protocol is pertinent and results will surely provide essential data on improvement of pain management of children presenting with a fracture to the ED. I have made comments and suggestions to improve the protocol. These are included below. Mainly, the manuscript requires improvement regarding the measures suggested to evaluate pain as well as the study procedures and some ethical issues related to consent.

I reviewed with great interest the manuscript of this protocol of a pilot study and provided the following comments.

**Abstract**

- Remove exclusion criteria and replace by measures that will be used to evaluate primary outcome.
- Should focus on the fact that this is a protocol for a pilot trial and thus not powered for efficacy. Also, Methods should mention analyses that will be done.

**Background and Rationale**

- Refrain from mention of references older than 10 years. The first three references are too old.
- Bioavailability of IN Fentanyl compared to IN Ketamine?
- Among studies who used IN Ketamine, how many required additional doses or other opioids?

**Aims and Hypotheses**

Clear, well written and in line with the Methods.

**Methods**

Some of the eligibility criteria are not clear, especially the ones related to the age groups and associated pain measures. The pain scales cited are different than the ones mentioned in the Outcomes section. Further, the Wong-Baker scale is valid starting from 4 years old but I would not recommend this scale as it measures more an emotional state that pain. The most recommended and validated scale for the 4-7 age group is the Faces Pain Scale Revised by Bieri et al. Also, I am not sure that the Adult Pain Rating Scale is a validated scale. I have never read anything on its psychometric properties. Again, I would not use this scale to measure pain for the 11-17 age group but rather the Visual Analogue Scale (VAS).

Regarding the exclusion criteria, it is not clear why you would want to exclude participants weighing more than 70 kg since you will...
probably recruit more teenage boys with fractures and they usually weigh more than 70 kg.

**Recruitment and consent**

-The delay before study drug administration might not be that long to shortcut the consent process. I was quite surprised by that comment and the fact that your IRB accepted that procedure since once the study drug is administered I don’t see that parents would want to withdraw their “consent”. It is not clear if this procedure is considered ethical.

**Interventions and blinding**

It is mentioned that the research nurse would not be blinded to study drugs. Although, you clearly show the opposite as the research nurse won’t know what she is administering. What is unblinded?

-Maximum dosage should be clearly indicated in the text for both study drugs. Also, the 6 hours study time period is not justified. We had a hard-time keeping patients more than 2 hours in the ED once they have been examined by an MD and their limb is immobilized by a cast or splint. Further, both study drugs only last for a maximum of one hour.

Side effects and SAE definitions should be moved to an appendix.

**Outcomes**

Why use four pain scales given that two of them (as specified earlier) are not valid measures? Further the VAS can be used with 7 years old children and older as reported by the IMPACCT study on pain scales.

**Sample size**

Even though this is a pilot study, you should adjust your sample size according to attrition which is usually high after 2 hours in the ED, especially if the patient was seen and received care.

**Statistical methods**

It seems that the statistics are those for the larger trial as the text of this section does not reflect analyses related to a pilot study. Your sample won’t be large enough to perform subgroup analyses as stated and further you can’t expect to assess impact with such a small sample within a pilot study design. Further, I don’t think that a DSMB is required for a pilot study. Also, it is not recommended that the Chair of the DSMB is from the same hospital as the PI and where the data collection will take place. Finally, the study biostatistician should be independent and not be aware of the interim results. At the same time, you would not perform interim analyses for a pilot study. This whole section should be reviewed and adapted to a pilot study design.
Thank you for this opportunity to review this important work. This is a well-written and planned study protocol. I commend the authors for piloting the methods prior to implementing a large-scale, costly study.

My main concern is related to the pain scales proposed to be used for collecting the key outcome of pain reduction; the proposed scales are not the currently recommended scales for the study age groups, as explained further, below. The WB face scale is often criticized for its use of tears, as culturally, this may not be how all children within your study population express pain, and can lead to under-reporting. Further, the Adult pain scale is not known to me, and needs further explanation, as the very least.

Specific feedback:
- Abstract: It is likely worthwhile to stress that this pain treatment will be offered at triage, as this is a key place to initiate pain treatment, early.
- Background & Rationale: The Borland study of IV morphine vs INF provides the incorrect dose for INF (it is NOT 150mcg/kg, but rather, 1.7mcg/kg). In describing the Graudins study, mentioning the sample size would be beneficial. Also, proportion of children experiencing adverse events is more useful, for comparison, rather than absolute numbers. You mentino that the Graudins study was underpowered to measure serious adverse events such as laryngospasm and chest wall rigidity. Given the rare occurrence of these, do you think your planned multi-centre study will be able to capture these? If not, I suggest removing this criticism. Your main argument for INSD ketamine is that it is opioid-sparing. There has been much published in this area, both for and against the use of opioids, recently. I would like to see more explicit justification for opioid sparing, especially given that the side effect profile is less favourable.
- Aims & Hypotheses: Hypotheses are clear. Primary aim mentions a 3-fold occurrence of side effects or 5% SAEs will preclude performing the larger trial. I would like to know the source/justification for these numbers. Did you survey your practitioners to determine this? Is this previously published guidelines? You use the term 'pain control'; it is my understanding that current concepts suggest that we manage or treat someone's pain, not 'control' it; I would respectfully suggest a change in nomenclature, to reflect this.
- Methods: Design and setting are adequately described. Eligibility Criteria indicate the use of the Wong-Baker and the Adult Pain Rating Scale. To my understanding, these are not the recommended pain measurement tools for pediatric pain research. I refer the authors to the Stinson Paper (Pain, 2006), where recommended scales are outlined for each age group. For the younger of your study group, it
I would recommend the Faces Pain Scale-Revised, and for the older, the Visual Analog Scale. I am not familiar with the 'adult pain rating scale', perhaps authors are referring to the Numerical Pain Scale? In either case, I urge you to reflect upon the choice of measures, as this is the core of your results, and the entire results can be dismissed by a reader, if the scoring tools were not felt to be appropriate. Whichever you choose, I suggest including them as an appendix to this protocol. Exclusion criteria: Are you concerned about children with significant nasal congestion, and how this might affect absorption? Concomitant Medications indicate that either ibu OR acetaminophen will be used. Given the emerging body of literature to suggest that ibuprofen is more efficacious than acetaminophen for MSK injury, will you be controlling for this factor, in your analyses?

Side Effect Definitions: It would be good to know where these definitions are from. Are they standardized, and based on literature standards (ie Bhatt, Annals of Emerg Med, 2009)? I also question the inclusion of nightmares in the same category as laryngospasm and apnea. While undesirable, I would not consider nightmares a SAE.

Allocation/Concealment: I am unclear as to why the administering nurse needs to be unblinded. We have conducted similar studies with oral meds at triage, and done this without unblinding. If there is a specific reason why this unblinding is essential, I think it needs to be explained in more detail, here, as I am not able to follow it, as explained. Having personnel unblinded will create a large criticism for this trial, and should be avoided, if possible.


Authors/Ethics/Monitoring/Auditing: well explained.

VERSION 1 – AUTHOR RESPONSE

Thank you for the thoughtful review of our manuscript. The reviewers’ comments were very helpful in clarifying the study protocol and led to significant revisions that have enhanced the final product. We have detailed the reviewers’ comments and our specific responses below. We are appreciative of the continued consideration of our work.

Abstract

Reviewer Comment: Remove exclusion criteria and replace by measures that will be used to evaluate primary outcome.

Author Response: We agree with the reviewer. The following language was cut from the abstract:

“Patients will be excluded for Glasgow Coma Score < 15, allergy or adverse reaction to ketamine or fentanyl, pregnancy, intoxication, age-defined hypotension, weight > 70kg, receipt of opioids prior to enrollment, or aberrant nasal anatomy.”

The description of the primary safety outcome was changed as follows:

“The primary safety outcome for this pilot trial will be the frequency of cumulative side effects and adverse events at 60 minutes after drug administration.”

The efficacy outcome was clarified as follows:

“The primary efficacy outcome will be exploratory and will be the mean reduction of pain scale scores at 20 minutes.”

Reviewer Comment: Should focus on the fact that this is a protocol for a pilot trial and thus not
powered for efficacy. Also, methods should mention analyses that will be done.

Author Response: We addressed this oversight. The first sentence under Methods and Analysis was changed to add the word “pilot:”
“This double-blind, randomized controlled, pilot trial will compare INSD ketamine (1mg/kg) to IN fentanyl (1.5 micrograms/kg) for analgesia in 80 children ages 4-17 years with acute pain from a suspected, single extremity fracture.”

After the description of the exploratory efficacy outcome, we added a sentence to reflect that we are not adequately powered to examine efficacy:
“The study is not powered to examine efficacy.”

Background and Rationale
Reviewer Comment: Refrain from mention of references older than 10 years. The first three references are too old.
Author Response: Thank you for pointing this out. We updated our references with the following citations:

Reviewer Comment: Bioavailability of IN Fentanyl compared to IN Ketamine?

Author Response: The intranasal bioavailability of IN fentanyl is 71% and is now referenced in the background with the following text and reference:
“IN fentanyl is the most frequently used and most widely studied intranasal analgesic with a reported bioavailability of 71%.12,13”

We also added the following additional supporting reference:

Reviewer Comment: Among studies who used IN Ketamine, how many required additional doses or other opioids?

Author Response: We examined the literature more closely for these observations. Additional text was added to the background of the protocol on page 3 and 4 as follows:
It is unclear if IN ketamine reduces opioid consumption in the treatment of painful conditions in the acute ED setting. Three studies of IN ketamine in the ED setting reported the number of patients requiring additional opioids for rescue analgesia. An observational study of 40 patients ages 11-79 years with pain treated in the ED using doses of IN ketamine of 0.5 mg/kg to 0.75 mg/kg reported that 3 patients failed to complete the protocol at 60 minutes because opioid rescue analgesia was required.11 A pilot, observational study of 28 children ages 3-13 years with fracture pain examined the effectiveness of intranasal ketamine for analgesia and recommended a dose of 1 mg/kg to achieve pain control.24 Eight patients or 33% required additional opioid analgesia.24 In contrast, a randomized controlled, double-blind trial of adult patients treated for pain in the ED compared intravenous ketamine at 0.3 mg/kg to intravenous morphine at 0.1 mg/kg and found no difference in the incidence of rescue fentanyl analgesia at 30 or 60 minutes.25 IN ketamine provides pain relief up
to one hour and may reduce opioid utilization during the ED stay on this basis alone.21,23

This reference was added to the protocol:


Methods

Reviewer Comment: Some of the eligibility criteria are not clear, especially the ones related to the age groups and associated pain measures. The pain scales cited are different than the ones mentioned in the Outcomes section. Further, the Wong-Baker scale is valid starting from four years old but I would not recommend this scale as it measures more an emotional state than pain. The most recommended and validated scale for the 4-7 age group is the Faces Pain Scales Revised by Bieri et al. Also, I am not sure that the Adult Pain Rating Scale is a validated scale. I have never read anything on its psychometric properties. Again, I would not use this scale to measure pain for the 11-17 year age group but rather the Visual Analog Scale (VAS).

Author Response: The reviewer raises important points that we support and that are integrated in our study design. We did not clearly communicate the manner in which we are utilizing the different pain scales. At our institution, the Wong-Baker (less than or equal to age 10 years) and Adult Pain Rating Scales (11-17-year age group) are used by nursing for the standard pain assessment. We agree completely with the reviewers that the Wong-Baker is suboptimal and the Adult Pain Rating Scale is not validated. To adapt to this nuance from our hospital's standard clinical practice, we use these suboptimal scales solely as part of the screening process to identify potentially eligible patients. However, after consent, our research associates obtain a baseline Faces Pain Scale-Revised (for children 4-10 years of age) or Visual Analog Scale pain score (for those 11-17 years of age). We will explore the efficacy outcome from the mean reduction in the FACES Pain-Revised Scores or Visual Analog Scale Scores. We did not explain this well in our protocol and made the following changes in response to this:

The exact language was amended as follows on Page 5 of the protocol under eligibility criteria:

"Standard clinical practice at our hospital is for nurses to use the Wong-Baker FACES Pain Rating Scale score (for children ages 4-10 years) or the Adult Pain Rating Scale score (for children ages 11-17 years) to quantify pain in triage. The triage nurses are asked to page a research associate for any patient with a suspected fracture and a Wong-Baker FACES Pain Rating Scale score of ≥4 or an Adult Pain Rating Scale score of ≥3. These scales are suboptimal for research and are used solely to screen potentially eligible patients. The FACES Pain-Revised Scale (for children ages 4-10 years) and Visual Analog Scale scores (for children ages 11-17) are obtained after consent as baseline measures of pain and used thereafter as study measures."

We agree with the reviewer that the literature does not support using the FACES Pain Revised Scale in children under the age of 4 years. We initially chose to include children as young as 3 years old based on prior similar studies, but agree that the more rigorous methodology would be to enroll children 4 years and older. Our eligibility criteria were amended to reflect this and this change will be made with our IRB and submitted to the FDA.

The exact text that was amended can be found on page 5 under eligibility criteria:

"Verbal children ages 4-17 years with a suspected, single extremity fracture requiring analgesia will be screened for enrollment."

The exact text from Pages 6 and 7 in the paragraph that demonstrates the requested changes is given:

"The patient's pain level will be recorded on a validated, age-appropriate pain scale. The FACES
Pain-Revised Scale (FPS-R) will be used for patients ages 4-10 years and the Visual Analog Scale (VAS) will be used for patients 11-17 years. The FPS-R and VAS scores will be used for the exploratory efficacy outcome measure as those scales are validated for research.26-29 The Wong-Baker FACES Pain Rating Scale (ages 4-10 years of age) and the Adult Pain Rating Scale (11-17 years) are referenced under the eligibility criteria and are used in accordance with standard measures available at triage to establish eligibility for enrollment based on institutional practice. These scales are not used as study measures."

Reviewer Comment: Regarding the exclusion criteria, it is not clear why you would want to exclude participants weighing more than 70 kg since you will probably recruit more teenage boys with fractures and they usually weigh more than 70 kg.

Author Response: Thank you for this observation. We strongly considered the recruitment advantages the reviewer points out. It is difficult to administer 1 mg/kg doses of ketamine and 1.5 mcg/kg of fentanyl at weights above 70 kg because these doses exceed the maximal volume of intranasal medicine that can be administered per nostril (1 mL). Volumes in excess of 1 mL per nostril are not adequately absorbed by the nasal mucosa and are often swallowed. For a pilot study, we felt the risk of inconsistent drug administration outweighed the benefits of including a larger population. I have included a letter to the editor from Annals of Emergency Medicine in May of 2007 that describes these limitations concisely.

Recruitment and consent
Reviewer Comment: The delay before study drug administration might not be that long to shortcut the consent process. I was quite surprised by that comment and the fact that your IRB accepted that procedure since once the study drug is administered I don’t see that parents would want to withdraw their “consent”. It is not clear if this procedure is considered ethical.

Author Response: We were not clear regarding the rigor of our consent process. We understand the reviewers concern. It was our IRB that insisted on a short form, followed by a long form, consent to avoid unethical delays in treatment. We have clarified this under Recruitment and Consent on page 5 of the protocol. Consent was administered in accordance with US21CFR50.27(b)(2).

The exact text used on page 5 is given below:
“Research coordinators will utilize a standard IRB-approved script to review the merits and risks of the study. An abbreviated initial short form consent process, conducted in accordance with US21CFR50.27(b)(2), was adopted from our standard consent. This initial short form consent was required by our IRB to avoid any unethical delays in analgesic administration. After study drug administration, a standard long form consent will be completed that adds more detailed information about protections consistent with HIPAA laws.”

Interventions and blinding
Reviewer Comment: It is mentioned that the research nurse would not be blinded to study drugs. Although, you clearly show the opposite as the research nurse won’t know what she is administering. What is unblinded?

Author Response: This was not as clear as it should have been in the protocol. We added the following text under Interventions and Blinding on page 6:
“The clinical nurse administering the study drug will be unblinded to the intervention. The physicians, patients, research associates and investigators will be blinded to the interventions. All study measurements will be made by a blinded research associate. One member of the research team will remain unblinded throughout the study to serve as the liaison with the investigational pharmacy and data safety monitoring board when needed, but will not enroll patients or participate in study data collection.”
Reviewer Comment: Maximum dosage should be clearly indicated in the text for both study drugs. Also, the 6 hours study time period is not justified. We had a hard time keeping patients more than 2 hours in the ED once they have been examined by an MD and their limb is immobilized by a cast or splint. Further, both study drugs only last for a maximum of one hour.

Author Response: The maximum dosages were added to the text of the protocol under Interventions and Blinding on Page 5 as follows:

"The maximum dose of ketamine a patient may receive will be 70 mg (1mg/kg) for the first dose and 35 mg (0.5 mg/kg) for the second dose or a total of 105 mg (1.5 mg/kg). The maximum dose of fentanyl a patient may receive will be 105 micrograms (1.5 mcg/kg) for the first dose or 53 micrograms (0.75 mcg/kg) for the second dose or total of 158 micrograms (2.25 mcg/kg)."

The 6-hour time frame was developed to explore novel side effects and serious adverse events among patients that receive sub-dissociative ketamine and then receive a dissociative dose of ketamine for sedation for closed reduction. Ketamine is the most commonly used agent in our ED for children with fractures requiring reduction. We agree that most side effects and adverse events will be seen in the first hour. We intentionally designed this to be conservative and will not be holding patients in the ED for study measures beyond the 60 minute assessment for adverse events.

We have clarified that the primary outcome of adverse events will be measured as cumulative effects at 60 minutes. The exact text change is found on page 6 under Outcome Measures:

"The primary safety outcome for this pilot trial will be the occurrence frequency of cumulative adverse events and side effects at 60 minutes after drug delivery."

We clarified the statement of the safety aim on page 4 under Aims and Hypotheses as follows:

Safety Aim: Compare the frequency of cumulative adverse events at 60 minutes after drug administration among children randomized to receive either intranasal sub-dissociative ketamine (IN ketamine) or intranasal fentanyl (IN fentanyl) for pain control in the emergency department. To fully characterize novel side effects, adverse events or additive effects of additional interventions such as sedation, we will collect data every 30 minutes for the first 2 hours and again at 6 hours unless the patient was already deemed safe for discharge.

Reviewer Comment: Side effects and SAE definitions should be moved to an appendix.

Author Response: This change was made. An appendix D was created for the side effect and SAE definitions.

Outcomes

Reviewer Comment: Why use four pain scales given that two of them (as specified earlier) are not valid measures? Further the VAS can be used with 7 years old children and older as reported by the IMPACCT study on pain scales.

Author Response: We agree with the reviewers that we are not clear about this very important aspect of the protocol. As stated above, our institution uses the Wong-Baker FACES Pain Rating Scale (for children ages 4-10 years) and Adult Pain Rating Scales (11-17 years age group) for nursing pain assessments. We agree completely with the reviewers that the Wong-Baker is suboptimal and the Adult Pain Rating Scale is not validated. These scores are solely used for screening potentially eligible children. We are analyzing our exploratory outcome of efficacy around the Faces Pain-Revised Scales and Visual Analog Scales. After consent, our research associates obtain a baseline Faces Pain Scale-Revised or Visual Analog Scale pain score and we will establish the mean reduction in pain scale scores based on these scales. We did not explain this well in our protocol and made the following changes in response to this:
The exact language was amended as follows on Page 5 of the protocol under eligibility criteria:

“Standard clinical practice at our hospital is for nurses to use the Wong-Baker FACES Pain Rating Scale score (for children ages 4-10 years) or the Adult Pain Rating Scale score (for children ages 11-17 years) to quantify pain in triage. The triage nurses are asked to page a research associate for any patient with a suspected fracture and a Wong-Baker FACES Pain Rating Scale score of ≥4 or an Adult Pain Rating Scale score of ≥3. These scales are suboptimal for research and are used solely to screen potentially eligible patients. The FACES Pain-Revised Scale (for children ages 4-10 years) and Visual Analog Scale scores (for children ages 11-17) are obtained after consent as baseline measures of pain and used thereafter as study measures.”

We agree with the reviewer that the literature does not support using the FACES Pain Revised Scale in children under the age of 4 years. We initially chose to include children as young as 3 years old based on prior similar studies, but agree that the more rigorous methodology would be to enroll children 4 years and older. Our eligibility criteria were amended to reflect this and this change will be made with our IRB and submitted to the FDA.

The exact text that was amended can be found on page 5 under eligibility criteria:

Verbal children ages 4-17 years with a suspected, single extremity fracture requiring analgesia will be screened for enrollment.

The exact text from Page 7 in the paragraph that demonstrates the requested changes is given:

The patient’s pain level will be recorded on a validated, age-appropriate pain scale. The FACES Pain-Revised Scale (FPS-R) will be used for patients ages 4-10 years and the Visual Analog Scale (VAS) will be used for patients 11-17 years. The FPS-R and VAS scores will be used for the exploratory efficacy outcome measure because that are validated for research.26-29 The Wong-Baker FACES Pain Rating Scale (ages 4-10 years of age) and the Adult Pain Rating Scale (11-17 years) are referenced under the eligibility criteria and are used in accordance with standard measures available at triage to establish eligibility for enrollment based on institutional practice. These scales are not used as study measures.

Sample size

Reviewer Comment: Even though this is a pilot study, you should adjust your sample size according to attrition which is usually high after 2 hours in the ED, especially if the patient was seen and received care.

Author Response: We have not communicated the rationale for the 6-hour time point here very well. We do not expect to see novel side effects or serious adverse events directly attributable to either drug in the study beyond the 2-hour mark. In fact, we expect that the drug’s effects likely diminish or extinguish at 1 hour. We recorded the events conservatively through 2 hours since this is a pilot trial and limited prior studies exist for children for sub-dissociative, intranasal ketamine.

The 6-hour time frame was developed to explore novel side effects and serious adverse events among patients that receive sub-dissociative ketamine and then receive a dissociative dose of ketamine for sedation for closed reduction. Ketamine is the most commonly used agent in our ED for children with fractures requiring reduction. A faculty member that reviewed the protocol initially raised this concern and felt we should extend the monitoring period for patients who remain in the department and undergo these additional procedures.

The protocol, as written, stops at discharge from the ED or 6 hours depending on what occurs first. The primary outcome assessment does not depend on the 6-hour time frame. The 6-hour time frame allows us to explore the possibility of novel occurrences in patients that receive ketamine for two different indications during the ED stay. This is why we did not adjust our sample size for attrition.

The text of the safety aim has been modified on page 4 to clarify this difference:

Safety Aim: Compare the frequency of cumulative adverse events at 60 minutes after drug administration among children randomized to receive either intranasal sub-dissociative ketamine (IN ketamine) or intranasal fentanyl (IN fentanyl) for pain control in the emergency department. To fully characterize novel side effects, adverse events or additive effects of additional interventions such as sedation, we will collect data every 30 minutes for the first 2 hours and again at 6 hours unless the
A couple of lines of text were modified in the abstract on page 2: The primary safety outcome for this pilot trial will be the frequency of cumulative side effects and adverse events at 60 minutes after drug administration. We will continue to assess for events in the first two hours after drug administration and again at 6 hours if the patient has not already been discharged.

Finally, this feedback was integrated into our discussion of sample size on page 7: We have not adjusted for attrition or loss to follow up because we do not anticipate missing data for our primary outcome of cumulative adverse events at 60 minutes after study drug administration.

Statistical methods
Reviewer Comment: It seems that the statistics are those for the larger trial as the text of this section does not reflect analyses related to a pilot study.

This feedback was addressed and the following text was amended in the opening statement under Statistical Methods:

Author Response: For assessing of feasibility of a multicenter trial, we will estimate the proportion of patients consented out of all potentially eligible patients, the time to consent, the proportion successfully randomized, and the proportion with blinding maintained. For assessing safety profiles, the two treatment groups will be compared on demographic and baseline variables using Student's t-test for interval data, the Wilcoxon rank sum test for ordinal data, and the chi-square test or Fisher's exact test for categorical data.

Reviewer Comment: Your sample won’t be large enough to perform subgroup analyses as stated and further you can’t expect to assess impact with such a small sample within a pilot study design.

Author Response: The following text was removed from the statistical methods in agreement with the reviewers:

DELETED TEXT: We will conduct stratified analyses by age if the number of children within each stratification level and treatment group is greater than 5.

DELETED TEXT: We will use generalized linear models to compare total dose of opioid pain medication between the two groups controlling for age group. We anticipate these data will have a large number with 0 requiring a two-part model such as a zero-inflated Poisson or negative binomial distribution for better model fit. Secondary analysis for any adverse event and total dose of opioid pain medication will control for baseline pain to assess the impact on the treatment effect and its significance.

Reviewer Comment: Further, I don’t think that a DSMB is required for a pilot study. Also it is not recommended that the Chair of the DSMB is from the same hospital as the PI and where the data collection will take place.

Author Response: Since this double-blind study involves a vulnerable population (children) and because ketamine lacks an FDA indication for sub-dissociative, intranasal dosing in children, we decided to include a DSMB. We appreciate the feedback regarding the selection of the DSMB Chair and will incorporate this suggestion in the larger subsequent trial.

Reviewer Comment: Finally, the study biostatistician should be independent and not be aware of the interim results. At the same time, you would not perform interim analyses for a pilot study. This whole section should be reviewed and adapted to a pilot study design.

Author Response: We agree fundamentally with the reviewer. Ideally, we would have a study biostatistician who is independent and not aware of the interim results. However, the study has a small budget and relies on the available statistics team at our institution. The statistician and her team reside in separate offices outside our department and they do not participate in the study team meetings and have no role in the study enrollment or data collection processes. While they are not fully independent, they are as independent as we could possibly keep them.

The text describing the monitoring reports may also be misleading and this was reworded as follows to address the reviewers concern:

The study biostatistics team will provide a report to the DSMB after the first five patients, and then
after every 10 patients (or in the event of a serious, unanticipated and related AE) to monitor the data for quality control and will review the occurrence of adverse events.

**VERSION 2 – REVIEW**

| REVIEWER           | Thomas Kurien  
|                   | Academic Orthopaedics, Trauma and Sports Medicine, University of Nottingham |
| REVIEW RETURNED   | 12-Jul-2016     |

**GENERAL COMMENTS**

Interesting paper and protocol, the authors have addressed the comments from the reviewers well and I believe this would be an good study with well thought out methodology. It is well written and I believe should be considered for publication
Study protocol of a randomised controlled trial of intranasal ketamine compared with intranasal fentanyl for analgesia in children with suspected, isolated extremity fractures in the paediatric emergency department

Stacy L Reynolds, Jonathan R Studnek, Kathleen Bryant, Kelly VanderHave, Eric Grossman, Charity G Moore, James Young, Melanie Hogg and Michael S Runyon

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-012190

Updated information and services can be found at:
http://bmjopen.bmj.com/content/6/9/e012190

These include:

References
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