PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) study: Protocol for an International Multicenter Randomized Controlled Trial
AUTHORS	Avidan, Michael; Fritz, Bradley; Maybrier, Hannah; Muench, Maxwell; Escallier, Krisztina; Chen, Yulong; Ben Abdallah, Arbi; Veselis, Robert; Hudetz, Judith; Pagel, P; Noh, Gyujeong; Pryor, Kane; Kaiser, Heiko; Arya, Virendra; Pong, Ryan; Jacobsohn, Eric; Grocott, Hilary; Choi, Stephen; Downey, Robert; Inouye, Sharon; Mashour, George

VERSION 1 - REVIEW

REVIEWER	frederick sieber johns hopkins medical institutions USA
REVIEW RETURNED	27-Jun-2014

GENERAL COMMENTS	Pragmatic trial examining effects of low dose intraoperative ketamine on incidence of postoperative delirium. Limitations include: 1. scientific basis of the trial is not compelling. One small study showing efficacy. Possible mechanism of efficacy not clear from basic science work presented. 2. Large study being performed without obvious source of funding. As a result some important areas skimped on particularly delirium training and quality control of delirium assessments throughout the study. 3. Several of the recruitment centers have unclear track records in this type of clinical investigation.

REVIEWER	Ulf Guenther Ulf Guenther MD, DESA, EDIC Attending Anesthesiologist Dept. of Anesthesiology & Intensive Care Medicine Bonn University Medical Center
REVIEW RETURNED	01-Jul-2014

GENERAL COMMENTS	The material submitted here is study protocol many clinicians have waited for. The protocol describes a multi-center study on the role of ketamine to prevent postoperative delirium and to reduce postoperative analgesic requirements. The protocol is appropriate to answer two key questions regarding

	both issues and of high clinical relevance. I gather that this study is already recruiting patients. So a statistician must have reviewed and approved the study protocol before. From my point of view, there are no flaws regarding the statistics, but I am not a particular expert in this field. This reviewer has two minor comments: Ketamine is commercially available as racemate R-ketamine and a s-enantiomer (S-ketamine) in some countries. The latter requires only half of the dose of R-ketamine. It should be made clear in the manuscript what kind of ketamine is used. The MS does not mention whether analgesic dosing during surgery is also recorded, though it seems highly probable. This is important, since higher doses of intraoperative opioid may contribute to postoperative hyperalgesia. Lidocaine, in turn, may have an effect similar to ketamine. Intraoperative use of these classes of substances should be clarified.

REVIEWER	Yoanna Skrobik MD FRCP(c) MSc Université de Montréal Québec, Canada
REVIEW RETURNED	08-Jul-2014

- The reviewer completed the checklist but made no further comments.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name frederick sieber
Institution and Country johns hopkins medical institutions
USA
Please state any competing interests or state 'None declared': none declared

Pragmatic trial examining effects of low dose intraoperative ketamine on incidence of postoperative delirium.
Limitations include:
1. scientific basis of the trial is not compelling. One small study showing efficacy. Possible mechanism of efficacy not clear from basic science work presented.

Given that the mechanism/s underlying postoperative delirium remain speculative and hypothetical, the scientific basis underlying any study to prevent postoperative delirium (e.g. avoidance of electroencephalographic burst suppression, promotion of sleep hygiene, dexmedetomidine administration, prevention of excessive anaesthetic depth, avoidance of general anaesthesia, administration of haloperidol, administration of rivastigmine, administration of donepezil, administration of dexamethasone) will not be compelling.

The reasons we have provided for ketamine as a potential agent to prevent postoperative delirium include: N-methyl-D-aspartate (NMDA) antagonism; inhibition of HCN1 receptors; anti-inflammatory actions; and a randomized, controlled trial with an impressive effect size. Apart from these reasons, there are other potential mechanisms. In animal experiments, ketamine increases cortical acetylcholine, which may be beneficial in the elderly since anti-cholinergic effects of perioperative drugs are hypothesized to be contributory factors to delirium. Also, ketamine potentially mitigates two

possible risk factors for delirium: postoperative pain and opioid use. Taken together, these motivations are stronger than those for many other candidate prophylactic measures for postoperative delirium.

In the protocol we have stated:

“There is a pharmacological rationale for using ketamine as a preventative measure against postoperative delirium based on its N-methyl-D-aspartate (NMDA) antagonism.21 Normally, excitatory amino acids such as glutamate and aspartate act as agonists at NMDA receptors, and, in the setting of surgery and inflammation, they might promote excitotoxic injury and apoptosis.21 As an NMDA antagonist, ketamine has the potential to protect against such neurological injury.22 Ketamine has also been posited to inhibit HCN1 receptors, which mediate the hyperpolarization-activated cation current.23 Such inhibition is pertinent to delirium because HCN1 channels are important for regulating states of consciousness24 and are up-regulated by inflammation.25 HCN1 receptors are also thought to play a critical role in neuropathic pain through inflammatory cascades.26

Based on the pharmacological rationale for neuroprotection, a 58-patient randomized, controlled trial was conducted to determine whether ketamine might prevent delirium after major cardiac surgery.27 There was a significant reduction in postoperative delirium from 31% to 3% with the administration of low dose ketamine (0.5 mg/kg) upon induction of anesthesia. While encouraging, this trial must be regarded as preliminary owing to its small sample size, and single center design. Interestingly, the same investigators also found that ketamine was associated with improved cognition beyond the immediate postoperative period.28 Differences between the ketamine and placebo groups were evident in tests of nonverbal memory, verbal memory, and executive function. The investigators found that C reactive protein, a non-specific inflammatory marker, was similar at baseline in the ketamine and the placebo groups. On the first postoperative day, C reactive protein was elevated in both groups, but was significantly higher in the placebo group. The investigators hypothesized that the neuroprotective effect of ketamine might have been, in part, attributable to its anti-inflammatory actions.28 In support of the plausibility of this hypothesis, ketamine use in another cardiac surgical population was similarly shown to attenuate postoperative increases in inflammatory markers.29”

Something important regarding our study, which does not necessarily apply to some other candidate preventative interventions for postoperative delirium, is that ketamine has another very compelling benefit for surgical patients: clinically relevant analgesia without respiratory depression. Indeed the reason that many clinicians currently do not administer ketamine routinely (as an analgesic) to (older) surgical patients is that they are concerned about its psycho-active side effects like hallucinations and delirium. If the PODCAST trial finds that ketamine is associated with postoperative analgesia (an expected outcome) with either decreased psycho-active side effects or no increase in psycho-active side effects, this will be a clinically relevant outcome with potential implications for standard of care.

2. Large study being performed without obvious source of funding. As a result some important areas skimped on particularly delirium training and quality control of delirium assessments throughout the study.

It is true that the PODCAST trial is being conducted on the basis of departmental funds at participating institutions. However, we have been diligent about ensuring that investigators at all sites have been thoroughly trained in delirium assessment and we are pursuing rigorous internal quality control to ensure that delirium assessment continues to be conducted to a high standard at all sites. In order to accomplish this we have taken the following specific measures:

1) A training day in Boston was run by Dr. Sharon Inouye and Dr. Ed Marcantonio for the PODCAST investigators. Dr. Inouye and Dr. Marcantonio are established experts in clinical delirium research.

Those who could not attend the training physically participated via WebEx.

2) A set of videos (specifically for private use in the study) was made to assess the inter-rater reliability of the delirium assessments among investigators. The results of this exercise will be published as a separate proof-of-concept study. The intention is to demonstrate that investigators around the world who are appropriately trained can assess delirium reliably and reproducibly. The reference standard for these assessments has been provided by Dr. Inouye's research team.

3) Different training/reinforcement videos (specifically for private use in the study) have been made to help to ensure the ongoing rigor of delirium assessments in the PODCAST trial.

4) A detailed manual of operations has been produced for investigators at all sites to address methodological questions and to ensure uniform approaches to the conduct of the trial at all the sites.

These aspects of training and quality control are described in the protocol as follows:

"Standardization of training and outcomes assessment
All study team members who perform delirium assessments will undergo a rigorous training process. For the initial training, representatives from each study site participated in a full-day training program led by Dr. Sharon Inouye, the original creator of the CAM. Those who attended this initial training will oversee the training of other team members at their sites. Trainees must demonstrate competence at both conducting CAM interviews and in scoring these interviews. For the initial part of training, trainees must conduct at least two satisfactory CAM interviews in the presence of a trained team member. These interviews will not be on patients enrolled in the PODCAST trial. To establish their ability to score CAM interviews reliably, trainees will accompany trained team members to conduct CAM interviews. A trained member of the research team will conduct each CAM interview for patients enrolled in the PODCAST trial. The trainee will observe the interview, but will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all twelve cognitive features assessed by the CAM on a minimum of two delirious and two non-delirious patients. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the PODCAST trial in the presence of a previously trained team member.

Assessment of the standardization and reliability of delirium assessments
After training, all PODCAST team members administering delirium assessments will be invited to participate in a project to demonstrate the validity and reliability of the CAM in our study population. Participants will view and rate eight videos of standard interviews depicting delirious and non-delirious patients. Participants will independently score the CAM for each scenario. Demographic information, level of education, level of clinical experience, and primary language will also be collected from all participants. Data will be de-identified. All scores and data will be submitted to the lead site, Washington University. The group's scores will then be compared to determine the reliability of delirium assessments across sites. Additionally, the group's scores will be compared to a set of "gold standard" scores for the videos (determined by Dr. Inouye's team) This comparison is intended to demonstrate validity of the CAM in our study setting. Overall, the goal of the project is to demonstrate standardization of the delirium outcome across all study sites."

3. Several of the recruitment centers have unclear track records in this type of clinical investigation.

All the sites and investigators involved in the PODCAST trial have appropriate training, expertise and resources to participate in the study. The PIs will take final responsibility for ensuring that the trial is conducted to a high standard at each participating site.

Reviewer: 2
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Please state any competing interests or state ‘None declared’: None declared

The material submitted here is study protocol many clinicians have waited for. The protocol describes a multi-center study on the role of ketamine to prevent postoperative delirium and to reduce postoperative analgesic requirements.

The protocol is appropriate to answer two key questions regarding both issues and of high clinical relevance.

We appreciate that the reviewer is emphasizing that there are two key issues addressed by the PODCAST trial: delirium and pain. Perhaps it is unfortunate that the title does not give sufficient prominence to pain.

I gather that this study is already recruiting patients. So a statistician must have reviewed and approved the study protocol before. From my point of view, there are no flaws regarding the statistics, but I am not a particular expert in this field.

The study protocol has been reviewed by a statistician.

This reviewer has two minor comments:
Ketamine is commercially available as racemate R-ketamine and a s-enantiomer (S-ketamine) in some countries. The latter requires only half of the dose of R-ketamine. It should be made clear in the manuscript what kind of ketamine is used.

R-ketamine is being used in the PODCAST trial. This has been clarified in the protocol.

The MS does not mention whether analgesic dosing during surgery is also recorded, though it seems highly probable. This is important, since higher doses of intraoperative opioid may contribute to postoperative hyperalgesia. Lidocaine, in turn, may have an effect similar to ketamine. Intraoperative use of these classes of substances should be clarified.

All analgesic drugs administered intraoperatively will be recorded in the research charts of PODCAST participants.