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Intraoperative ketamine does not affect postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial

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Declaration of Interests

No authors have financial, intellectual or other conflicts of interest to declare.

Ethics Approval

Ethics committees at all participating locations and Washington University School of Medicine in St. Louis, Missouri approved the study prior to enrollment at the respective site.

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Abstract

Background—Delirium and pain are common and serious postoperative complications. Subanaesthetic ketamine is often administered intraoperatively for postoperative analgesia and to spare postoperative opioids. Some evidence also suggests that ketamine prevents delirium. The primary purpose of this trial was to evaluate the effectiveness of ketamine in preventing postoperative delirium in older adults after major surgery. Secondary outcomes, viewed as strongly related to delirium, were postoperative pain and opioid consumption.

Methods—This was a multicentre, international, randomised trial that enrolled adults older than 60 undergoing major cardiac and noncardiac surgery under general anaesthesia. Participants were enrolled prior to surgery and gave written informed consent. We used a computer-generated randomisation sequence. Patients at study sites were randomised to one of three study groups in blocks of 15 to receive intraoperative administration of (i) placebo (intravenous normal saline), (ii) low dose ketamine (0.5 mg/kg) or (iii) high dose ketamine (1 mg/kg). Study drug was administered following induction of anaesthesia, prior to surgical incision. Participants, clinicians, and investigators were all masked to group assignment. Delirium and pain were assessed twice daily in the first three postoperative days using the Confusion Assessment Method and Visual Analog Scale, respectively. Postoperative opioid use was recorded, and hallucinations and nightmares were assessed. Analyses were performed by intention-to-treat and adverse events were evaluated. The Prevention of Delirium and Complications Associated with Surgical Treatments [PODCAST] trial is registered in clinicaltrials.gov; NCT01690988

Findings—Between February 6, 2014 and June 26, 2016, 1360 patients assessed and 672 were randomised, with 222 in the placebo group, 227 in the low dose ketamine group, and 223 in the high dose ketamine group. There was no difference in postoperative delirium incidence between those in the combined ketamine groups and those who received placebo (19.45% vs. 19.82%, respectively; absolute difference, 0.36%; 95% CI, −6.07% to 7.38%; p=0.92). There were no significant differences among the three groups in maximum pain scores (p=0.88) or median opioid consumption (p=0.47) over time. There were more postoperative hallucinations (p=0.01) and nightmares (p=0.03) with escalating doses of ketamine. Adverse events (cardiovascular, renal, infectious, gastrointestinal, bleeding), whether viewed individually (P value for each >0.40) or collectively (82/222 [36.9%] in placebo group, 90/227 [39.6%] in low dose ketamine group, 91/223 in high dose ketamine group [40.8%]; P=0.69), did not differ significantly across the three groups.

Interpretation—The administration of a single subanaesthetic dose of ketamine to older adults during major surgery did not show evidence of reducing postoperative delirium, pain, or opioid consumption, and might cause harm by inducing negative experiences. Given current evidence and guidelines related to ketamine and postoperative analgesia, the unexpected secondary findings regarding pain and opioid consumption warrant replication or refutation in subsequent research.

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Introduction

Delirium is the most common postoperative neurologic complication in adults older than 60 and is associated with increased morbidity and mortality.[1] Acute and fluctuating alterations of consciousness, attention, and cognition are characteristic features of delirium.[1] The multifactorial aetiology and obscure pathophysiology of delirium have made it challenging to prevent and treat.[1] Pain, its treatment with opioids, and the inflammatory response to injury are all likely risk factors for delirium in surgical patients [1] A medication that both provided analgesia and prevented delirium would be an important advance for perioperative care. A postoperative infusion of dexmedetomidine at 0.1 mcg/kg/hour has shown promise for both delirium prevention and pain alleviation.[2] However, these findings are preliminary and warrant replication in further study; dexmedetomidine is costly, requires continuous intravenous infusion, and postoperative dexmedetomidine can currently only be administered on intensive care units. To date, although certain intraoperative approaches have shown early promise in efficacy trials,[3,4] no anaesthetic technique or intraoperative medications have been definitively shown to prevent or decrease postoperative delirium.

Ketamine is an intravenous anaesthetic with diverse therapeutic effects, and it has been reported in systematic reviews that intraoperative subanaesthetic ketamine administration reduces postoperative markers of inflammation[5] as well as postoperative pain and opioid consumption.[6–9] Furthermore, delirium and depression in elderly people appear to be overlapping syndromes caused by similar pathophysiological mechanisms,[10] and ketamine is a rapid-acting antidepressant agent.[11] Despite these suggested advantageous properties, ketamine is a psychoactive drug with known hallucinogenic properties[12] that could also theoretically contribute to the development of postoperative delirium. However, a small, single-centre trial in cardiac surgery patients found that an intraoperative subanaesthetic bolus of ketamine was associated with a reduction in the incidence of postoperative delirium from 31% to 3%, without apparent negative effect.[4] Ketamine has also been shown in a systematic review to decrease emergence delirium in children,[13] to speed recovery from general anaesthesia in rodents,[14] and a growing body of both pre-clinical and clinical evidence suggests that ketamine has neuroprotective properties.[15] Low dose intraoperative ketamine was also found to be associated with improved cognition one week after cardiac surgery.[16] Since a single administration of subanaesthetic ketamine has anti-depressant effects lasting several days,[11] it is biologically plausible that it might also provide a sustained positive effect on cognition and pain that outlasts its more immediate pharmacologic actions. In addition to these theoretical benefits, ketamine is inexpensive and there is extensive experience among anaesthetists internationally in its use over six decades; it can be given as a bolus intraoperatively with minimal cardiorespiratory side effects.

Before recommending widespread administration of an intraoperative bolus of subanaesthetic ketamine, demonstrating that ketamine decreases either delirium or pain or

both without incurring adverse effects in a large, pragmatic trial was warranted. Based on a synthesis of existing evidence, we hypothesised that a subanaesthetic dose of ketamine, administered following induction of general anaesthesia to older patients, would reduce postoperative delirium (primary outcome) and postoperative pain and/or opioid consumption (related secondary outcomes). To test these hypotheses, we conducted the multicentre, international, randomised controlled Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) trial.[17]

Methods

A full description of the methods for the PODCAST trial was published.[17]

Trial Design

We conducted a randomised controlled trial at Washington University, University of Michigan, Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center, Medical College of Wisconsin, Hartford Hospital (U.S.); two hospitals of the University of Manitoba (Canada); Asan Medical Center (South Korea); and the Post-Graduate Institute of Medical Education and Research -Chandigarh (India). Local ethics committees at each institution approved the trial protocol and written informed consent was obtained from each patient on either the day of surgery or during a preoperative clinic or inpatient visit. Internal audits were conducted at each site, the data were periodically checked for quality, and a data safety monitoring board met twice during the course of the study. (The PODCAST trial is registered in clinicaltrials.gov; NCT01690988)

Participants

Patients were included if they were 60 years and older, competent to provide informed consent, and undergoing major open cardiac (e.g., coronary artery bypass graft, valve replacement) or non-cardiac surgeries (e.g., thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynecologic surgery, open urologic surgery, major orthopaedic or spine surgery, hepatobiliary surgery and major otolaryngologic surgery) under general anaesthesia. The exclusion criteria included patients with delirium prior to surgery; an allergy to ketamine; those for whom a significant elevation of blood pressure would constitute a serious hazard (e.g., phaeochromocytoma, aortic dissection); patients with drug misuse history; patients taking anti-psychotic medications; patients with a weight outside the range of 50 kg – 200 kg. At the time of enrollment, patients underwent the same delirium and pain evaluation that was used postoperatively (described in the Outcomes section).

Interventions

As a pragmatic trial, decisions about anaesthetic technique were at the discretion of the anaesthesiology team assigned to each patient. The only exceptions were the administration of the study drugs and the instruction to clinicians not to administer any ketamine. Following induction of anaesthesia and before surgical incision, a dose of 0.5 or 1 mg/kg ketamine or an equivalent volume of normal saline was injected via a reliable intravenous catheter.

Randomisation and Masking

Subjects were block-randomised by the coordinating centre using computer generated randomisation in blocks of 15 patients. The randomisation codes were sent to participating hospital pharmacists, who assigned study numbers to enrolled patients. Each block of 15 patients contained equal numbers in each group (1:1:1 ratio −0.5 mg/kg ketamine [Lo-K]: 1 mg/kg ketamine [Hi-K]: saline placebo [P]) to balance the randomisation across sites and maintain homogeneity between groups. Study identifiers were documented in the REDCap database. Prepared formulations of either saline placebo or ketamine were directly delivered to the operating room. Randomisation codes were concealed until the primary analysis was completed. Clinicians, patients and study team members were blinded to the study drug. The study syringes were prepared by pharmacists such that the contents of the syringes (ketamine vs. saline) or ketamine concentration (if they contained ketamine) could not be determined by visual inspection.

Outcomes

Primary outcomes—Trained members of the research team who were blinded to group assignment assessed patients for delirium (primary outcome) using the Confusion Assessment Method (CAM)[18] or the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[19,20] for patients who were unable to speak (e.g., still intubated) in the intensive care unit. These methods (the CAM and the CAM-ICU) are reliable and have been found to be consistent with the DSM-IV diagnostic criteria for delirium.[20–22] There was a rigorous process of standardisation and training of delirium assessment in this multicentre study.[17] The severity of delirium was assessed by the maximum daily score of the CAM-S, a severity scale for patients who screen positive for delirium based on the CAM.

Delirium assessments were performed when patients could be aroused sufficiently (Richmond Agitation and Sedation Score −3 or higher).[23] Patients were assessed for delirium twice per day from the first to the third postoperative day in the morning and in the afternoon or evening, with at least 6 hours elapsing between assessments. Patients were also assessed on the day of surgery at least two hours after surgery end time. The new onset of delirium after the third postoperative day was assumed to be unrelated directly to anaesthetic or other intraoperative factors.

Secondary outcomes—Acute pain was assessed prior to surgery and then postoperatively by using the Behavioral Pain Scale (BPS)[24] or the Behavioral Pain Scale for the Non-Intubated patient (BPS-NI)[25] and the 10-cm Visual Analog Scale (VAS)[26] at the same times as patients were assessed for delirium. The BPS-NI has been shown to be a valid and reliable tool for measuring pain in delirious patients.[25] Interviewers rated the BPS or BPS-NI before asking the patient to complete the VAS to prevent bias in the BPS and BPS-NI assessments. Postoperative daily opioids and sedatives administered were determined using the patient's electronic health record and quantified for the postoperative period until the final delirium assessment was complete.

Sample Size

Based on published delirium studies in the scientific literature, we estimated the incidence of postoperative delirium to be between 20% and 25% in a mixed major surgical population of older patients.[1] Although Hudetz et al found that ketamine was associated with a reduction in delirium incidence from 31% to 3% (absolute reduction, 28%; 95% CI, 8% to 46%),[4] we considered a 10% absolute reduction (corresponding to a number needed to treat of 10 patients) to be more realistic while still remaining within the lower bound of the confidence interval for the effect size found by Hudetz et al.[4] The sample size for the primary outcome of this study was calculated with continuity correction, and was based on a ratio of exposed (combined ketamine groups) to unexposed (control) of 2 to 1. Assuming a two-tailed type 1 error rate of 5%, a sample size of 600 was found to give greater than 80% power to detect a decrease in the incidence of delirium from 25% in the control group (P) to 15% in the combined ketamine groups (Lo-K plus Hi-K).

Statistical Analysis

Analyses were conducted with an intention-to-treat approach, excluding patients without any delirium assessments.[27] Normality of distribution of continuous outcomes was assessed with the Shapiro-Wilk test; parametric or non-parametric tests were applied accordingly. For the incidence of delirium (the primary outcome of the PODCAST trial), we used the chi squared test to compare the P group with the combined ketamine groups (Lo-K plus Hi-K). All other analyses in this manuscript were for secondary outcomes. For trend analyses relating to dose escalations, the Cochran-Armitage test was used. For multivariable analyses related to delirium, in the trial protocol we proposed conducting (i) a Cox proportional hazards model for recurrent events to investigate differences in time to delirium onset across the study groups; (ii) a Poisson Hurdle model as a way to model both the incidence and count of delirium episodes; and (iii) a mixed effect analysis to model continuous outcomes over time. As planned we did conduct three types of multivariable analyses for secondary analyses relating to delirium, but with some methodological alterations from what we pre-specified. The Cox proportional hazards and Poisson Hurdle model were appropriately estimated; the mixed effects model was not. We therefore did not conduct the mixed effect model. We decided to conduct a post hoc logistic regression, which was not specified in the trial protocol. First, we conducted logistic regression to evaluate further whether any of the study groups was independently associated with incident delirium, controlling for known risk factors for this outcome. We repeated the logistic regression as sensitivity analyses to account for missing delirium assessments, assuming that missing assessments were either all positive or all negative. Second, we applied the Cox proportional-hazards model as specified. Third, we conducted a binomial hurdle regression, as specified. To decrease the likelihood of overfitting, potentially leading to inferential problems,[28] and to provide unbiased and stable estimates, variables for the regression models were conservatively pre-selected based on both established risk factors[29,30] and the number of delirium outcomes. We chose to limit the ratio of variables to outcomes to 1:10, and the same variables were used in all the regression models. For the most part, the data measuring different aspects of delirium met the required assumptions of their specific regression models, and the overall fit of each model was adequate. For outcomes, such as severity of delirium (as assessed by CAM-S), visual analog pain scales, behavioural pain scales, and opioid consumption, we

used repeated measures analysis of variance and covariance tests to detect the main effects. We used mixed-effects regression models with compound symmetry for repeated covariance type to assess differences among the subgroups in continuous outcome variables over time (e.g., postoperative pain scores and opioid consumption). For comparisons of proportions across groups (incidence of postoperative nausea or vomiting, and adverse events), we used chi squared analyses. All statistical testing was two-sided and $p < 0.05$ was regarded as significant. Interim analyses were neither planned nor conducted. Further explanations of our statistical analyses are provided in the supplementary online appendix. All statistical testing was with SAS® V9.3 for Windows (SAS Institute Inc. Cary, NC) and STATA® SE V14.2 (StatCorp LP, College Station, TX).

Authors MSA, HRM, ABA, and GAM were responsible for the submission of the manuscript.

Results

This study was conducted and reported in conformance to CONSORT guidelines for randomised trials.[31] Patients were enrolled to the study between February 6, 2014 and June 26, 2016. Figure 1 shows the CONSORT diagram for recruitment to the trial.

Overall, 672 patients were randomised, of whom 222 were in the P group, 227 were in the Lo-K group, and 223 were in the Hi-K group. Appendix 1 shows the breakdown of patients by study site. Protocol deviations included patients not receiving the study drug (n=15), receiving open-label ketamine (n=7) in addition to the study drug, patients requiring a second surgery within postoperative days 0–3 (n=9), and study drug given after surgical incision (n=1).

Patient characteristics and types of surgery were balanced among groups, and are shown in Table 1. The incidence of delirium over postoperative days 1 to 3 was 19.82% in group P, 17.65% in group Lo-K, and 21.30% in group Hi-K. For the primary outcome of the PODCAST study, i.e., postoperative delirium incidence in the combined ketamine groups compared with those who received placebo, there was no difference found (19.45%% vs. 19.82%, respectively; absolute difference; 0.36%; 95% CI, −6.07% to 7.38%; $p = 0.92$). There was also no significant trend in delirium incidence across the three treatment groups by the Cochran-Armitage test ($p = 0.80$). Similarly, in the logistic regression model, neither Lo-K (odds ratio [OR], 0.90; 95% CI, 0.54 to 1.50) nor Hi-K (OR, 0.97; 95% CI, 0.59 to 1.61) independently predicted decreased risk for postoperative delirium (Table 2). Furthermore, after adjustment for potential confounders, time to delirium onset, duration of delirium, and delirium severity did not differ significantly among the three groups over postoperative days 1 to 3 (Tables 3–6). There was also no significant difference in risk for delirium across the three groups in the logistic regression sensitivity analyses. Age per year over sixty (OR, 1.07; 95% CI, 1.04 to 1.10), cardiac surgery (OR, 2.81; 95% CI, 1.66 to 4.76), and history of depression (OR, 2.21; 95% CI, 1.21 to 4.03) were independent predictors of delirium (Table 2). Analyses not shown in the manuscript are presented in the supplementary appendix.

By VAS measurements, there were no apparent differences among the three groups in pain at any of the postoperative time points (Table 5). Postoperative opioid consumption was similar across the three groups at all times (Table 6). The absence of a significant effect of ketamine was reinforced by the findings of the mixed effects models for maximum pain ($F_{[2,633]}=0.12$, $p=0.88$) and median opioid consumption ($F_{[2,399]}=0.75$, $p=0.47$).

Adverse events (cardiovascular, renal, infectious, gastrointestinal, bleeding) did not differ significantly across the three groups, whether viewed individually (P value for each >0.40) or collectively (82/222 [36.9%] in placebo group, 90/227 [39.6%] in low dose ketamine group, 91/223 in high dose ketamine group [40.8%]; p=0.69). Further details of these events are provided in the supplementary online appendix. The overall proportion of patients who complained of postoperative nausea or vomiting over three postoperative days was high (285/672 [42.4%]), but there was no significant difference in the incidence of this complication across the three groups (P=92/222 [41.4%], Lo-K=90/227 [39.6%], Hi-K=83/223 [37.2%]; p=0.66). Further details on nausea and vomiting are reported in the supplementary appendix. With increasing ketamine dose, more patients reported hallucinations (P=40/222 [18.0%], Lo-K=45/227 [19.8%], Hi-K=62/223 [27.8%]; p=0.01) and nightmares (P=18/222 [8.1%], Lo-K=27/227 [11.9%], Hi-K=34/223 [15.2%]; p=0.03) over three postoperative days.

Discussion

The key findings of the PODCAST trial were that administration of a subanaesthetic dose of ketamine in patients >60 years of age undergoing major surgery did not reduce the incidence of postoperative delirium, affect postoperative pain, or decrease postoperative opioid administration. These findings are contrary to the hypotheses of the trial and are in conflict with previously published evidence and guidelines.[4,9,12] It is likely that conflicting findings reflect a well-described phenomenon in medical research: large effectiveness trials often do not replicate the results of small efficacy studies or meta-analysis based on small studies.[32–34]

Methodological strengths of the PODCAST trial support generalisability. There was consistency and rigor in delirium assessment training and, since delirium assessments were conducted even on weekends and holidays, few assessments were missed. The findings were unchanged when, in sensitivity analyses, missing delirium assessments were all coded either as positive or negative. Since pain is subjective, delirium might prevent patients from being able to report their pain reliably. We believe that this is a limitation that might hamper many studies focusing on postoperative pain, especially those including older patients. We attempted to address this in PODCAST by incorporating both traditional subjective pain rating scales as well as independent observer-based pain ratings.[24,25] External validity of the trial is enhanced by its pragmatic protocol, inclusion of both cardiac and major noncardiac surgery, and a multicentre, international design.

Despite a previous study finding a large (28% absolute reduction; P = 0.01) decrease in delirium with ketamine,[4] the *a priori* probability that ketamine prevents delirium might still be considered low given the known psychoactive effects of the drug.[35] However, delirium is

a common and major complication of surgery that is associated with increased mortality and that is difficult to prevent,[1] which motivated further investigation of this low-risk, pragmatic intervention. Furthermore, the plausibility of ketamine's beneficial effect on postoperative delirium is enhanced by evidence of its (i) positive effects on cognition one week after surgery,[16] (ii) anti-inflammatory effects,[5] (iii) neuroprotective actions,[15] (iv) acceleration of recovery from general anaesthesia,[14] and (v) rapid and lasting anti-depressant actions.[11] Nonetheless, PODCAST did not replicate the finding that ketamine prevents delirium. On the other hand, the study also did not find an increase in postoperative delirium incidence attributable to either of the ketamine interventions.

In contrast to the delirium results, the findings of PODCAST in relation to pain and opioids were especially unexpected.[6–9] Ketamine's molecular actions include glutamatergic N-methyl-D-aspartate antagonism and hyperpolarization-activated cyclic nucleotide-gated-1 inhibition, both of which are associated with analgesic effects.[35] A recent systematic review, in which the intraoperative ketamine dose was ≤0.5 mg/kg in the majority of studies, concluded: "Intravenous ketamine is an effective adjunct for postoperative analgesia. Particular benefit was observed in painful procedures, including upper abdominal, thoracic, and major orthopaedic surgeries. The analgesic effect of ketamine was independent of the type of intraoperative opioid administered, timing of ketamine administration, and ketamine dose."[9] In another systematic review, not only was intraoperative subanaesthetic administration of ketamine linked with a decrease in visual analog pain scores up to 48 hours postoperatively, it was also associated with a clinically meaningful 15 mg decrease in 24 hour postoperative morphine consumption.[7] However, most of the studies included in the systematic reviews have been much smaller than PODCAST, and timing and dosage of ketamine have been highly variable.[7,9] Based on data from these reviews, 2016 guidelines on prevention of postoperative pain recommend the consideration of intraoperative ketamine as an analgesic adjunct.[12] Importantly, these recommendations pertain to similar doses and for similar surgeries studied in the PODCAST trial.[12] Furthermore, the operating theatre pharmacists at centres in the PODCAST trial have reported that, independently of the study, usage of intraoperative ketamine has escalated approximately three-fold at most sites over the last four years. The consistent results in relation to opioid consumption and pain (which were collected independently of each other) provide convergent validity, and reinforce the plausibility of the negative findings. However, considering (i) the importance of finding safe analgesic alternatives to opioids; (ii) promising previous evidence regarding the analgesic efficacy of subanaesthetic ketamine; and (iii) that pain was a secondary outcome of the PODCAST trial; subsequent research should be conducted to confirm or refute the lack of meaningful postoperative analgesia with intraoperative ketamine.

Regarding adverse events, the trial did not find that there was an increase in any systemic adverse events (cardiovascular, renal, infectious, gastrointestinal, bleeding) potentially associated with subanaesthetic ketamine administration in the perioperative period. Similarly, the incidence of postoperative nausea or vomiting did not differ significantly among groups, although the overall incidence of nausea or vomiting was high. However, side effects such as hallucinations and nightmares, which have previously been observed following administration of intraoperative ketamine, were increased for at least three days after surgery.

As with most trials, PODCAST had important limitations. Although PODCAST included over 600 patients, it was explicitly designed with the notion that a larger trial might be needed to answer more precisely the question regarding delirium prevention.[17] Although the sample size calculation for this study was predicated on an absolute reduction in delirium incidence of 10%, we specified in the protocol for the trial that we considered the minimum clinically important effect size to be 2%, which corresponds to a number needed to treat of 50 surgical patients to prevent one episode of delirium.[17] Even though there was an estimated lack of clinically meaningful (0.36%) and statistically significant (p=0.92) decrease in delirium incidence with ketamine, this could be a false negative finding. The 95% confidence interval for the ketamine effect was 6.1% increase to 7.4% decrease. If ketamine does prevent delirium, it is likely that the effect is small, and a large trial (e.g., 10,000 patients) would be needed to clarify the effect.[17] It might, however, be more rational in future research to pursue alternative agents for which more compelling evidence exists, such as postoperative dexmedetomidine infusion.[2] Some variables that have previously been linked to delirium and pain were not available, and their omission in the analysis might have decreased the accuracy of these predictive models. PODCAST included only older surgical patients, which was appropriate given the higher incidence of delirium in this population. It is possible that younger patients will derive analgesic benefit from intraoperative administration of subanaesthetic ketamine. Finally, to realize meaningful postoperative analgesic benefit, increased doses or prolonged infusions of ketamine might be required.[36] However, the doses administered in the PODCAST trial are consistent with current guidelines[12] and, even if increased doses were efficacious, the postoperative hallucinations and nightmares resulting from intraoperative ketamine might prove prohibitive.

In conclusion, the results of the PODCAST trial suggest that, despite current evidence and guidelines, the administration of a subanaesthetic ketamine dose during surgery is not useful in preventing postoperative delirium (primary outcome) or reducing postoperative pain and minimizing opioid consumption (related secondary outcomes). Instead, the net effect of ketamine might be deleterious since it increases the incidence of postoperative nightmares and hallucinations. As one of the largest pragmatic trials examining the effectiveness of intraoperative ketamine, these findings are compelling. Based on the weight of current evidence, the negative result in relation to delirium is probably true: ketamine does not prevent delirium. In relation to pain, PODCAST presents evidence that, for older patients undergoing major surgeries, intraoperative administration of a single subanaesthetic ketamine dose might have no meaningful analgesic or opioid sparing effect in the postoperative period. If these results were to be confirmed in subsequent research, current pain guidelines, clinical practice, and the search for effective alternatives to opioids would need to be modified accordingly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in Context

Evidence before this study

Delirium and pain are both common and serious complications of surgery. These complications cause distress to patients and family members, and are associated with worse postoperative outcomes. Opioids are the mainstay drugs to treat postoperative pain, but also cause delirium and are associated with life-threatening complications and addiction. There is currently no pharmacological treatment for delirium. In order to assess the effect of perioperative ketamine on postoperative delirium and pain, we did a systematic search of randomised trials and systematic reviews published in any language. We searched the following databases up to February 2014 (Start of enrollment to the PODCAST trial): MEDLINE, PubMed, Cochrane Central Register of Controlled trials, Web of Science, metaRegister of controlled trials, LILACS, African Health-line, POPLINE, MedCarib, CINAHL, and Clinicaltrials.gov using the search terms (i) ketamine and postoperative delirium, and (ii) ketamine and postoperative pain. The systematic search for “ketamine” and “postoperative delirium” included all randomised controlled trials with older surgical patients published between 1964 (when ketamine was introduced in clinical practice) and 2014. We identified six studies with a total of 357 patients. Of the six trials, two showed a decrease in delirium with ketamine, one showed an increase in delirium, one had equivocal results, and in two trials there were no patients with delirium. In contrast to the dearth of studies examining the effect of ketamine on postoperative delirium, there have been many studies examining the effect of perioperative ketamine on postoperative pain, with ketamine administered at various doses, at different times, and for variable durations. The vast majority of these studies enrolled fewer than 100 patients, and a few enrolled up to 150 patients. A systematic review of 70 of these trials involving 4701 patients published in 2011 showed that subanaesthetic dose ketamine decreased pain for up to 48 hours and requirement for opioids after surgery. The systematic search for “ketamine” and “postoperative pain” included randomised controlled trials with older surgical patients published between 2011 and 2014, to complement the 2011 systematic review. Twenty-eight additional studies with a total of 2,159 patients were identified. Fifteen trials showed no decrease in pain with ketamine, eleven found a decrease in pain with ketamine, and two trials had ambiguous findings. Taking into consideration the totality of the evidence, 2016 guidelines recommended that perioperative ketamine as an analgesic adjunct is likely to be effective at decreasing postoperative pain and opioid requirements.

Added value of this study

This international pragmatic study does not support the evidence that a single intraoperative bolus administration of subanaesthetic ketamine decreases the incidence of postoperative delirium, the severity of pain, or the requirement for postoperative opioids. On the other hand, this study suggests that intraoperative ketamine might increase the incidence of postoperative nightmares and hallucinations.

Implications of all available evidence

Taking all the evidence into account, the increasingly common clinical practice of administering a single subanaesthetic intraoperative bolus of ketamine should be reconsidered. The likelihood that ketamine prevents postoperative delirium is low. Considering (i) the importance of finding safe analgesic alternatives to opioids, (ii) promising previous evidence regarding the analgesic efficacy of subanaesthetic ketamine, and (iii) that pain was a secondary outcome of the PODCAST trial, subsequent research should be conducted to confirm or refute the observed lack of meaningful postoperative analgesia with intraoperative ketamine.

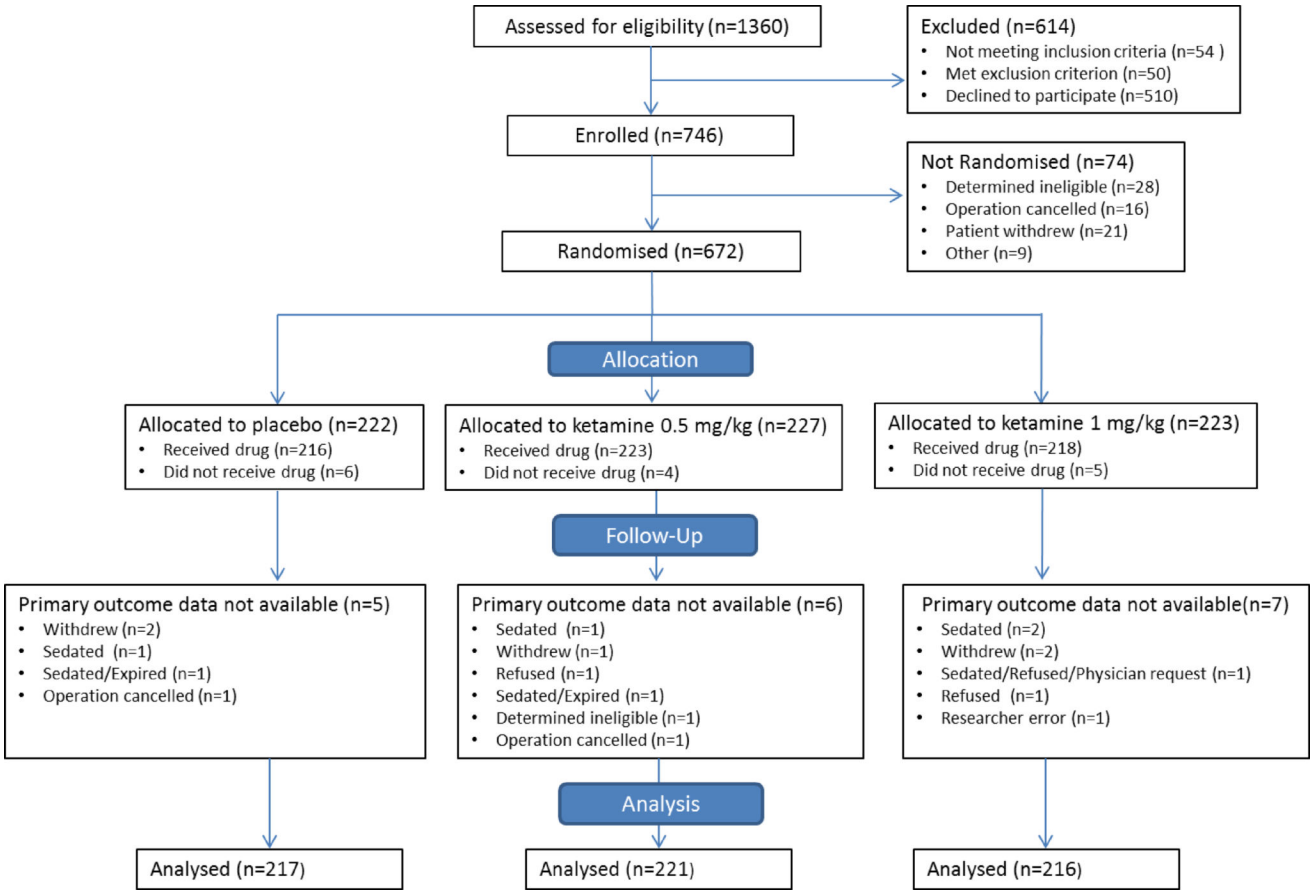

Figure 1.

CONSORT flow diagram of participants. Reasons for not receiving drug were: i) Placebo group −1 provider refused, 4 researcher/provider errors, 1 no reason was given; ii) ketamine 0.5 mg/kg group - 3 researcher/provider errors, 1 provider refused; iii) 4 researcher/provider errors, 1 patient determined ineligible after randomization.

Table 1

Patient characteristics and types of surgery/anaesthesia. Lo-K, low dose (0.5 mg/kg) ketamine group. Hi-K, high dose ketamine group (1 mg/kg).

	All Groups 672 N(%)	Placebo 222 N(%)	Lo-K 227 N(%)	Hi-K 223 N(%)
Female Sex	254(38%)	39%	37%	38%
Mean Age (SD) in years	70(7.1)	70(6.9)	70(7.2)	70(7.3)
Range	60 – 95	60 – 91	60 – 90	60 – 95
Education (college or higher)	178(26%)	27%	26%	26%
Median (IQR) Number of Comorbidities	3(2 – 4)	3(2 – 3)	3(2 – 4)	3(1 – 4)
Median (IQR) Charlson Comorbidity Index (age adjusted)	5(3 – 6)	5(3 – 6)	5(4 – 6)	5(3 – 6)
History of Obstructive Sleep Apnoea	108(16%)	14%	15%	19%
History of depression	75(11%)	11%	9%	13%
History of falls (Last 6 months)	108(16%)	17%	18%	14%
Alcohol use	262(40%)	44%	41%	36%
Median units/week (IQR)	5(2 – 10)	5(2 – 14)	4(2 – 7)	5(2 – 10)
Type of surgery				
Cardiac	206(31%)	30%	31%	31%
Ears/Nose/Throat	8(1%)	0.5%	1%	2%
Gastrointestinal	115(17%)	21%	19%	12%
Gynaecologic	36(5%)	4%	7%	5%
Hepatobiliary-Pancreatic	61(9%)	13%	4%	10%
Orthopaedic/Spine	74(11%)	9%	12%	12%
Thoracic	65(10%)	10%	9%	10%
Urologic	47(7%)	7%	7%	7%
Vascular	45(7%)	6%	7%	7%
Other	15(2%)	0.5%	3%	3%
Type of anaesthesia				
General	444(66%)	65%	67%	67%
General plus regional	227(34%)	35%	33%	33%
(epidural, spinal, nerve block)				

Table 2

Logistic regression model including 628 patients predicting incident postoperative delirium. O.R., odds ratio. OSA, obstructive sleep apnoea. Age is per year over sixty. Log Likelihood ratio = 59.73; the overall model was significant (p<0.0001), C-Statistic = 0.697 indicating reasonably good predictive ability of the model, and Hosmer-Lemeshow lack-of-fit test was nonsignificant (p= 0.11) indicating appropriate model fit.

	Coef.	P > | z |	O.R.	95% Con	f. Interval
Study Arms					
Lo-K Study Arm	−0.106	0.686	0.900	0.539	1.501
Hi-K Study Arm	−0.028	0.914	0.973	0.587	1.611
Canadian Sites	0.014	0.962	1.014	0.579	1.774
Female	0.155	0.498	1.167	0.746	1.826
Age	0.066	0.000	1.068	1.037	1.100
Charlson Comorbidity Index	0.080	0.089	1.083	0.988	1.187
Falls (Within past six months)	0.017	0.951	1.017	0.586	1.768
History of OSA	0.497	0.069	1.644	0.962	2.812
History of Depression	0.778	0.011	2.176	1.198	3.955
Alcohol Use (Weekly)	−0.357	0.115	0.700	0.449	1.091
Intraop. Midazolam Administered	0.015	0.791	1.016	0.906	1.138
Intraop. Opiates Administered	0.000	0.538	1.000	0.999	1.001
Surgery Type (Cardiac vs. the rest)	1.018	0.000	2.768	1.645	4.658
Intercept	−6.760	0.000	--		

Table 3

Positive delirium episodes over three postoperative days, based on the confusion assessment method (CAM) or the confusion assessment method for the intensive care unit (CAM-ICU). In total, 18 patients did not have any delirium assessments over the three-day period. Lo-K, low dose (0.5 mg/kg) ketamine group. Hi-K, high dose ketamine group (1 mg/kg).

Time (Number Assessed)	All Groups	Placebo	Lo-K	Hi-K
All Patients Randomized	*672 (100%)*	*222(33%)*	*227(34%)*	*223(33%)*
Postoperative Day 1				
AM (n =563)	44(8%)	11(6%)	16(8%)	17(9%)
PM (n =583)	49(8%)	17(9%)	11(6%)	21(11%)
Either (n =623)	72(12%)	20(10%)	22(10%)	30(14%)
Postoperative Day 2				
AM (n =561)	50(9%)	18(10%)	12(6%)	20(11%)
PM (n =548)	56(10%)	20(11%)	14(8%)	22(12%)
Either (n =613)	77(13%)	27(13%)	21(10%)	29(14%)
Postoperative Day 3				
AM (n =518)	41(8%)	18(10%)	9(5%)	14(8%)
PM (n =485)	32(7%)	14(9%)	8(5%)	10(6%)
Either (n =571)	51(9%)	22(12%)	12(6%)	17(9%)
Any Postoperative Day				
AM (n =637)	99(16%)	34(16%)	29(14%)	36(17%)
PM (n =639)	93(15%)	33(15%)	24(11%)	36(17%)
Either (n =654)	128(20%)	43(20%)	39(18%)	46(21%)

Table 4

Duration and severity of delirium. CAM, confusion assessment method. IQR, inter quartile range. Lo-K, low dose (0.5 mg/kg) ketamine group. Hi-K, high dose ketamine group (1 mg/kg). The n for Maximum Daily Score refers to delirium episodes.

	All Groups	**Placebo**	**Lo-K**	**Hi-K**
	672 N(%)/Median(IQR)	**222(33%) N(%)/Median(IQR)**	**227(34%) N(%)/Median(IQR)**	**223(33%) N(%)/Median(IQR)**
Frequency of Positive Assessments (am/pm)				
0	526(**80%**)	80%	82%	79%
1	55(**8%**)	8%	10%	8%
2	35(**5%**)	5%	5%	6%
3	18(**3%**)	3%	0.5%	5%
4	10(**2%**)	2%	1%	1%
5	7(**1%**)	1%	1%	1%
6 (n =654)	3(**0.5%**)	0.5%	0%	1%
Duration of Delirium (Days)				
None	526(**80%**)	80%	82%	79%
One	72(**11%**)	11%	12%	11%
Two	32(**5%**)	6%	4%	6%
Three (n =654)	24(**4%**)	4%	2%	5%
Severity (Among CAM/CAMICU Positive Patients)				
Post-Operative Day 1				
Maximum Daily Score (n =71)				
-Short Form	**4**(3 – 4)	**4**(3 – 5)	**4**(3 – 5)	**4**(3 – 5)
-Long Form	**7**(6 – 9)	**7**(6 – 9)	**7**(6 – 9)	**8**(6 – 8)
Post-Operative Day 2				
Maximum Daily Score (n =72)				
-Short Form	**4**(3 – 5)	**4**(3 – 5)	**4**(3 – 5)	**5**(3 – 5)
-Long Form	**8**(4 – 9)	**8**(5 – 10)	**6**(5 – 8)	**8**(6 – 9)
Post-Operative Day 3				
Maximum Daily Score (n =51)				
-Short Form	**4**(3 – 5)	**4**(3 – 5)	**4**(3 – 4)	**5**(3 – 5)
-Long Form	**8**(6 – 9)	**7**(6 – 9)	**7**(6 – 9)	**8**(6 – 9)

Table 5

Postoperative pain levels among by visual analogue scale (VAS) for pain, 0–100 mm. Lo-K, low dose (0.5 mg/kg) ketamine group. Hi-K, high dose ketamine group (1 mg/kg).

	All Groups	Placebo	Lo-K	Hi-K
	672 Median(IQR)	222 (33%) Median(IQR)	227 (34%) Median(IQR)	223 (33%) Median(IQR)
Post-Operative Day 1				
AM				
-Pain level at rest (n =492)	**22**(5 – 47)	24(10 – 45.5)	21.5(5 – 45)	20(5 – 50)
-Pain level when taking a deep breath (n =490)	**40**(13 – 70)	43(18 – 67)	34.5(9 – 67)	46(13 – 73)
-Pain level when moving (n =485)	**49**(22 – 76)	46(27 – 75)	48(19 – 77)	50(20 – 76)
PM				
-Pain level at rest (n =532)	**18.5**(4 – 44)	20(6 – 39)	17(4 – 46)	16(4 – 45)
-Pain level when taking a deep breath (n =529)	**36**(10 – 67)	38(16 – 63)	34.5(10 – 69)	35.5(9.5 – 70)
-Pain level when moving (n =527)	**45**(21 – 74)	45(27 – 70)	45(21 – 75)	45(18 – 74)
Post-Operative Day 2				
AM				
-Pain level at rest (n =519)	**14**(3 – 40)	15(4 – 38)	13(3 – 42)	15(3 – 38)
-Pain level when taking a deep breath (n =517)	**35**(11 – 60)	34(18 – 64)	34.5(10 – 56)	35.5(8 – 64)
-Pain level when moving (n =516)	**42**(19 – 71)	42(21 – 70)	44(17 – 72)	41.5(18 – 71)
PM				
-Pain level at rest (n =504)				
	11(2 – 33)	11.5(3 – 35)	10(1 – 32)	10(2 – 33)
-Pain level when taking a deep breath (n =503)	**33**(11 – 58)	34.5(13 – 62)	29(8.5 – 54)	33(10 – 55)
-Pain level when moving (n =502)	**40.5**(16 – 69)	42.5(18.5 – 69)	36.5(15 – 68.5)	41.5(14 – 68)
Post-Operative Day 3				
AM				
-Pain level at rest (n =487)	**10**(1 –30)	10(1.3 – 30)	10(0 – 27)	9.5(2 – 29)
-Pain level when taking a deep breath (n =517)	**35**(11 – 60)	34(18 – 64)	34.5(10 – 56)	35.5(8 – 64)
-Pain level when moving (n =488)	**36**(12 – 61)	35.5(14 – 59.5)	34(15 – 60)	38(10 – 63)
PM				
-Pain level at rest (n =452)	**10**(1 – 28)	9.5(2 – 25)	8(0 – 29)	10(2 – 29)
-Pain level when taking a deep breath (n =453)	**29**(8 – 53)	29.5(10 – 53)	28(8 – 53)	33(7 – 54)
-Pain level when moving (n =450)	**35**(10 – 60)	38(12.5 – 62.5)	33(10 – 59)	35(8 – 60)

Table 6

Postoperative opioids in morphine equivalents. Lo-K, low dose (0.5 mg/kg) ketamine group. Hi-K, high dose ketamine group (1 mg/kg). The conversion table that was used to convert opioids to morphine equivalents is provided in the supplementary online appendix.

Total PO morphine equivalent **(mg)**	**All Groups** **672** **Median(IQR)**	**Placebo** **222(33%)** **Median(IQR)**	**Lo-K** **227(34%)** **Median(IQR)**	**Hi-K** **223(33%)** **Median(IQR)**
-POD 0 (n=598)	**17.5**(8 – 48)	17.4(8 – 48.8)	17(8 – 50)	18(7.5 – 41.6)
-POD 1 (n=605)	**32**(17 – 68)	**33**(16.6 – 78)	**32**(17.7 – 63)	**30**(16 – 59)
-POD 2 (n=559)	**24**(12 – 48)	**24.9**(12 – 52)	**24**(12.3 – 44)	**22.3**(12 – 49.1)
-POD 3 (n=450)	**18.7**(8 – 40)	**21.8**(10 – 42)	**16.6**(8 – 38.5)	**16**(8 – 37.5)
-Overall (n=629)	**70**(34.9 – 140.8)	**72**(36.5 – 161.4)	**67.7**(37.5 – 120.3)	**66.4**(34 – 138)