Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial

*Michael S Avidan, Hannah R Maybrier, Arbi Ben Abdallah, Eric Jacobsohn, Phillip E Vlisides, Kane O Pryor, Robert A Veselis, Hillary P Grocott, Daniel A Emmert, Emma M Rogers, Robert J Downey, Heidi Yulico, Gyu-Jeong Noh, Yonghun H Lee, Christine M Waszynski, Virendra K Arya, Paul S Pagel, Judith A Hudetz, Maxwell R Muench, Bradley A Fritz, Witold Waberski, Sharon K Inouye, George A Mashour, on behalf of the PODCAST Research Group**

Summary

Background **Delirium is a common and serious postoperative complication. Subanaesthetic ketamine is often administered intraoperatively for postoperative analgesia, and some evidence suggests that ketamine prevents delirium. The primary purpose of this trial was to assess the effectiveness of ketamine for prevention of postoperative delirium in older adults.**

Methods **The Prevention of Delirium and Complications Associated with Surgical Treatments [PODCAST] study is a multicentre, international randomised trial that enrolled adults older than 60 years undergoing major cardiac and non-cardiac surgery under general anaesthesia. Using a computer-generated randomisation sequence we randomly assigned patients to one of three groups in blocks of 15 to receive placebo (normal saline), low-dose ketamine (0·5 mg/kg), or high dose ketamine (1·0 mg/kg) after induction of anaesthesia, before surgical incision. Participants, clinicians, and investigators were blinded to group assignment. Delirium was assessed twice daily in the first 3 postoperative days using the Confusion Assessment Method. We did analyses by intention-to-treat and assessed adverse events. This trial is registered with clinicaltrials.gov, number NCT01690988.**

Findings **Between Feb 6, 2014, and June 26, 2016, 1360 patients were assessed, and 672 were randomly assigned, with 222 in the placebo group, 227 in the 0·5 mg/kg ketamine group, and 223 in the 1·0 mg/kg ketamine group. There was no difference in delirium incidence between patients in the combined ketamine groups and the placebo group (19·45% *vs* 19·82%, respectively; absolute difference 0·36%, 95% CI –6·07 to 7·38, p=0·92). There were more postoperative hallucinations (p=0·01) and nightmares (p=0·03) with increasing ketamine doses compared with placebo. Adverse events (cardiovascular, renal, infectious, gastrointestinal, and bleeding), whether viewed individually (p value for each >0·40) or collectively (36·9% in placebo, 39·6% in 0·5 mg/kg ketamine, and 40·8% in 1·0 mg/kg ketamine groups, p=0·69), did not differ significantly across groups.**

Interpretation **A single subanaesthetic dose of ketamine did not decrease delirium in older adults after major surgery, and might cause harm by inducing negative experiences.**

Funding **National Institutes of Health and Cancer Center Support.**

Introduction

Delirium is the most common postoperative neurological complication in adults older than 60 years 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 cause 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 drug that both provides analgesia and prevents delirium would be an important advance for perioperative care. A postoperative infusion of dexmedetomidine (0·1 µg/kg per h) 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 at present, postoperative dexmedetomidine can only be administered on intensive care units. So far, although some intraoperative approaches have shown early promise in efficacy trials,[3,4] no anaesthetic technique or intraoperative drugs 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

Published **Online** May 30, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31467-8

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(17)31504-0

*PODCAST Research Group members are listed at the end of the paper

Department of Anesthesiology, Washington University School of Medicine, Saint Louis, MO, USA (Prof M S Avidan MBBCh, H R Maybrier BS, Arbi Ben Abdallah PhD, D A Emmert MD, M R Muench BS, B A Fritz MD); **Department of Anesthesiology and Department of Internal Medicine** (Prof E Jacobsohn MBBCh), **and Department of Anesthesia and Perioperative Medicine** (Prof H P Grocott MD), **University of Manitoba, Winnipeg, MB, Canada; Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA** (P E Vlisides MD, Prof G A Mashour MD); **Department of Anesthesiology, Weill Cornell Medicine, New York City, NY, US** (K O Pryor MBBS, E M Rogers BS); **Department of Neuroanesthesiology** (Prof R A Veselis MD), **Department of Surgery** (R J Downey MD), **and Department of Anesthesiology** (H Yulico, DNP), **Memorial Sloan Kettering Cancer Center, New York City, NY, USA; Department of Anesthesiology, Asan Medical Center, Seoul, South Korea** (Prof G-J Noh MD, Y M Lee MD); **Department of Medicine, Hartford Hospital, Hartford, CT, USA** (C M Waszynski, DNP);

Department of Anaesthesiology and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India (Prof V K Arya MD)**; Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, USA** (Prof P S Pagel MD, J A Hudetz PhD)**; Department of Anesthesiology, Hartford Hospital, Hartford, Connecticut, USA** (W Waberski MD)**; and Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, and Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA** (Prof S K Inouye MD)

Correspondence to: Dr Michael Avidan, Department of Anesthesiology, Washington University School of Medicine, St Louis, MO 63110, USA **avidanm@wustl.edu**

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. At present, there is 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 for studies published up to Feb 5, 2014, (the start of enrolment into 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 following search terms: "ketamine and postoperative delirium" and "ketamine and postoperative pain." The systematic search for "ketamine" and "postoperative delirium" included all randomised controlled trials with surgical patients aged 60 years or older 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 a subanaesthetic dose of ketamine decreased pain for up to 48 h and decreased 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. 28 additional studies with a total of 2159 patients were identified. 15 trials showed no decrease in pain with ketamine, 11 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 in older adults. 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 the importance of finding safe analgesic alternatives to opioids, promising previous evidence regarding the analgesic efficacy of subanaesthetic ketamine, and that pain was a secondary outcome of the PODCAST trial, subsequent research should be done to confirm or refute the observed absence of meaningful postoperative analgesia with intraoperative ketamine.

in elderly people seem to be overlapping syndromes caused by similar pathophysiological mechanisms,[10] and ketamine is a rapid-acting antidepressant drug.[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 patients who had cardiac surgery found that an intraoperative subanaesthetic bolus of ketamine was associated with a reduction in the incidence of post-operative 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] and to speed recovery from general anaesthesia in rodents,[14] and a growing body of both pre-clinical and clinical evidence suggests that ketamine has neuro-protective properties.[15] Low-dose intraoperative ketamine was also associated with improved cognition 1 week after cardiac surgery.[16] Because a single administration of subanaesthetic ketamine has antidepressant 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 pharmacological actions. In addition to these theoretical benefits, ketamine is inexpensive, and has been used extensively by anaesthetists around the world for over 50 years; 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 after induction of general anaesthesia to older patients, would reduce postoperative delirium (primary outcome) and postoperative pain or opioid consumption, or both (related secondary outcomes).[17]

Methods

Study design and participants

We did a multicentre, international, randomised controlled prevention of delirium and complications associated with surgical treatments (PODCAST) trial at Washington University, University of Michigan, Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center, Medical College of Wisconsin, Hartford Hospital (USA); 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). A full description of the methods for the PODCAST trial has been published.[17] Patients were included if they were aged 60 years and older, competent to provide informed consent, and undergoing major open cardiac (eg, coronary artery bypass graft or valve replacement) or non-cardiac surgeries (eg, thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynaecological surgery, open urological surgery, major orthopaedic or spine surgery, hepatobiliary surgery, and major otolaryngological surgery) under general anaesthesia. The exclusion criteria included patients with delirium before surgery, an allergy to ketamine, individuals for whom a significant elevation of blood pressure would constitute a serious hazard (eg, phaeochromocytoma or aortic dissection), patients with a history of drug misuse, patients taking antipsychotic drugs, and patients with a weight outside the range of 50–200 kg. At the time of enrolment, patients underwent the same delirium and pain assessment that was used postoperatively (described in the outcomes section).

As this was 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. After induction of anaesthesia and before surgical incision, a dose of 0·5 or 1·0 mg/kg ketamine or an equivalent volume of normal saline was injected via a reliable intravenous catheter. 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 done at each site, the data were periodically checked for quality, and a data safety monitoring board met twice during the course of the study.

Randomisation and masking

Participants 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 of 0·5 mg/kg ketamine: 1 mg/kg ketamine: saline placebo) 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

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 (eg, still intubated) in the intensive care unit. These methods (CAM and the CAM-ICU) are reliable and have been consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition 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 done 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 h elapsing between assessments. Patients were also assessed on the day of surgery at least 2 h after surgery end time. The new onset of delirium after the third postoperative day was assumed to be unrelated to anaesthetic or other intraoperative factors. Acute pain was assessed before 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 time as patients were assessed for delirium. The BPS-NI is 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 from the patient's medical record and quantified for the postoperative period until the final delirium assessment was complete.

Statistical analyses

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

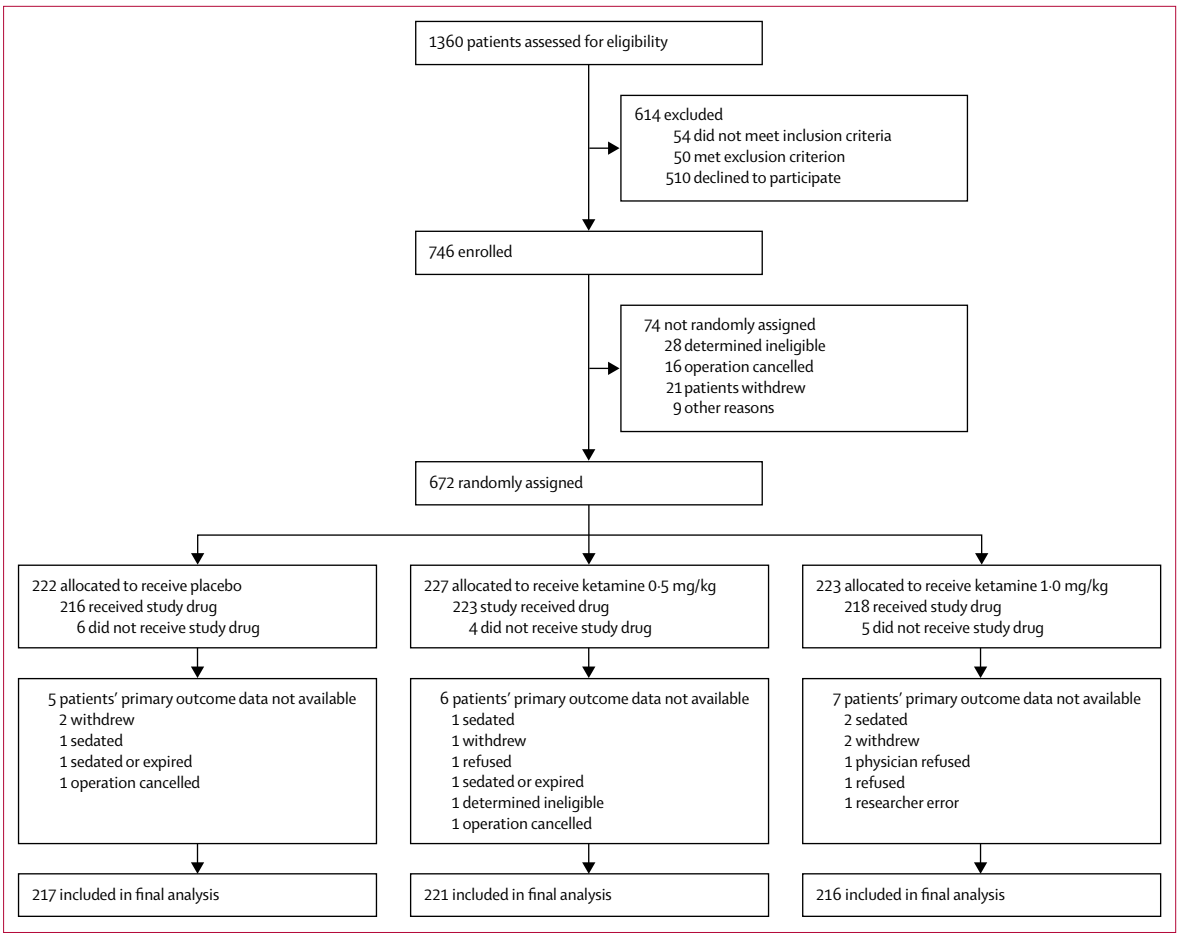

***Figure*: CONSORT flow diagram of participants**
Reasons for not receiving drug were: i) Placebo group—1 provider refused, 4 researcher/provider errors, 1 no reason was given; ii) ketamine 0·5 mg/kg group—3 researcher/provider errors, 1 provider refused; iii) 4 researcher/provider errors, 1 patient determined ineligible after randomisation.

surgical population of older patients.[1] Although Hudetz and colleagues[4] found that ketamine was associated with a reduction in delirium incidence from 31% to 3% (absolute reduction 28%, 95% CI 8–46), we considered a 10% absolute reduction (corresponding to a number needed to treat of ten patients) to be more realistic while still remaining within the lower bound of the confidence interval for the effect size found by Hudetz and colleagues.[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 0·5 mg/kg and 1·0 mg/kg ketamine groups) to unexposed (control) of 2:1. Assuming a two-tailed type I error rate of 5%, a sample size of 600 was needed to give greater than 80% power to detect a decrease in the incidence of delirium from 25% in the control group (placebo) to 15% in the combined 0·5 mg/kg and 1·0 mg/kg ketamine groups.

Analyses were done 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, we used the χ^2 test to compare the placebo group with the combined 0·5 mg/kg and 1·0 mg/kg ketamine groups. All other analyses in this study were for secondary outcomes. For trend analyses relating to dose escalations, we used the Cochran-Armitage test. For multivariable analyses related to delirium, in the trial protocol we proposed doing a Cox proportional hazards model for recurrent events to investigate differences in time to delirium onset across the study groups, a Poisson Hurdle model as a way to model both the incidence and count of delirium episodes, and a mixed-effect analysis to model continuous outcomes over time. As planned, we did do 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 use the mixed-effects model. We decided to do a post-hoc logistic

regression, which was not specified in the trial protocol. First, we did logistic regression to further assess whether any of the study groups were 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 did 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 preselected 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 (eg, postoperative pain scores and opioid consumption). For comparisons of proportions across groups (incidence of postoperative nausea or vomiting, and adverse events), we used χ^2 analyses. All statistical testing was two-sided and p value less than 0·05 was regarded as significant. Interim analyses were neither planned nor conducted. Further explanations of our statistical analyses are provided in the appendix. All statistical testing was with SAS version 9.3 for Windows and STATA SE version 14.2. The PODCAST trial is registered with clinicaltrials.gov, number NCT01690988.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The principal investigators (MSA and GAM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

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

Overall, 672 patients were randomly assigned, of whom 222 were in the placebo group, 227 were in the 0·5 mg/kg ketamine group, and 223 were in the 1·0 mg/kg ketamine group (see appendix for the breakdown of patients by study site). Protocol deviations included patients not receiving the study drug (n=15), those 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 those given the study drug after surgical incision (n=1).

	All groups (n=672)	Placebo (n=222)	0·5 mg/kg ketamine (n=227)	1·0 mg/kg ketamine (n=223)
Women	254 (38%)	87 (39%)	83 (37%)	84 (38%)
Mean age (years)	70 (7·1)	70 (6·9)	70 (7·2)	70 (7·3)
Full age range (years)	60–95	60–91	60–90	60–95
Education (university or higher)	178 (26%)	59 (27%)	60 (26%)	59 (26%)
Number of comorbidities	3 (2–4)	3 (2–3)	3 (2–4)	3 (1–4)
Charlson comorbidity index (age adjusted)	5 (3–6)	5 (3–6)	5 (4–6)	5 (3–6)
History of obstructive sleep apnoea	108 (16%)	32 (14%)	34 (15%)	42 (19%)
History of depression	75 (11%)	25 (11%)	21 (9%)	29 (13%)
History of falls (last 6 months)	108 (16%)	37 (17%)	40 (18%)	31 (14%)
Alcohol use	262 (40%)	95 (44%)	89 (41%)	78 (36%)
Units per week	5 (2–10)	5 (2–14)	4 (2–7)	5 (2–10)
Type of surgery				
Cardiac	206 (31%)	66 (30%)	70 (31%)	70 (31%)
Ears, nose, or throat	8 (1%)	1 (<1%)	3 (1%)	4 (2%)
Gastrointestinal	115 (17%)	46 (21%)	42 (19%)	27 (12%)
Gynaecological	36 (5%)	9 (4%)	15 (7%)	12 (5%)
Hepatobiliary-pancreatic	61 (9%)	28 (13%)	10 (4%)	23 (10%)
Orthopaedic or spine	74 (11%)	20 (9%)	27 (12%)	27 (12%)
Thoracic	65 (10%)	22 (10%)	21 (9%)	22 (10%)
Urological	47 (7%)	16 (7%)	16 (7%)	15 (7%)
Vascular	45 (7%)	13 (6%)	16 (7%)	16 (7%)
Other	15 (2%)	1 (<1%)	7 (3%)	7 (3%)
Type of anaesthesia				
General	444 (66%)	143 (64%)	152 (67%)	149 (67%)
General plus regional (ie, epidural, spinal, or nerve block)	228 (34%)	79 (36%)	75 (33%)	74 (33%)

Data are mean (SD), median (IQR), and n (%), unless otherwise stated.

Table 1: **Patient characteristics and types of surgery and anaesthesia**

See Online for appendix

Patient characteristics and types of surgery were balanced between groups (table 1). The incidence of delirium over postoperative days 1–3 was 19·82% in the placebo group, 17·65% in the 0·5 mg/kg ketamine group, and 21·30% in the 1·0 mg/kg ketamine group. For the primary outcome of the PODCAST study (ie, postoperative delirium incidence in the combined ketamine groups compared with those who received placebo), no difference was 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 difference in delirium incidence across the three treatment groups by the Cochran-Armitage test (p=0.80). Similarly, in the logistic regression model, neither the 0·5 mg/kg ketamine group (odds ratio [OR] 0·90, 95% CI 0·54–1·50) nor the 1·0 mg/kg

	Coefficient	p>|z|*	Odds ratio (95% CI)
0·5 mg/kg ketamine group	–0·106	0·686	0·900 (0·539–1·501)
1·0 mg/kg ketamine group	–0·028	0·914	0·973 (0·587–1·611)
Canadian sites	0·014	0·962	1·014 (0·579–1·774)
Women	0·155	0·498	1·167 (0·746–1·826)
Age (years)*	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 6 months)	0·017	0·951	1·017 (0·586–1·768)
History of obstructive sleep apnoea	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)
Intraoperative midazolam administered	0·015	0·791	1·016 (0·906–1·138)
Intraoperative 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	..

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 not significant (p=0·11), indicating appropriate model fit. In total, 18 patients did not have any delirium assessments over the 3-day period. *The z value is the regression coefficient divided by its standard error.

Table 2: **Logistic regression model including 628 patients predicting incident postoperative delirium**

ketamine group (0·97, 0·59–1·61) 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 between the three groups over postoperative days 1–3 (appendix). There was also no significant difference in risk for delirium across the three groups in the logistic regression sensitivity analyses. Age per year over 60 years (OR 1·068, 95% CI 1·037–1·100), cardiac surgery (2·768, 1·645–4·658), and history of depression (2·176, 1·198–3·955) were independent predictors of delirium (table 2). Analyses not shown in the manuscript are presented in the appendix.

By VAS measurements, there were no apparent differences in pain between the three groups at any of the postoperative timepoints (table 3). Postoperative opioid consumption was similar across the three groups at all times (table 4). The absence of a significant effect of ketamine was reinforced by the findings of the mixed effects models for maximum pain (F [2633]=0·12, p=0·88) and median opioid consumption (F [2399]=0·75, p=0·47).

Adverse events (cardiovascular, renal, infectious, and gastrointestinal bleeding) did not differ significantly across the three groups, whether viewed individually (p value for each >0·40) or collectively (82 [37%] of 222 patients had adverse events in the placebo group, 90 [40%] of 227 in the 0·5 mg/kg ketamine group, and 91 [41%] of 223 in the 1·0 mg/kg ketamine group; p=0·69; appendix). The overall proportion of patients who complained of postoperative nausea or vomiting over three postoperative days was high (285 [42%] of 672), but there was no significant difference in the incidence of this complication across the three groups (92 [41%] of 222 in the placebo group, 90 [40%] of 227 in the 0·5 mg/kg ketamine group, and 83 [37%] of 223 in the 1·0 mg/kg ketamine group; p=0·66). Further details on nausea and vomiting are reported in the appendix. With increasing ketamine dose, more patients reported hallucinations (40 [18%] of 222 in the placebo group, 45 [20%] of 227 in the 0·5 mg/kg ketamine group, and 62 [28%] of 223 in the 1·0 mg/kg ketamine group; p=0·01) and nightmares (18 [8%] of 222, 27 [12%] of 227, and 34 [15%] of 223, respectively; p=0·03) over 3 postoperative days.

Discussion

In this study, we found that administration of a subanaesthetic dose of ketamine in patients aged 60 years or older 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 occurrence in medical research: large effectiveness trials often do not replicate the results of small efficacy studies or meta-analyses based on small studies.[32–34]

Methodological strengths of the PODCAST trial support generalisability. There was consistency and rigor in delirium assessment training and, because delirium assessments were done 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. Because 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 non-cardiac 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 positive effects on cognition 1 week after surgery,[16] anti-inflammatory effects,[5] neuroprotective actions,[15] acceleration of recovery from general anaesthesia,[14] and rapid and lasting anti-depressant actions.[11] Nonetheless, PODCAST did not replicate the

finding that ketamine prevents delirium. However, 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 hyperpolarisation-activated cyclic nucleotide-gated-1 inhibition, both of which are associated with analgesic effects.[35] A recent systematic review,[9] in which the intraoperative ketamine dose was 0·5 mg/kg or less in most of the 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." In another systematic review,[7] not only was intraoperative subanaesthetic administration of ketamine linked with a decrease in visual analog pain scores up to 48 h postoperatively, it was also associated with a clinically meaningful 15 mg decrease in 24 h postoperative morphine consumption. However, most of the studies included in the systematic reviews have been much smaller than PODCAST, and timing and dose 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 pharmacists in operating theatre at centres in the PODCAST trial have reported that, independently of the study, use of intraoperative ketamine has escalated by approximately three-times at most sites over the last 4 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 the importance of finding safe analgesic alternatives to opioids, promising previous evidence regarding the analgesic efficacy of subanaesthetic ketamine, and that pain was a secondary outcome of the PODCAST trial, subsequent research should be done to confirm or refute the absence 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, or bleeding) potentially associated with subanaesthetic ketamine administration in the perioperative period. Similarly, the incidence of postoperative nausea or vomiting did not differ significantly between groups, although the overall incidence of nausea or vomiting was high. However, side-effects such as hallucinations and nightmares, which have previously been observed after administration of intraoperative ketamine, were increased for at least 3 days after surgery.

	All groups (n=672)	Placebo (n=222)	0·5 mg/kg ketamine (n=227)	1·0 mg/kg ketamine (n=223)
Postoperative day 1				
am				
Pain level at rest (n=492)	22 (5–47)	24 (10–46)	22 (5–45)	20 (5–50)
Pain level when taking a deep breath (n=490)	40 (13–70)	43 (18–67)	35 (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)	19 (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)	35 (10–69)	36 (10–70)
Pain level when moving (n=527)	45 (21–74)	45 (27–70)	45 (21–75)	45 (18–74)
Postoperative 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)	35 (10–56)	36 (8–64)
Pain level when moving (n=516)	42 (19–71)	42 (21–70)	44 (17–72)	42 (18–71)
pm				
Pain level at rest (n=504)	11 (2–33)	12 (3–35)	10 (1–32)	10 (2–33)
Pain level when taking a deep breath (n=503)	33 (11–58)	35 (13–62)	29 (9–54)	33 (10–55)
Pain level when moving (n=502)	41 (16–69)	43 (18·5–69)	37 (15–69)	42 (14–68)
Postoperative day 3				
am				
Pain level at rest (n=487)	10 (1–30)	10 (1–30)	10 (0–27)	10 (2–29)
Pain level when taking a deep breath (n=517)	35 (11–60)	34 (18–64)	35 (10–56)	36 (8–64)
Pain level when moving (n=488)	36 (12–1)	36 (14–60)	34 (15–60)	38 (10–63)
pm				
Pain level at rest (n=452)	10 (1–28)	10 (2–25)	8 (0–29)	10 (2–29)
Pain level when taking a deep breath (n=453)	29 (8–53)	30 (10–53)	28 (8–53)	33 (7–54)
Pain level when moving (n=450)	35 (10–60)	38 (13–63)	33 (10–59)	35 (8–60)

Data are median (IQR). Numbers are rounded to the nearest mm.

Table 3: **Postoperative pain levels by visual analogue scale for pain, 0–100 mm**

	All groups (n=672)	Placebo (n=222)	0·5 mg/kg ketamine (n=227)	1·0 mg/kg ketamine (n=223)
Morphine equivalents POD0 (n=598)	18 (8–48)	17 (8–49)	17 (8–50)	18 (8–42)
Morphine equivalents POD1 (n=605)	32 (17–68)	33 (17–78)	32 (18–63)	30 (16–59)
Morphine equivalents POD2 (n=559)	24 (12–48)	25 (12–52)	24 (12–44)	22 (12–49)
Morphine equivalents POD3 (n=450)	19 (8–40)	22 (10–42)	17 (8–39)	16 (8–38)

Data are median (IQR). Numbers are rounded to the nearest mg. The conversion table that was used to convert opioids to morphine equivalents in mg is provided in the appendix. Data were not available after hospital discharge. POD=postoperative day.

Table 4: **Postoperative opioids in morphine equivalents**

As with most trials, PODCAST had important limitations. Although PODCAST included more than 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 absence of clinically meaningful (0·36%) and significant decrease (p=0·92) in delirium incidence with ketamine, this could be a false-negative finding. The 95% CI 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 (eg, 10 000 patients) would be needed to clarify the effect.[17] It might, however, be more rational in future research to pursue alternative drugs 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 analyses might have decreased the accuracy of these predictive models. PODCAST included only older surgical patients, which was appropriate given the increased incidence of delirium in this population. It is possible that younger patients will derive analgesic benefit from intraoperative administration of subanaesthetic ketamine. Finally, to realise 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 present 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 present evidence and guidelines, the administration of a subanaesthetic ketamine dose during surgery is not useful for preventing postoperative delirium (primary outcome) or reducing postoperative pain and minimising opioid consumption (related secondary outcomes). Instead, the net effect of ketamine might be deleterious because 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 present 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, present pain guidelines, clinical practice, and the search for effective alternatives to opioids would need to be modified accordingly.

Contributors

MSA and GAM contributed to the study design, data interpretation, overseeing study conduct, and writing the manuscript. DAE, PEV, KOP, RJD, EJ, VKA, PSP, JAH, RAV, HPG, and GJ-N contributed to the study design, data interpretation, overseeing study conduct at local site, and editing the manuscript. HRM contributed to patient recruitment, data collection, overseeing study conduct, creation of manual of operations, and editing the manuscript. ABA contributed to data analysis, data interpretation, study design, and editing the manuscript. BAF contributed to creation of manual of operations and electronic database. MRM contributed to patient recruitment, data collection, and creation of manual of operations. SKI contributed to study design, editing the manuscript, and consultation for delirium assessment. EMR, HY, YHL, CMW, and WW contributed to patient recruitment and data collection.

PODCAST Research Group

Ginika P Apakama (Washington University School of Medicine, St Louis, MO, USA), Karen G Aquino University of Manitoba, Winnipeg, MB, Canada), Virendra K Arya, Postgraduate Institute of Medical Education and Research, Chandigarh, India), Michael S Avidan (Washington University School of Medicine, St Louis, MO, USA), Arbi Ben Abdallah (Washington University School of Medicine, St Louis, MO, USA), Robert S Dicks (Hartford Hospital, Hartford, CT, USA), Robert J Downey (Memorial Sloan Kettering Cancer Center, New York, NY, USA), Daniel A Emmert (Washington University School of Medicine, St Louis, MO, USA), Krisztina E Escallier (Washington University School of Medicine, St Louis, MO, USA), Bradley A Fritz (Washington University School of Medicine, St Louis, MO, USA), Hussein Fardous (University of Michigan, Ann Arbor, MI, USA), Duane J Funk (University of Manitoba, Winnipeg, MB, Canada), Keith E Gipson (Hartford Hospital, Hartford, CT, USA), Leonard N Girardi (Weill Cornell Medicine, New York, NY, USA), Hillary Grocott (University of Manitoba, Winnipeg, MB, Canada), Alison T Gruber (Weill Cornell Medicine, New York, NY, USA), Judith A Hudetz (Medical College of Wisconsin, Milwaukee, WI, USA), Sharon K Inouye, Institute for Aging Research, Hebrew SeniorLife, Beth Israel Deaconness Medical Center, Boston, MA, USA), Natalia S Ivascu (Weill Cornell Medicine, New York, NY, USA), Eric Jacobsohn (University of Manitoba, Winnipeg, MB, Canada), Aveek Jayant (Postgraduate Institute of Medical Education and Research, Chandigarh, India), Hessam H Kashani (University of Manitoba, Winnipeg, MB, Canada), Morvarid S Kavosh (University of Manitoba, Winnipeg, MB, Canada), Bryan S Kunkler (University of Michigan Ann Arbor, MI, USA), Yonghun Lee (Asan Medical Center, Seoul, South Korea), Eric J Lenze (Washington University School of Medicine, St. Louis, MO, USA), George A Mashour (University of Michigan, Ann Arbor, MI, USA), Hannah R Maybrier (Washington University School of Medicine, St Louis, MO, USA), Amy S McKinney (University of Michigan, Ann Arbor, MI, USA), Sherry L McKinnon (Washington University School of Medicine, St Louis, MO, USA), Angela M Mickle (Washington University School of Medicine, St Louis, MO, USA), Marita Monterola (University of Manitoba, Winnipeg, MB, Canada), Maxwell R Muench (Washington University School of Medicine, St Louis, MO, USA), Matthew R Murphy (Washington University School of Medicine, St Louis, MO, USA), Gyujeong Noh (Asan Medical Center, Seoul, South Korea), Paul S Pagel (Medical College of Wisconsin, Milwaukee, WI, USA), Kane O Pryor (Weill Cornell Medicine, New York, NY, USA), Emma M Rogers, Weill Cornell Medicine (New York, NY, USA), Mariya Redko (Weill Cornell Medicine, New York, NY, USA), Eva M Schmitt (Institute for Aging Research, Boston, MA, USA), Lingesh Sivanesan (Hartford Hospital, Hartford, CT, USA), Michele L Steinkamp (Weill Cornell Medicine, New York, NY, USA), Bethany Tellor (Washington University School of Medicine, St Louis, MO, USA), Sunu Thomas (University of Manitoba, Winnipeg, MB, Canada), Ravi T Upadhyayula (Washington University School of Medicine, St Louis, MO, USA), Robert A Veselis (Memorial Sloan Kettering Cancer Center, New York, NY, USA), Philip E Vlisides (University of Michigan, Ann Arbor, MI, USA), Christine Waszynski (Hartford Hospital, Hartford, CT, USA), and Heidi Yulico (Memorial Sloan Kettering Cancer Center, New York, NY, USA).

Declaration of interests
We declare no competing interests.

Acknowledgments
This study was funded by the National Institutes of Health (NIDUS Grant: NIA R24AG054259, and grant T32GM103730) and the NIH/NCI Cancer Center Support Grant (P30 CA008748). The Dr Seymour and Rose T Brown Endowed Chair supported the Washington University coordinating role. All the participating international institutions provided generous additional support for the study. We thank Jamila Burton, Jordan Oberhaus, Sandeep Grover, Doyang Park, Jeongsim Yang, Austin Ficara, Candice Johnson, and Lucas Luong for their help with recruitment and data collection; Kathryn Vehe, Kristopher Bakos, Unnikrishnan VS, and Amy Skyles for their help with dispensation of study drug; and Charles Hantler, Simon Haroutounian, and Anshuman Sharma for their participation on the data safety monitoring board.

References

1 Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014; **383:** 911–22.
2 Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **388:** 1893–902.
3 Chan MT, Cheng BC, Lee TM, Gin T, Group CT. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013; **25:** 33–42.
4 Hudetz JA, Patterson KM, Iqbal Z, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2009; **23:** 651–57.
5 Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg* 2012; **115:** 934–43.
6 Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of ketamine in acute postoperative pain management: a narrative review. *Biomed Res Int* 2015; **2015:** 749837.
7 Elia N, Tramer MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain* 2005; **113:** 61–70.
8 Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). *Acta Anaesthesiol Scand* 2005; **49:** 1405–28.
9 Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* 2011; **58:** 911–23.
10 O'Sullivan R, Inouye SK, Meagher D. Delirium and depression: inter-relationship and clinical overlap in elderly people. *Lancet Psychiatry* 2014; **1:** 303–11.
11 Kishimoto T, Chawla JM, Hagi K, et al. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med* 2016; **46:** 1459–72.
12 Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016; **17:** 131–57.
13 Costi D, Cyna AM, Ahmed S, et al. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. *Cochrane Database Syst Rev* 2014; **9:** CD007084.
14 Hambrecht-Wiedbusch VS, Li D, Mashour GA. Paradoxical emergence: administration of subanesthetic ketamine during isoflurane aesthesia induces burst suppression but accelerates recovery. *Anesthesiology* 2017; **126:** 482–94.
15 Hudetz JA, Pagel PS. Neuroprotection by ketamine: a review of the experimental and clinical evidence. *J Cardiothorac Vasc Anesth* 2010; **24:** 131–42.
16 Hudetz JA, Iqbal Z, Gandhi SD, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiol Scand* 2009; **53:** 864–72.
17 Avidan MS, Fritz BA, Maybrier HR, et al. The prevention of delirium and complications associated with surgical treatments (PODCAST) study: protocol for an international multicentre randomised controlled trial. *BMJ Open* 2014; **4:** e005651.
18 Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990; **113:** 941–48.
19 Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286:** 2703–10.
20 Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; **29:** 1370–79.
21 Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? *Crit Care Med* 2010; **38:** 409–18.
22 Plaschke K, von Haken R, Scholz M, et al. Comparison of the confusion assessment method for the intensive care unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s). *Intensive Care Med* 2008; **34:** 431–36.
23 Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; **289:** 2983–91.
24 Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med* 2001; **29:** 2258–63.
25 Chanques G, Payen JF, Mercier G, et al. Assessing pain in non-intubated critically ill patients unable to self report: an adaptation of the Behavioral Pain Scale. *Intensive Care Med* 2009; **35:** 2060–67.
26 Kjeldsen HB, Klausen TW, Rosenberg J. Preferred Presentation of the Visual Analog Scale for Measurement of Postoperative Pain. *Pain Pract* 2015; **16:** 980–84.
27 Alshurafa M, Briel M, Akl EA, et al. Inconsistent definitions for intention-to-treat in relation to missing outcome data: systematic review of the methods literature. *PLoS One* 2012; **7:** e49163.
28 Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004; **66:** 411–21.
29 Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. *J Am Geriatr Soc* 2006; **54:** 1578–89.
30 Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. *J Card Surg* 2012; **27:** 481–92.
31 Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010; **7:** e1000251.
32 Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol* 2008; **61:** 763–69.
33 Open Science C. PSYCHOLOGY. Estimating the reproducibility of psychological science. *Science* 2015; **349:** aac4716.
34 Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005; **2:** e124.
35 Li L, Vlisides PE. Ketamine: 50 years of modulating the mind. *Front Hum Neurosci* 2016; **10:** 612.
36 Himmelseher S, Durieux ME. Ketamine for perioperative pain management. *Anesthesiology* 2005; **102:** 211–20.