DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Monday December 11, 2017
1800 HOURS

LOCATION:
Pan Chancho Restaurant
44 Princess Street

PRESENTING ARTICLES:
Dr. Asad Mir-Ghassemi & Dr. Alaa Sabbahi

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SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

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, Hilary 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

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

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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. 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

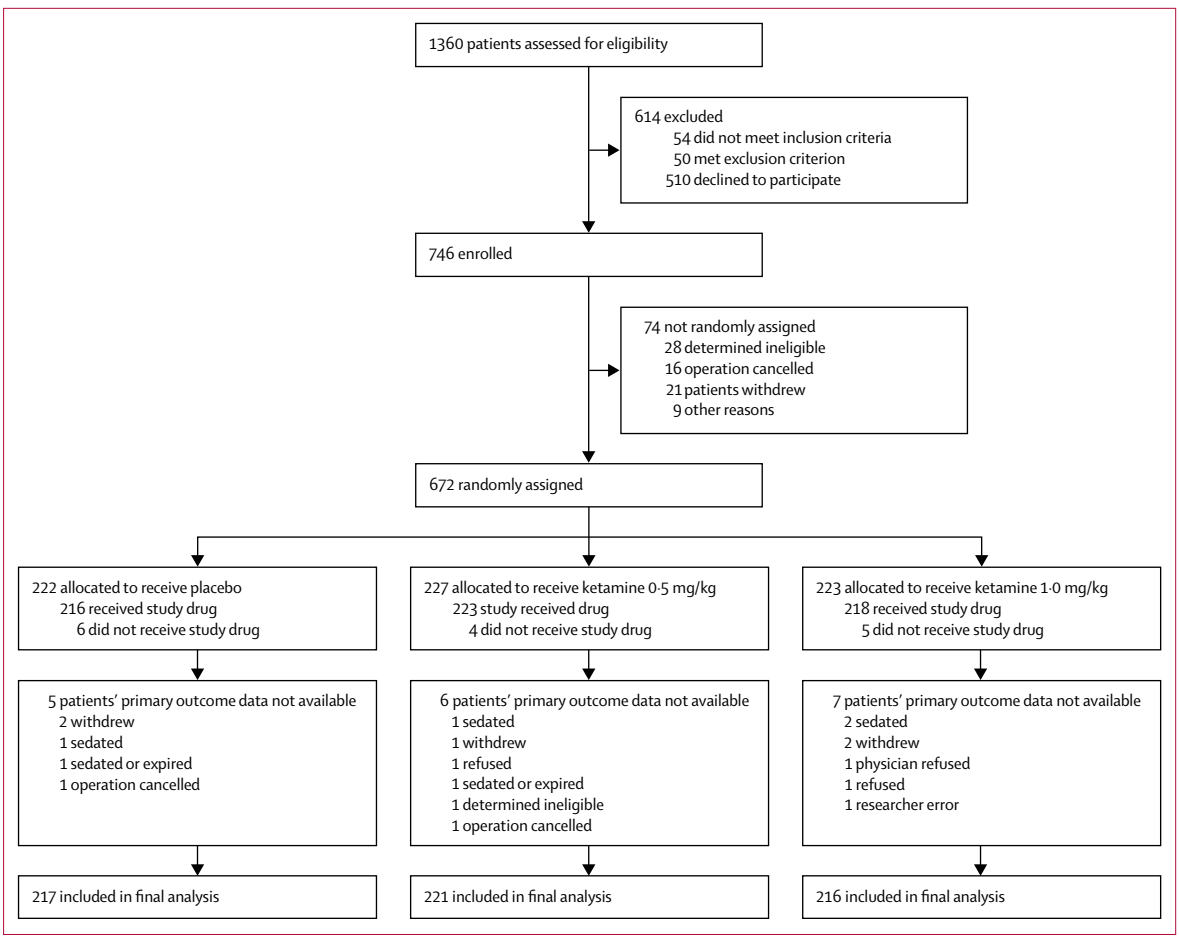

***Figure*: CONSORT flow diagram of participants**
Reasons for not receiving drug were: i) Placebo group—1 provider refused, 4 researcher/provider errors, 1 no reason was given; ii) ketamine 0·5 mg/kg group—3 researcher/provider errors, 1 provider refused; iii) 4 researcher/provider errors, 1 patient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

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Declaration of interests
We declare no competing interests.

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JAMA Surgery | Original Investigation

Effect of a Modified Hospital Elder Life Program on Delirium and Length of Hospital Stay in Patients Undergoing Abdominal Surgery
A Cluster Randomized Clinical Trial

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IMPORTANCE Older patients undergoing abdominal surgery commonly experience preventable delirium, which extends their hospital length of stay (LOS).

OBJECTIVE To examine whether a modified Hospital Elder Life Program (mHELP) reduces incident delirium and LOS in older patients undergoing abdominal surgery.

DESIGN, SETTING, AND PARTICIPANTS This cluster randomized clinical trial of 577 eligible patients enrolled 377 older patients (≥65 years of age) undergoing gastrectomy, pancreaticoduodenectomy, and colectomy at a 2000-bed urban medical center in Taipei, Taiwan, from August 1, 2009, through October 31, 2012. Consecutive older patients scheduled for elective abdominal surgery with expected LOS longer than 6 days were enrolled, with a recruitment rate of 65.3%. Participants were cluster randomized by room to receive the mHELP or usual care.

INTERVENTIONS The intervention (implemented by an mHELP nurse) consisted of 3 protocols administered daily: orienting communication, oral and nutritional assistance, and early mobilization. Intervention group participants received all 3 mHELP protocols postoperatively, in addition to usual care, as soon as they arrived in the inpatient ward and until hospital discharge. Adherence to protocols was tracked daily.

MAIN OUTCOMES AND MEASURES Presence of delirium was assessed daily by 2 trained nurses who were masked to intervention status by using the Confusion Assessment Method. Data on LOS were abstracted from the medical record.

RESULTS Of 577 eligible patients, 377 (65.3%) were enrolled and randomly assigned to the mHELP (n = 197; mean [SD] age, 74.3 [5.8] years; 111 [56.4%] male) or control (n = 180; mean [SD] age, 74.8 [6.0] years; 103 [57.2%] male) group. Postoperative delirium occurred in 13 of 196 (6.6%) mHELP participants vs 27 of 179 (15.1%) control individuals, representing a relative risk of 0.44 in the mHELP group (95% CI, 0.23-0.83; P = .008). Intervention group participants received the mHELP for a median of 7 days (interquartile range, 6-10 days) and had a shorter median LOS (12.0 days) than control participants (14.0 days) (P = .04).

CONCLUSIONS AND RELEVANCE For older patients undergoing abdominal surgery who received the mHELP, the odds of delirium were reduced by 56% and LOS was reduced by 2 days. Our findings support using the mHELP to advance postoperative care for older patients undergoing major abdominal surgery.

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Invited Commentary
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Supplemental content

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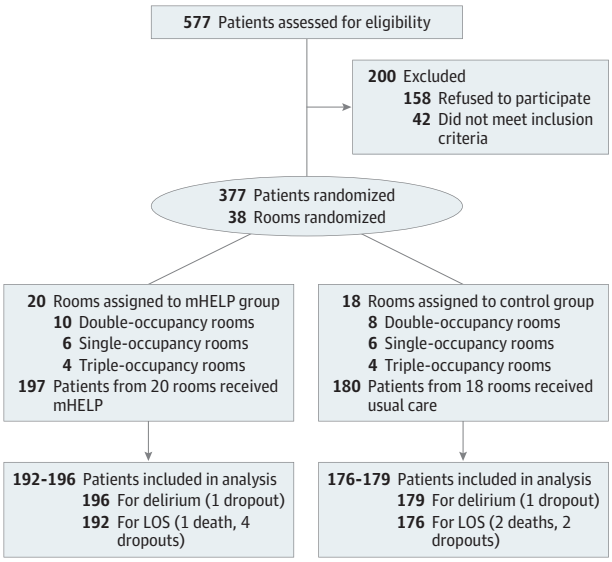
Patients undergoing abdominal surgery often develop delirium, which greatly influences their postoperative course of clinical recovery and length of hospital stay (LOS).[1-3] Delirium affects 13% to 50% of patients undergoing noncardiac surgery,[4] and the health care costs attributable to delirium are more than $164 billion per year in the United States.[5,6] Older surgical patients (≥65 years of age) have a particularly high risk for developing delirium, with detrimental effects on their recovery.[6] Delirium has been associated with alterations in cholinergic activity, inflammatory processes induced by neural signaling, and excessive depth of anesthesia and sedation.[7,8] Delirium may also be precipitated by factors such as infection, malnutrition, electrolyte and fluid imbalances, anemia, and social isolation.[4,9,10] Nevertheless, 30% to 40% of cases of delirium are preventable[11]; thus, implementing effective interventions to prevent incident delirium and reduce LOS is a clinical priority.

We hypothesized that delirium and LOS would be reduced by protocols such as orienting communication (ie, orientation and engaged conversation), oral and nutritional assistance (ie, brushing teeth, oral-facial exercise, and postoperative dietary education), and early mobilization.[12-14] These protocols, initially developed in 2008, were modified from the Hospital Elder Life Program (HELP), which is cost-effective and has been disseminated widely.[15-17] Our unique innovation was to select 3 core protocols and allow them to be delivered during daily care by trained nursing staff for feasibility and scalability.[12] For this cluster randomized clinical trial (RCT), we evaluated the effects of the modified Hospital Elder Life Program (mHELP) on delirium incidence and LOS in a sample of older patients (≥65 years of age) undergoing major elective abdominal surgery, primarily for resection of malignant tumors. As a subgroup analysis, effects were stratified by type of abdominal surgery.

Figure 1. CONSORT Flow Study Diagram



LOS indicates length of stay; mHELP, modified Hospital Elder Life Program.

Key Points

Question Does a modified Hospital Elder Life Program reduce incident delirium and hospital length of stay in patients undergoing abdominal surgery?

Findings In this cluster randomized clinical trial of 377 older patients undergoing elective abdominal surgery, postoperative delirium occurred in fewer patients in the intervention group than in the control group. Hospital length of stay was also significantly shorter in the intervention group.

Meaning The modified Hospital Elder Life Program strongly may benefit older patients undergoing abdominal surgery, with significant reduction of delirium incidence and hospital length of stay.

Methods

Although cluster randomization is less efficient than individual randomization because outcomes can be correlated between clusters (often reflected as the intraclass correlation [ICC]),[18] this design minimizes contamination among participants in different groups by ensuring that all participants in one room belong to the same group. Physicians and hospital staff (surgeons, residents, and nurses) at the study site were aware of a pending nursing intervention study but were masked to study hypothesis, group allocation, and specific protocols of mHELP. Moreover, outcome assessors were masked to group assignment, and room assignments were rerandomized every 20 patients to minimize potential unmasking of the randomization scheme. The trial protocol can be found in Supplement 1. This cluster RCT was approved by the Research Ethics Review Committee at the National Taiwan University Hospital and registered at clinicaltrials.gov.

Patient Selection

Consecutive older patients (≥65 years of age) admitted to two 36-bed gastrointestinal wards of a 2000-bed urban medical center in Taipei, Taiwan, were screened for enrollment from August 1, 2009, through October 31, 2012. Patients were enrolled if they met 2 criteria: scheduled for elective abdominal surgery and expected LOS longer than 6 days. Participants were cluster randomized to groups with an allocation ratio of 1:1 based on a computer-generated list. Cluster randomization by room was necessary because most patient units in Taiwan are double- or triple-occupancy rooms, threatening cross-contamination if patients were individually randomized. This randomization approach was facilitated by both gastrointestinal wards having the same layout: 6 single-occupancy rooms (3 each randomly assigned to the control and mHELP groups), 9 double-occupancy rooms (4 randomly assigned to the control group and 5 to the mHELP group), and 4 triple-occupancy rooms (2 randomly assigned to each group) (**Figure 1**). Participants in the 38 rooms formed 318 clusters during the 3-year study period. Written informed consent was obtained for every participant in the study, and all study data were deidentified.

Intervention and Usual Care

The intervention (mHELP) was implemented by a trained mHELP nurse (registered nurse who had 2 years of medical-surgical experience and who was trained on site for 1 month before the intervention start)[12] who did not assess any outcomes. The intervention consisted of the daily hospital-based mHELP comprising 3 core nursing protocols: orienting communication, oral and nutritional assistance, and early mobilization (eAppendix 1 in Supplement 2).[12] In addition to usual perioperative care (eAppendix 2 in Supplement 2), participants received all 3 mHELP protocols postoperatively as soon as they arrived in the inpatient ward, immediately after interim intensive care stays, and until hospital discharge. All protocols were tracked daily with adherence rated on a Likert-type scale from 0 (no adherence) to 3 (full implementation and adherence).

Usual care consisted of standard hospital care provided by surgeons, residents, nurses, and physical therapists (as needed) in the general surgery wards. All participants were encouraged to ambulate and did so as tolerated. The mHELP nurses did not provide services to participants assigned to the control group. However, the same attending physicians provided care to participants in the mHELP and control groups.

Study Data

Two outcome assessors specially trained for delirium assessment collected outcome data from Monday through Saturday. Presence of delirium was assessed by the Confusion Assessment Method[19] based on a brief daily cognitive screen and interview to rate 4 core delirium symptoms. Participants were considered to have delirium if they had the first (acute onset and fluctuating course) and second (inattention) core symptoms and the third (altered consciousness) or fourth (disorganized thinking) symptom. The Confusion Assessment Method is a widely used, standardized method for identifying delirium that has a sensitivity of 94% (95% CI, 91%-97%) and a specificity of 89% (95% CI, 85%-94%) compared with clinical expert ratings and an interrater reliability of 0.70 to 1.00.[20] Changes in mental status were also solicited from family members or nurses. The outcome assessors did not communicate with the mHELP nurses and were masked to participants' intervention status.

Patient characteristics obtained from in-person interviews included age, sex, and educational level. Baseline clinical factors included presurgical Charlson comorbidity index (higher scores indicate greater mortality risk),[21] presurgical cognitive status measured using the Mini-Mental State Examination (score range, 0-30; 30 indicates no impairment),[22] functional status measured using the Barthel Index (score range, 0-100; 100 indicates total independence),[23] nutritional status measured using the Mini-Nutritional Assessment (score range, 0-30; 30 indicates normal status),[24] and depressive status measured using the Geriatric Depression Scale Short Form (score range, 0-15; 15 indicates depression).[25] Other clinical data abstracted from medical records included diagnosis (gastric cancer, pancreatic or periampullary cancer, colorectal cancer, or other), malignant tumor (yes/no), tumor stage (0 to IV), type of surgery (total or subtotal gastrectomy; right hemicolectomy; left hemicolectomy, lower anterior resection, or anterior resection; pancreaticoduodenectomy; or other), duration of surgery (minutes), laparoscopic surgery (yes/no), intensive care unit (ICU) admission (yes/no), and length of ICU stay (days). The LOS data were abstracted from the medical record at discharge.

Statistical Analysis

Data were analyzed using an intention-to-treat approach. All analyses were performed with SAS statistical software, version 9.3 (SAS Institute Inc) and R software, version 3.2.1 (R Foundation for Statistical Computing). Sample characteristics were compared by treatment group at baseline. Data were reported as number (percentage), mean (SD), or median (interquartile range [IQR]) when not normally distributed.

An important feature of cluster RCTs is the extent of within-cluster correlation for end points. The ICC, defined as the ratio of between-cluster variance to total variance, refers to the proportion of variance attributed to the cluster level. The ICC and its 95% CI were calculated for each outcome using the ICCest function in the R software ICC, which adopted the variance components from a 1-way analysis of variance for the calculation.[26] Of note, all ICCs for each outcome (eAppendix 3 in Supplement 2) were not significantly different from 0 and some were even less than 0, suggesting that the true ICCs are small and adjustment for cluster effect is not indicated.[27] We thus analyzed treatment effects using standard statistical methods not accounting for within-cluster correlation. Kaplan-Meier analysis and the log-rank test were further used to compare the cumulative incidence of delirium, defined as the probability that delirium would develop during hospitalization, between study groups. All statistical tests were 2-tailed, and $P < .05$ was considered to indicate statistical significance. To correct for multiple comparisons, the significance of the intervention effect for each of the 5 surgical types was assessed at Bonferroni-corrected $P = .01$ (0.05/5).[28]

Results

Of 577 eligible patients, 377 (65.3%) were enrolled and randomly assigned to the mHELP (n = 197; mean [SD] age, 74.3 [5.8] years; 111 [56.4%] male) or control (n = 180; mean [SD] age, 74.8 [6.0] years; 103 [57.2%] male) group (Figure 1 and **Table 1**).[29] The mHELP and control groups did not differ significantly in terms of any baseline characteristics, including presurgical cognitive status or other functional measures. The primary indication for surgery was malignant tumor (178 [90.4%] for the mHELP group vs 165 [91.7%] for the control group; $P = .64$).

Intervention Adherence

Participants and family caregivers reported positive perceptions of the mHELP protocols. The median start time of the intervention protocols was postoperative day 1 (IQR, 1-3 days), with 120 of 196 participants (61.2%) starting by postoperative day 1 and 173 participants (88.3%) receiving mHELP components no later than postoperative day 3. The reason for the de-

Table 1. Participants' Baseline Characteristics by Group[a]

Characteristic	mHELP (n = 197)	Control (n = 180)	*P* Value[b]
Age, mean (SD), y	74.3 (5.8)	74.8 (6.0)	.38
Male sex	111 (56.4)	103 (57.2)	.95[c]
Educational level			
Illiterate	25 (12.7)	29 (16.1)	.54[c]
Elementary or middle school	90 (45.7)	84 (46.7)	
High school and above	82 (41.6)	67 (37.2)	
Presurgical Charlson comorbidity index, mean (SD)	1.6 (1.9)	1.5 (1.7)	.83
Presurgical Charlson comorbidity index			
0	67 (34.0)	59 (32.8)	.55[c]
1	49 (24.9)	51 (28.3)	
≥2	81 (41.1)	70 (38.9)	
Presurgical scores, mean (SD)			
Cognitive MMSE[d]	27.0 (3.8)	26.8 (3.1)	.61
Functional BI[e]	97.1 (10.1)	97.7 (6.2)	.50
Nutritional MNA[f]	24.7 (3.7)	24.5 (3.9)	.70
Depressive GDS[g]	2.5 (2.6)	2.7 (2.8)	.49
Diagnosis			
Gastric cancer	39 (19.8)	41 (22.8)	.78[c]
Pancreatic or periampullary cancer	28 (14.2)	24 (13.3)	
Colorectal cancer	111 (56.4)	102 (56.7)	
Other[h]	19 (9.6)	13 (7.2)	
Malignant tumor	178 (90.4)	165 (91.7)	.64[c]
Tumor stage[i]			
0	2 (1.1)	6 (3.6)	.24[c]
I	45 (25.3)	52 (31.5)	
II	54 (30.3)	35 (21.2)	
III	49 (27.5)	51 (30.9)	
IV	28 (15.7)	21 (12.7)	
Type of surgery[j]			
Total or subtotal gastrectomy	43 (21.9)	43 (24.0)	.52[c]
Right hemicolectomy	32 (16.3)	32 (17.9)	
Left hemicolectomy, LAR, or AR	67 (34.2)	67 (37.4)	
Pancreaticoduodenectomy	25 (12.8)	21 (11.7)	
Other[k]	29 (14.8)	16 (8.9)	
Duration of surgery, median (IQR), min	195 (105)	213 (98)	.10
Laparoscopy	84 (42.6)	93 (51.6)	.10[c]
ICU admission after surgery	100 (50.8)	98 (54.4)	.47[c]
Length of ICU stay, mean (SD), d	2.8 (6.5)	2.4 (3.8)	.58

Abbreviations: AR, anterior resection; BI, Barthel Index; GDS, 15-item Geriatric Depression Scale; ICU, intensive care unit; IQR, interquartile range; LAR, lower anterior resection; mHELP, modified Hospital Elder Life Program; MMSE, Mini-Mental State Examination; MNA, Mini-Nutritional Assessment.

[a] Data are presented as number (percentage) of study participants unless otherwise indicated.

[b] Significance was determined by Mann-Whitney test unless otherwise indicated.

[c] Significance determined by χ^2 test.

[d] Scores range from 0 to 30, with higher scores indicating better cognitive status.

[e] Scores range from 0 to 100, with higher scores indicating better independence in activities of daily living.

[f] Scores range from 0 to 30, with higher scores indicating better nutritional status.

[g] Scores range from 0 to 15, with higher scores indicating more depressive symptoms.

[h] Diagnoses included splenic tumor, mesothelioma, gastrointestinal stromal tumor, pseudomyxoma peritonei duodenum tumor, distal common bile duct tumor, pancreatic tumor, colon poly, and fistula.

[i] n = 178 for the mHELP group and 165 for the control group.

[j] n = 196 for the mHELP group and 179 for the control group.

[k] Open splenectomy, transverse colon partial resection, Hartmann procedure with adhesiolysis and bladder lithotripsy, abdominoperineal resection, or laparoscopic debulking surgery.

lay in the remaining 23 participants (11.7%) receiving mHELP components later than postoperative day 3 was that their ICU stay was prolonged beyond 3 days. Nevertheless, overall adherence to the protocols was good; 166 participants (84.3%) had mean scores of 2 or higher (range, 0-3), indicating moderately good adherence. Mean adherence scores for orienting communication and early mobilization were slightly higher than for oral and nutritional assistance (2.6 and 2.5 vs 2.3). In total, participants in the mHELP group received a median of 7 days (IQR, 6-10 days) of the mHELP protocols, and the mean (SD) time spent with each participant per session was 34.1 (16.0) minutes (median, 30 minutes; IQR, 25-40 minutes). No adverse events or unintended effects were reported as intervention related in the mHELP group.

Effects on Delirium

During hospitalization, 40 cases (10.6%) of incident delirium occurred in both groups. In the group that received mHELP, delirium developed in 13 cases (6.6%), whereas the control group had 27 cases (15.1%) (**Table 2**). These differences were statistically significant with a relative risk of 0.44 for delirium (95% CI, 0.23-0.83; $P = .008$), demonstrating a risk reduction of 56%. In absolute terms, the number of cases needed to treat to prevent 1 case of delirium was 11.8. The mHELP also had significant effects for cumulative incidence of delirium ($\chi^2 = 5.87$, $P = .02$) (**Figure 2**). Stratified by surgical type, participants who underwent total or subtotal gastrectomy and received mHELP had reduced delirium (1 [2.3%] in the mHELP group vs 8 [18.6%] in the control group; $P = .03$).

Table 2. Delirium and Length of Hospital Stay Outcomes

Characteristic	mHELP	Control	*P* Value[a]
Delirium, No./total No. (%)[b]	13/196 (6.6)	27/179 (15.1)	.008[c]
Total or subtotal gastrectomy	1/43 (2.3)	8/43 (18.6)	.03[d]
Right hemicolectomy	1/32 (3.1)	2/32 (6.3)	>.99[d]
Left hemicolectomy, LAR, or AR	6/67 (9.0)	10/67 (14.9)	.43[d]
Pancreaticoduodenectomy	2/25 (8.0)	6/21 (28.6)	.12[d]
Other[d]	3/29 (10.3)	1/16 (6.3)	>.99[d]
Length of stay, median (IQR), d[e]	12.0 (6)	14.0 (9)	.04
Total or subtotal gastrectomy	12.0 (5)	18.0 (17)	<.001
Right hemicolectomy	12.0 (4)	13.0 (5.5)	.12
Left hemicolectomy, LAR, or AR	12.0 (6)	12.0 (5)	.79
Pancreaticoduodenectomy	16.0 (12)	25.5 (25)	.28
Other[f]	12.0 (15)	13.5 (7.5)	.95

Abbreviations: AR, anterior resection; IQR, interquartile range; LAR, lower anterior resection; mHELP, modified Hospital Elder Life Program.

[a] Significance was determined by Mann-Whitney test unless indicated otherwise. Significance of the intervention effect for each of the 5 surgical types was assessed at the Bonferroni-corrected *P* value of .01 (0.05/5).

[b] n = 196 for the mHELP group and 179 for the control group.

[c] Significance determined by χ^2 test.

[d] Significance determined by Fisher exact test.

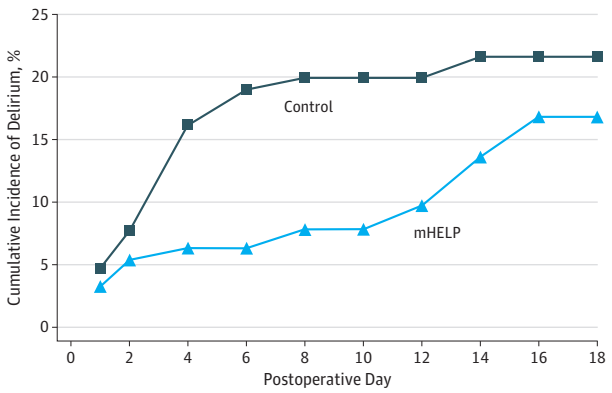
[e] n = 192 for the mHELP group and 176 for the control group.

[f] Procedures such as open splenectomy, transverse colon partial resection, Hartmann procedure with adhesiolysis and bladder lithotripsy, abdominoperineal resection, and laparoscopic debulking surgery.

Effects on LOS

The mHELP and control groups differed significantly in median LOS (12.0 vs 14.0 days; *P* = .04) (Table 2). Stratified by surgical type, participants who underwent total or subtotal gastrectomy had significantly shorter LOS (12.0 vs 18.0 days; *P* < .001) with mHELP. Delayed implementation of mHELP components in 23 participants (11.7%) was attributable to a prolonged ICU stay of 3 days or longer. In this mHELP subgroup, delirium incidence was lower than that in the control subgroup (4 of 23 [17.4%] vs 6 of 20 [30.0%]), a difference that did not reach significance (*P* = .47). Moreover, LOS did not differ significantly between these subgroups (21.0 vs 21.0 days; *P* = .80).

Figure 2. Cumulative Incidence of Delirium by Group



The cumulative incidence of delirium was defined as the probability of the development of delirium during hospitalization. Data on patients were censored at the time of discharge or death. The difference between the groups was significant (χ^2 = 5.87; *P* = .02 by the log-rank test). Because of the smaller sample sizes, the figure does not extend beyond 18 days. mHELP indicates modified Hospital Elder Life Program.

Discussion

The mHELP strongly benefitted older patients undergoing abdominal surgery for resection of malignant tumor, with significant reduction of delirium incidence by 56% and hospital LOS by 2 days. As shown in Figure 2, development of delirium is not only delayed but also reduced for patients who received mHELP. Stratified by surgical type, patients who underwent gastrectomy benefited more from mHELP, with a 6-day shorter LOS than in the control group (12.0 vs 18.0 days; *P* < .001). This subgroup also experienced a trend toward reduced delirium incidence. The mechanism for this greater benefit in patients undergoing gastrectomy is unclear, requiring further research to understand factors that may magnify or attenuate the mHELP effects and to define the effect of mHELP in various surgical procedures.

Consistent with our RCT findings, a 14-study meta-analysis[17] found that multicomponent, nonpharmacologic interventions including at least 2 to 6 components (ie, cognition, mobilization, hydration, hearing, vision, and sleep-wake cycle) in 4 randomized or matched trials (mostly medical inpatients; one focusing on surgical patients) effectively reduced incident delirium by 44% with a trend toward reducing LOS. The mHELP targets similar components (orienting communication, oral and nutritional assistance, and early mobilization) with a unique extension to brushing teeth and oral-facial exercise to improve dry mouth and swallowing efficacy, thus facilitating oral intake. We postulated that increasing older patients' attention to and engagement with the postoperative recovery environment,[30] increasing their swallowing efficacy and nutritional and fluid repletion,[23,26,31] and augmenting physical activity[32,33] would prevent delirium and reduce LOS. Future research is needed to elucidate the mechanisms of the intervention effect; possible research areas include neu-

ropsychological measures, such as executive functioning and attention; physiology of swallowing efficacy; nutritional and fluid parameters; or inflammatory markers.

We note that other delirium prevention approaches for older hospitalized adults have included proactive geriatric consultation,[34] training family members,[35,36] sustained education,[37-39] and single-component interventions, such as bright light, music therapy, and use of software to detect medications that may cause delirium.[40] Not all studies[35,36,38,39,41] included surgical patients or documented efficacy in reducing delirium incidence. An important issue noted by researchers in most of these studies[35,39,41] was that assuring adherence to the interventions was a key factor for success and was not always achievable across settings.[41]

Indeed, the 3 mHELP protocols might seem commonsensical, yet the key to their effectiveness may lie in their consistent daily application.[42] In this study, we had a full-time-equivalent trained mHELP nurse to consistently deliver all 3 protocols to 196 patients, spending approximately 30 minutes with each patient daily. Thus, with an additional 30 minutes of nursing time per older patient, mHELP reduced delirium by 56% and shortened LOS by 2 days, which will greatly reduce medical costs. By extrapolation, older patients in the United States had 7.96 million surgical hospital stays in 2012, with a mean cost of $11 600 per stay.[43] Thus, mHELP could have prevented approximately 674 576 cases of delirium in the surgical service in 2012, resulting in a Medicare cost savings of approximately $10 000 per case[44] or $6.7 billion for the year.[4,5] By cutting 2 days from LOS (of 14 days in controls; a 14% reduction), implementation of mHELP could have saved $1624 per hospital stay or $12.9 billion per year in Medicare costs for the hospital stay.

Limitations

Several caveats about this study are worthy of comment. First, we did not adjust for the cluster effect because of very small ICCs, indicating weak between-cluster correlations for each outcome. To gain efficiency, future trials may use individual randomization instead of cluster randomization. Second, with a sample size of 377, post hoc analysis indicated that our study was powered at 81% for delirium and 80% for LOS to detect group differences as a whole but was underpowered for subgroup analyses by surgical type. Third, 9 of 377 participants (2.4% attrition rate, including 3 deaths and 6 dropouts) had missing outcome values, which might have biased the study findings. However, this bias was likely minimized by attrition rates not differing significantly between the intervention and control groups (2.5% vs 2.2%). Fourth, participants from both groups received care from the same surgeons and nurses; that is, some participants in the control group may have received mHELP components through crossover (contamination) effects. However, the effect of this contamination would have underestimated the mHELP effects. Fifth, we did not collect data on postoperative complications, which are important risk factors for delirium and might have also been affected by mHELP and contributed to the study findings. Sixth, our trial was conducted without an enhanced recovery after surgery (ERAS) program that involved epidural or regional anesthesia, minimally invasive techniques, fluid and pain management, and aggressive postoperative rehabilitation.[45] Although this omission may limit generalizability to centers using ERAS, mHELP may still present important advantages. For medical centers unable to initiate a full ERAS program, mHELP may be considered to be a useful starting point to advance care for vulnerable older patients. Moreover, for centers with ERAS already implemented, mHELP provides feasible, structured, postoperative care protocols that target cognition, nutrition, and ambulation to augment the ERAS program and enhance recovery.

Conclusions

Delirium, which is recognized as the most common surgical complication in older patients, has been associated with increased morbidity and mortality, prolonged hospital stays, higher medical costs, and greater likelihood of institutionalization.[6,46] Older patients undergoing major abdominal surgery for resection of malignant tumor had markedly reduced rates of incident delirium and shorter LOS when they received mHELP, which included 3 nurse-administered protocols: orienting communication, oral and nutritional assistance, and early mobilization. The key to the effectiveness of the 3 mHELP components is their consistent and daily application, with high adherence rates.[42] Medical centers that want to advance postoperative care for older patients might consider mHELP as a highly effective starting point for delirium prevention.

ARTICLE INFORMATION

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Invited Commentary

Interventions to Reduce Postoperative Delirium
Aligning Surgical Care With Patients' Needs and Priorities

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In this issue of *JAMA Surgery*, Chen and colleagues[1] report a cluster randomized clinical trial of a modified Hospital Elder Life Program encompassing multicomponent nonpharmacologic interventions to reduce postoperative delirium in older adults undergoing major abdominal surgery. The interventions include orienting communications, oral and nutritional assistance, and early mobilization in addition to usual postoperative care, together requiring 30 additional minutes of care per day yet significantly reducing the incidence of postoperative delirium and length of hospital stay. The authors report that these simple interventions with minimal risk can have profound effects that are scalable and may be easily incorporated into existing postoperative protocols.

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Delirium affects 13% to 50% of surgical patients and is estimated to cost $152 billion per year in the United States.[2,3] Postoperative delirium is associated with increased length of hospital stay, rates of nonhome discharge, and mortality rates.[3] Furthermore, delirium can affect postoperative function and long-term prognosis in addition to leading to a substantially higher risk of persistent cognitive decline and the development of dementia and depression.[4] Cognitive impairments affect the ability to care for oneself, restrict social functioning, and decrease decision-making capacity. Most recently, Pusswald et al[5] reported an association between self-reported impairments in cognition and reduced health-related quality of life. A significant focus has been made on modifiable factors to improve postoperative outcomes in older adults, yet few studies, at least in the general surgery literature, examine postoperative interventions to reduce the incidence of delirium in this patient population.[6]

This study highlights not only a feasible and effective intervention but also notably outcome measures that are most important to patients. Delirium, subsequent cognitive decline, and potential for dementia are distressing to patients and families, leading to decreased or loss of functional ability (including threatened loss of independent living), depressive symptoms, and poorer quality of life. It is critical that we continue to examine these long-term outcomes of surgery on older adults and find measures to reduce these burdensome effects. Hospital Elder Life Programs have been implemented at more than 200 sites in the United States and worldwide, with an overall reduction in postoperative delirium by 30%.[7] However, this study and most available delirium intervention literature fail to address the surgical intensive care unit patient population. Future studies in these settings are warranted, which may further mitigate the incidence of delirium and its sequelae. Nonetheless, interventions such as these not only reduce health care cost but also improve patient quality of life and address patient priorities that may not be measured by typical surgical quality metrics, such as death and complications. The surgical community should take notice of this important work because it may serve as a cost-effective model for achieving outcomes that are meaningful to surgeons and their patients.

ARTICLE INFORMATION

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