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Pilot Study

PILOT STUDY

Ketamine for postoperative avoidance of depressive symptoms: the K-PASS feasibility randomised trial

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Abstract

Background: Surgical patients with previous depression frequently experience postoperative depressive symptoms. This study's objective was to determine the feasibility of a placebo-controlled trial testing the impact of a sustained ketamine infusion on postoperative depressive symptoms.

Methods: This single-centre, triple-blind, placebo-controlled randomised clinical trial included adult patients with depression scheduled for inpatient surgery. After surgery, patients were randomly allocated to receive ketamine (0.5 mg kg^{-1} over 10 min followed by 0.3 mg kg^{-1} h^{-1} for 3 h) or an equal volume of normal saline. Depressive symptoms were measured using the Montgomery–Asberg Depression Rating Scale. On post-infusion day 1, participants guessed which intervention they received. Feasibility endpoints included the fraction of patients approached who were randomised, the fraction of randomised patients who completed the study infusion, and the fraction of scheduled depression assessments that were completed.

Results: In total, 32 patients were allocated a treatment, including 31/101 patients approached after a protocol change (31%, 1.5 patients per week). The study infusion was completed without interruption in 30/32 patients (94%). In each group, 7/16 participants correctly guessed which intervention they received. Depression assessments were completed at 170/192 scheduled time points (89%). Between baseline and post-infusion day 4 (pre-specified time point of interest), median depressive symptoms decreased in both groups, with difference-in-differences of −1.00 point (95% confidence interval −3.23 to 1.73) with ketamine compared with placebo. However, the between-group difference did not persist at other time points.

Conclusions: Patient recruitment, medication administration, and clinical outcome measurement appear to be highly feasible, with blinding maintained. A fully powered trial may be warranted.

Clinical trial registration: NCT05233566.

Keywords: clinical trial; depression; feasibility trial; ketamine; postoperative depression

Postoperative depressive symptoms are an under-recognised clinical problem. Between 25% and 50% of patients presenting for elective surgery have depression.[1–4] Patients with active symptoms of depression before surgery are most likely to experience depressive symptoms after their surgery.[5–7] However, lifetime history of depression is an independent risk factor for postoperative depressive symptoms, even if symptoms are well controlled before

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surgery.[8,9] Patients who experience depressive symptoms after surgery have increased pain, increased hospital readmissions, and increased mortality.[10–12]

Ketamine is an efficacious agent for treatment of depressive symptoms. The drug's antidepressant effects may be related to *N*-methyl-D-aspartate (NMDA) receptor antagonism, although other molecular targets may contribute.[13–15] Numerous trials enrolling patients with treatment-resistant depression have shown a rapid reduction in depressive symptoms after a 0.5 mg kg^{-1} ketamine bolus, typically delivered over 40 min.[16–19] In the context of surgery with general anaesthesia, peri-induction ketamine boluses have been associated with reduced postoperative depressive symptoms in patients with a history of depression[20–22] but not in a general population of older adults.[23] Although the antidepressant effects of ketamine tend to last a few days,[24] repeated i.v. boluses can produce sustained antidepressant effects.[25,26] This approach is not ideal after surgery because ketamine administration is often not permitted in general surgical units where postoperative recovery occurs. An alternative to repeated dosing would be a sustained infusion before the patient leaves the perioperative care setting. To maximise the expected antidepressant effects, such an infusion may be administered after surgery to avoid concurrent gamma-aminobutyric acid (GABA) agonist medications that are known to decrease the antidepressant effects of ketamine.[27,28] In a pilot study enrolling non-surgical patients with treatment-resistant depression, a sustained infusion of sub-anaesthetic dose ketamine produced reductions in depressive symptom severity lasting several weeks.[29,30] The efficacy of a sustained ketamine infusion to prevent depressive symptoms after surgery in at-risk patients has not been established. The objective of this study was to assess the feasibility of conducting a randomised clinical trial to test this hypothesis.

Methods

Overall trial design

To achieve the study objective, we conducted a single-centre, triple-blind, randomised, placebo-controlled feasibility trial. Participants were randomly allocated on a 1:1 basis to receive ketamine or normal saline placebo after surgery. The trial was conducted at Barnes-Jewish Hospital, a large university-affiliated quaternary referral centre in St. Louis, Missouri, USA. The study protocol was approved by the institutional review board of Washington University in St. Louis (approval #202201107). The trial was registered on clinicaltrials.gov (NCT05233566, first posted 10 February 2022). This report is written in accordance with the CONSORT extension for pilot and feasibility trials.[31]

The trial protocol was revised in August 2022 to increase eligibility and enrolment. In the original published protocol,[32] patients with a history of depression undergoing surgery with planned intensive care unit (ICU) admission were randomly allocated to receive 8 h of ketamine or placebo. This design was chosen because local hospital policy permits ketamine administration in ICUs but not on postoperative wards. However, very few patients were identified who met this inclusion criterion. Therefore, the inclusion criteria were modified to include any patient with a history of depression undergoing major surgery with hospital admission. The infusion duration was reduced to 3 h, and administration was moved to the post-anaesthesia care unit (PACU).

Participants

Before the protocol revision, the inclusion criteria included patients aged ≥18 yr with a history of depression undergoing surgery at Barnes-Jewish Hospital with planned ICU admission. A history of depression was identified either by a diagnosis documented in the electronic health record or by the presence of an antidepressant on the preoperative home medication list (Supplementary material, Appendix A, Text A.1). After the protocol revision, the inclusion criteria included patients aged ≥18 yr with a history of depression undergoing non-ambulatory surgery scheduled for at least 2 h. Exclusion criteria included emergent surgery, bipolar disorder, dementia, known or suspected elevation in intracranial pressure, carotid endarterectomy, arteriovenous malformation repair, subarachnoid haemorrhage, conditions where significant elevation in blood pressure would be hazardous, pregnancy or lactation, allergy to ketamine, concurrent antipsychotic medication, inability to converse in English, or concurrent enrolment in another interventional trial. Although the inclusion criteria did not restrict to certain surgical disciplines, the recruitment strategy involved partnerships with neurosurgery, vascular surgery, and cardiac surgery (i.e. subspecialties expected to have the most ICU admissions). Therefore, the patient population was effectively limited to these subspecialties. Potentially eligible patients were identified by screening the operating room schedule and the anaesthesia preoperative clinic schedule. All participants provided written, informed consent.

Randomisation

After surgery and extubation, participants were randomly allocated on a 1:1 basis to receive either ketamine or normal saline. The randomisation sequence was generated by the investigational pharmacy in blocks of four using random numbers. Participants, clinical care providers (surgeons, anaesthesiologists, nurses), and research staff (including those involved with recruitment and outcome assessment) were blinded to treatment allocation. The appearance of the medication was identical in both groups. The research staff who performed depression assessments were not present during administration of the study medication. To assess blinding, participants were asked 1 day after the infusion to guess whether they had received ketamine or normal saline.

Interventions

The study medication was administered as a bolus loading dose (ketamine 0.5 mg kg^{-1} or equal volume of normal saline) over 10 min, followed by a continuous infusion (ketamine 0.3 mg kg^{-1} h^{-1} or equal rate of normal saline). Doses were calculated using actual body weight. To minimise the GABAergic effects from anaesthetic agents, administration began in the operating room immediately after tracheal extubation. Open-label ketamine was not permitted during or after surgery. Otherwise, all components of the anaesthetic plan were at the discretion of the clinical care team.

Measurements

Before surgery, participants completed surveys including the Generalized Anxiety Disorder 7-item scale (GAD-7),[33] the Alcohol Use Disorders Identification Test (AUDIT),[34] the Drug Abuse Screening Test (DAST-10),[35] and the Childhood

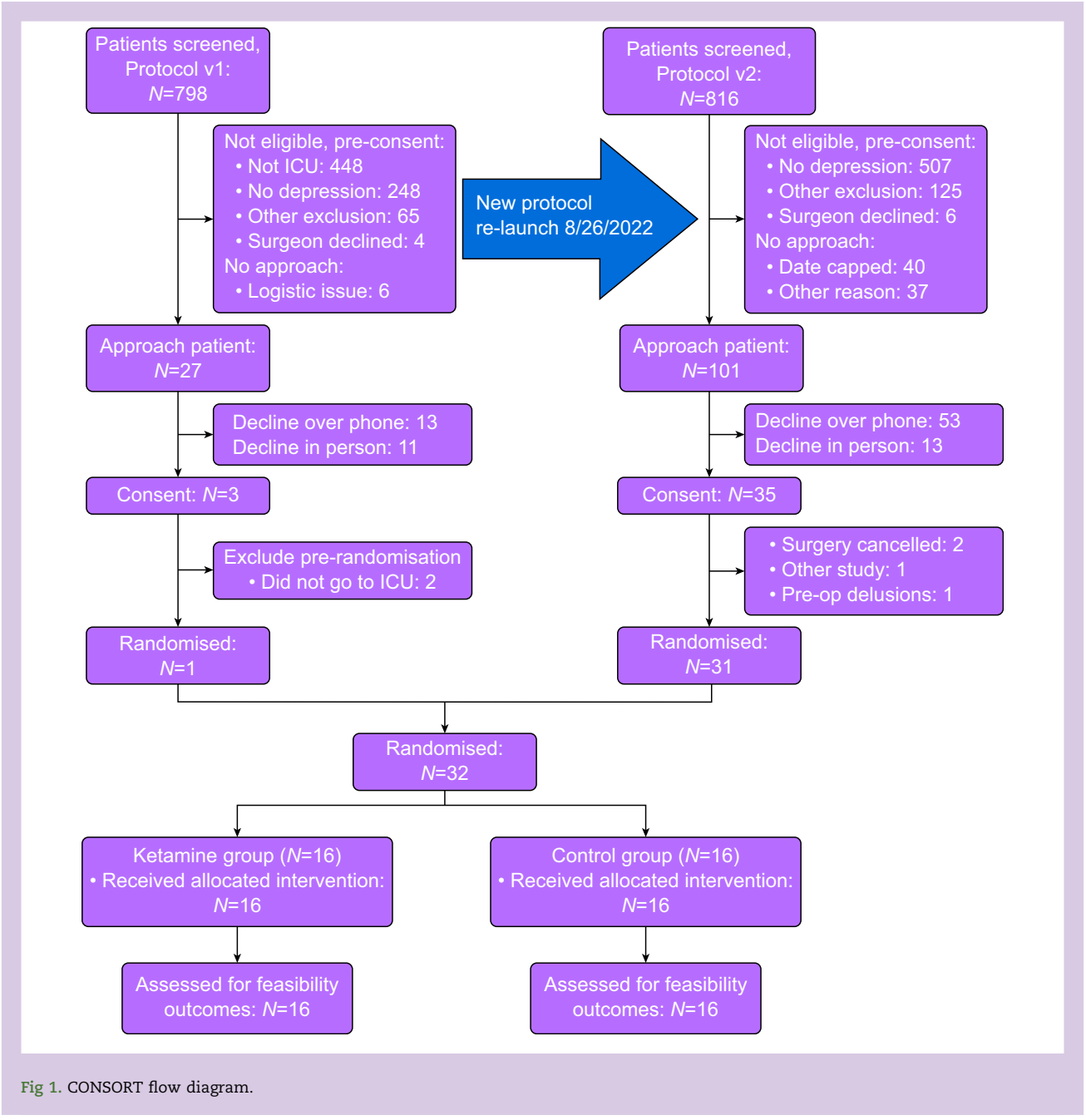

Fig 1. CONSORT flow diagram.

Trauma Questionnaire (CTQ).[36] Midway through the study medication infusion, participants were asked to rate the presence and severity of several side-effects. In addition, research staff assessed participants for psychotomimetic side-effects using the Brief Psychiatric Rating Scale (BPRS) four-item positive symptom subscale[29,37] and a six-item modification of the Clinical Administered Dissociative State Scale (CADSS-6).

Depressive symptoms were measured by trained research staff before surgery and on post-infusion days 1, 2, 4, 7, and 14 using the Montgomery-Asberg Depression Rating Scale (MADRS).[38,39] The MADRS is a validated tool[40] that produces a score between 0 and 60, with higher scores indicating more severe symptoms. MADRS assessment occurred in person if the participant was in the hospital and over the telephone otherwise. The pre-specified primary measure of depressive symptoms was the change in MADRS from baseline to post-infusion day 4.[32]

Pain was assessed concurrently with each MADRS assessment using a 10-cm visual analogue scale and an 11-point numeric rating scale. Participants rated their pain at rest, when taking a deep breath or coughing, and with movement. In addition, the total opioid dose (in oral morphine milligram equivalents) administered between the start of the study

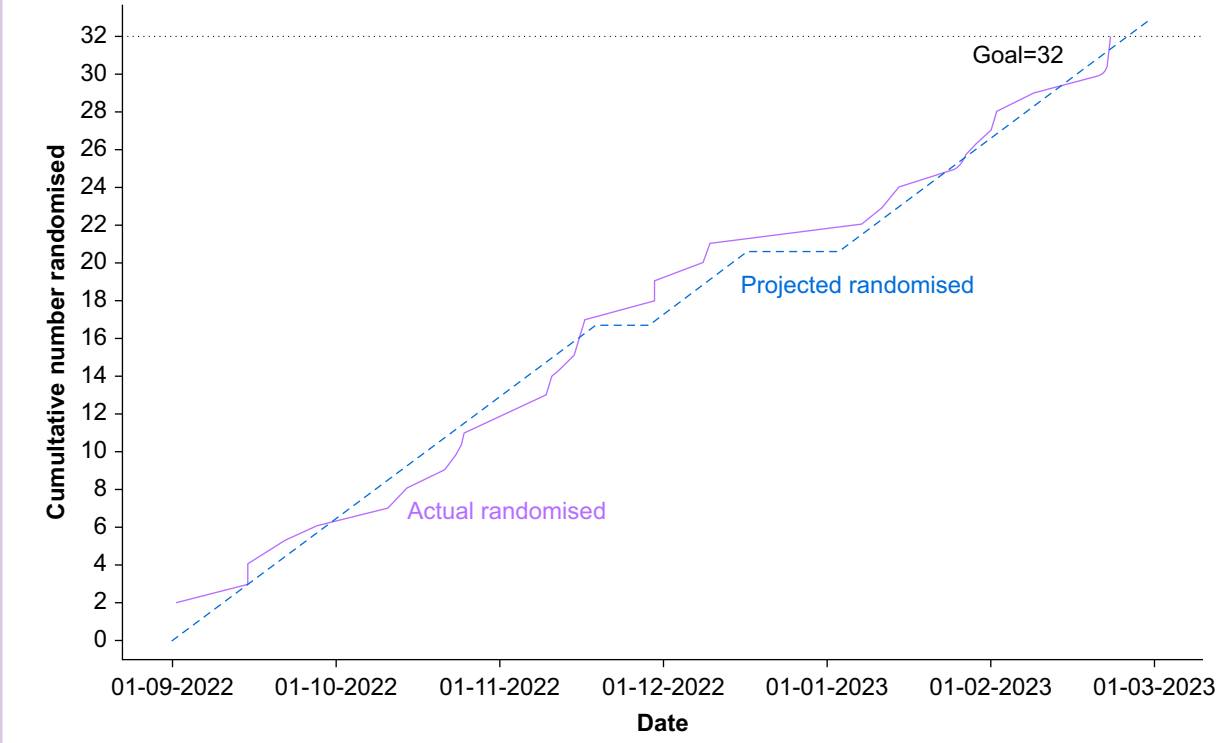

Fig 2. Cumulative number of participants randomised over time under the revised protocol. The 'projected randomised' line shows a rate of 1.5 participants per week, with planned breaks around Thanksgiving and winter holidays.

medication infusion and 07:00 am on post-infusion day 2 was retrieved from the electronic health record.

Limited frontal electroencephalograms were obtained using a wireless dry electrode device (DREEM, Rhythm, New York, NY, USA) before surgery, during the study medication infusion, and during sleep after the infusion. Electroencephalogram findings will be presented separately.

Feasibility outcomes

This trial had three feasibility outcomes: (1) the fraction of patients invited to participate who were enrolled and randomly allocated, (2) the fraction of randomly allocated patients who completed the entire study medication infusion, and (3) the fraction of randomly allocated patients with MADRS assessments at the scheduled time points.

Analytical methods and sample size

Each feasibility outcome was quantified using a proportion and 95% confidence interval (CI). The sample size of 32 was selected to allow the primary descriptive endpoints to be measured with acceptable levels of precision (plus or minus 15% for recruitment rate, plus or minus 10% for medication completion rate, and plus or minus 7% for MADRS completion rate). This feasibility study was not powered to test for a difference in MADRS scores between the ketamine group and the control group, but the change in MADRS score between baseline and post-infusion day 4 was calculated for each patient, and median regression (R package quantreg, Koenker, 2023, https://CRAN.R-project.org/package=quantreg) was used to obtain a point estimate for the difference-in-differences between groups, adjusting for baseline MADRS score. Analysis occurred in R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Recruitment

Recruitment began on 11 April 2022, and the revised protocol took effect 26 August 2022. Recruitment concluded on 17 February 2023 because the target enrolment was achieved. A total of 32 participants were included between 5 May 2022 and 21 February 2023. Follow-up ended on 8 March 2023.

Under the original protocol, one patient was randomly allocated to a group out of 27 approached (3.7%, 95% CI 0.1–19.0%). Two patients consented but were not included because they ultimately were not admitted to the ICU after surgery (Fig 1). Under the revised protocol, 31 patients were randomly allocated to a group out of 101 approached (30.7%, 95% CI 21.9–40.7%). Patients who consented were more likely to be female compared with patients who were approached but did not consent (28/35=80% *vs* 38/66=58%, P=0.04). Patients who consented were also younger than those who were approached but did not consent (median [inter-quartile range, IQR] age 45 yr [37.5–61.5 yr] *vs* 63 yr [53–70 yr], P<0.001). Approximately 1.5 participants were randomly allocated to a group each week (Fig 2). Preoperative depressive symptom severity ranged from asymptomatic to severe (Table 1).

Table 1 Characteristics of participants. ASA, American Society of Anesthesiologists; IQR, inter-quartile range; MADRS, Montgomery–Asberg Depression Rating Scale; SD, standard deviation.

	Ketamine group (*N*=16)	Control group (*N*=16)
Age (yr), mean [range]	47.4 [23–75]	48.5 [23–75]
Height (cm), mean (SD)	169.6 (8.6)	162.2 (11.1)
Weight (kg), mean (SD)	84.5 (16.2)	81.5 (16.0)
Sex, *n* (%)		
Female	11 (69)	15 (94)
Male	5 (31)	1 (6)
Race, *n* (%)		
American Indian/Alaska native	1 (6)	0 (0)
Black or African American	0 (0)	1 (6)
More than one race	0 (0)	1 (6)
White	15 (94)	14 (88)
Ethnicity, *n* (%)		
Not Hispanic	16 (100)	16 (100)
Currently taking oral antidepressant	15 (94)	12 (75)
ASA physical status, *n* (%)		
1	1 (6)	0 (0)
2	8 (50)	9 (56)
3	6 (38)	6 (38)
4	1 (6)	1 (6)
Surgery service, *n* (%)		
Cardiac	1 (6)	1 (6)
Neurosurgery	9 (56)	11 (69)
Vascular	6 (38)	4 (25)
Preoperative MADRS, median [IQR]	14.5 [9–21]	12.5 [6–23.5]
Preoperative MADRS—categorised, *n* (%)		
0–6 (No symptoms)	3 (19)	5 (31)
7–19 (Mild)	6 (38)	5 (31)
20–34 (Moderate)	6 (38)	5 (31)
35–60 (Severe)	1 (6)	1 (6)
Living Situation, *n* (%)		
Alone	2 (12)	3 (19)
With others	14 (88)	13 (81)
Employment status		
Disabled	1 (6)	2 (12)
Homemaker	1 (6)	1 (6)
Other	0 (0)	3 (19)
Retired	3 (19)	5 (31)
Student	1 (6)	0 (0)
Work outside the home	10 (62)	5 (31)
Marital status, *n* (%)		
Divorced	1 (6)	2 (12)
Married	10 (62)	8 (50)
Single	5 (31)	5 (31)
Unknown or not reported	0 (0)	1 (6)
Generalized Anxiety Disorder-7 (GAD-7) Questionnaire	8 [2–13]	8 [3.5–15.5]
Alcohol Use Disorders Identification Test (AUDIT)	1 [0–2]	1 [0–3.5]
Drug Abuse Screening Test (DAST)	0 [0–1]	0 [0–0]
Childhood Trauma Questionnaire		
Emotional Abuse Subscale	7 [5–12]	8 [5–10.5]
Physical Abuse Subscale	6 [5–7]	5 [5–8]
Sexual Abuse Subscale	5 [5–5]	5 [5–11.5]
Emotional Neglect Subscale	6 [5–12]	8.5 [6–11.5]
Physical Neglect Subscale	5 [5–8]	6.5 [5–9]
Total score	37 [29–42]	36.5 [31.5–56]

Study medication administration

The study medication was administered on the day of surgery for 28 out of 32 participants (87.5%), including 15 in the ketamine group and 13 in the control group. Administration was delayed until postoperative day 1 for three participants (all in the control group) and until postoperative day 2 for one participant (who was in the ketamine group) because of ongoing mechanical ventilation. Among the 28 participants who received the study medication on the day of surgery, the median time from tracheal extubation to start of the study medication was 4 min (IQR 2–7 min). Midazolam was administered before surgery to 25 out of 32 participants (78%), including 12 in the ketamine group and 13 in the control group. Other details about anaesthetic technique, such as propofol doses or volatile anaesthetic use, were not collected.

The study medication was administered with no interruptions in 30 out of 32 participants (93.8%, 95% CI 79.9–99.2%), including 15 participants in each group. For one participant in the ketamine group, the infusion was temporarily stopped after about 90 min because they became apnoeic in the PACU: this resolved after the participant received naloxone. This event was reviewed by an independent safety monitor, who classified the event as unlikely to be related to the study medication. For one participant in the control group, the infusion was stopped when the participant had multiple seizures in the neurologic ICU while recovering from brain tumour resection. The participant had a reduced level of consciousness for several days, and the study infusion was never resumed.

Psychotomimetic side-effects as rated by the BPRS and CADSS were rarely reported during the study medication infusion (Table 2). In both groups, the most common patient-reported side-effect was feeling tired or fatigued, followed by foggy thinking and poor concentration. When asked the following day, seven out of 16 participants in the ketamine group and seven out of 16 participants in the control group correctly guessed which treatment they received. One participant in the control group died on postoperative day 13.

Collection of clinical outcomes

Depression assessments using the MADRS were completed at 170 of 192 time points at which they were planned (89%, 95% CI 83–93%, Fig 3). Depressive symptom trajectories are shown for the two groups in Fig 4 and for individual patients in Figure A1 (Appendix A, Supplementary material). Median (IQR) MADRS scores were 14.5 (9–21) at baseline and 4 (2–16) on post-infusion day 4 (the pre-specified time point of interest) in the ketamine group, and they were 12.5 (6–23.5) at baseline and 6 (3.5–12) on post-infusion day 4 in the control group. After adjusting for preoperative MADRS score, the median change in MADRS score from baseline to post-infusion day 4 had a difference between groups of −1.00 points (95% CI −3.23 to 1.73 points) in the ketamine group compared with the control group (Table A1, Appendix A, Supplementary material). In a *post hoc* subgroup analysis of patients with preoperative MADRS score >6 (i.e. at least mild symptoms), the between-group difference was −1.76 points (95% CI −3.63 to 2.77 points; Table A2, Appendix A, Supplementary material).

Pain was measured with the visual analogue scale during 99 of 170 assessments, while the numeric rating scale was completed at 167 of 170 assessments (Fig. A2, Appendix A, Supplementary material). Pain trajectories of individual

Table 2 Participant experiences during infusion. HR, heart rate; IQR, inter-quartile range; PACU, post-anaesthesia care unit; SBP, systolic blood pressure.

	Ketamine group (N=16)	Control group (N=16)	P
Refused or unable to participate in interview, *n* (%)	**0 (0)**	**3 (19)**	
Patient-reported side-effects, *n* (%)			
Dizziness	5 (31)	2 (15)	0.41
Headache	1 (6)	3 (23)	0.30
Palpitations	1 (6)	0 (0)	1.00
Thinking feels foggy	9 (56)	4 (31)	0.26
Trouble with concentration/ memory	7 (44)	3 (23)	0.43
Seeing double	2 (12)	1 (8)	1.00
Nausea	3 (19)	1 (8)	0.61
Vomiting	3 (19)	1 (8)	0.61
Tired or fatigued	12 (75)	10 (77)	1.00
Richmond Agitation and Sedation Scale, *n* (%)			0.55
−1 (Drowsy)	5 (31)	5 (38)	
0 (Alert and calm)	11 (69)	7 (54)	
1 (Restless)	0 (0)	1 (8)	
Clinical Administered Dissociative State Scale—Modified, *n* (%)			0.32
0 (No symptoms)	9 (56)	11 (85)	
1	3 (19)	0 (0)	
2	1 (6)	0 (0)	
3	1 (6)	0 (0)	
4	2 (12)	1 (8)	
6	0 (0)	1 (8)	
Brief Psychiatric Rating Scale—Four-Item Positive Subscale, *n* (%)			
Conceptual disorganisation			0.19
1 (No symptoms)	15 (94)	11 (85)	
2	0 (0)	2 (15)	
3	1 (6)	0 (0)	
Suspiciousness			—
1 (No symptoms)	16 (100)	13 (100)	
Hallucinatory behaviour			0.19
1 (No symptoms)	16 (100)	11 (85)	
2	0 (0)	1 (8)	
3	0 (0)	1 (8)	
Unusual thought content			—
1 (No symptoms)	16 (100)	13 (100)	
Abnormal vital signs during infusion, *n* (%)			
Noteworthy hypertension (SBP>180 or antihypertensive med given)	2 (12)	2 (12)	1.00
Tachycardia (HR>100)	4 (25)	6 (38)	0.70
PACU length of stay (h), median [IQR]	4.0 [3.8–4.9]	5.2 [4.5–9]	0.04
Hospital length of stay (days), median [IQR]	4 [2.5–4]	3 [2.5–4.5]	0.97

patients and of the two randomisation groups at rest, when taking a deep breath or coughing, and with movement are shown in Figures A.3-6, Appendix A, Supplementary material). The cumulative postoperative opioid exposure between the start of the study medication infusion and 07:00 am on post-infusion day 2 was 78.2 (IQR 52.5–219) oral morphine milligram equivalents in the ketamine group and 118 (IQR 32.2–179.5) oral morphine milligram equivalents in the control group.

Discussion

We have demonstrated the feasibility of conducting a randomised clinical trial examining the efficacy of a sustained sub-anaesthetic ketamine infusion to prevent postoperative depressive symptoms in surgical patients with depression. After a protocol revision, participants were recruited and randomised at a rate of 1.5 participants per week. The study medication was administered successfully and was well tolerated by participants. Depressive symptoms were measured at 89% of the planned time points.

Several details of the novel ketamine dosing regimen had important implications for the trial protocol, which in turn impacted recruitment. Unlike many prior investigators, we chose to administer ketamine after surgery rather than intraoperatively because concurrent exposure to other medications may limit ketamine's antidepressant activity. Benzodiazepines reduce the effect of ketamine on depressive symptoms,[27,28] potentially because both drugs act on $GABA_A$ interneurons.[41,42] Other drugs with $GABA_A$ receptor agonism, such as propofol and volatile anaesthetics, may have similar interactions with ketamine, although their impact on ketamine antidepressant activity has not been specifically studied. In addition to postoperative administration, another novel aspect of the intervention was the use of a sustained infusion rather than a single 0.5 mg kg^{-1} bolus. This was expected to result in persistent symptom improvement, as previously seen with a 96-h infusion in patients with treatment-resistant depression.[29] To make a sustained infusion practical in a real postoperative clinical setting, our original protocol called for 8 h of ketamine treatment in the ICU, but recruitment proved poor. Reducing the infusion duration to 3 h allowed us to remove the restrictive inclusion criterion of ICU admission, improving recruitment feasibility and potentially increasing the generalisability of the findings as well.

The study medication was administered safely with minimal side-effects, and participants guessed their treatment allocation with no higher accuracy than chance. Successful maintenance of patient blinding is a major difference from previous ketamine studies. One potential interpretation is that the ketamine dose used in this study was not sufficient to generate noticeable side-effects that would lead to unblinding. This interpretation seems less likely because side-effects such as poor concentration and foggy thinking were reported at clinically meaningfully higher rates in the ketamine group than the control group, even though these differences did not achieve statistical significance. Of note, participants in the ketamine group received a higher total dose (1.4 mg kg^{-1}) compared with patients in most other studies. A second interpretation is that the ketamine group did experience noticeable side-effects, but they were unable to remember the experience when asked to guess their treatment allocation the following day.

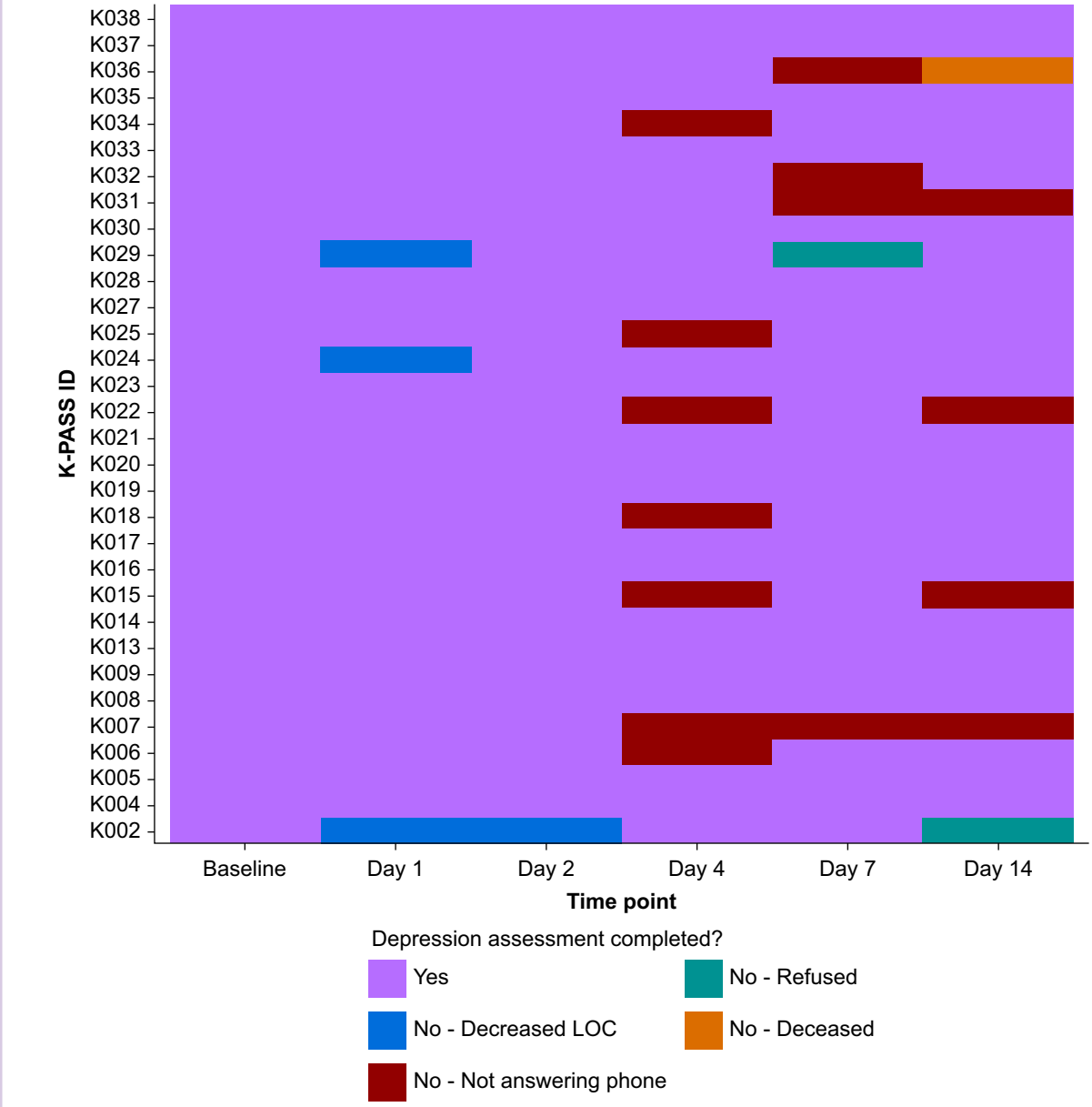

Fig 3. Completion pattern for depression assessments. LOC, level of consciousness.

The patterns of depressive symptoms seen in this study can inform future research. Although this study was not powered to detect a difference in depressive symptoms between the two groups, we observed an encouraging point estimate at the pre-specified time point of post-infusion day 4. The favourable results within the first 4 days must be weighed against the less favourable results at later time points, especially as the sustained ketamine infusion was hypothesised to produce longer-term benefits. Worsening of depressive symptoms was rarely observed, including in the control group. This contrasts with the PODCAST trial, in which 63% of patients who screened positive for depressive symptoms on postoperative day 3 did not screen positive for depressive symptoms before surgery.[23] This motivated the *post hoc* subgroup analysis limited to patients with active depressive symptoms before surgery. The point estimate suggested a stronger effect of ketamine in this subgroup. Therefore, it would be appropriate for a future study to enrol only patients with active depressive symptoms.

This trial has strengths. First, continuous re-evaluation of progress throughout the trial facilitated protocol changes that enhanced feasibility. Second, blinding of patients was maintained more effectively than in many previous trials. Third, loss-to-follow-up rates were low. Fourth, depressive symptoms were measured by experienced staff members using a validated tool. This trial also has some limitations that should be noted. First, this was a feasibility study and was therefore not powered to detect clinically meaningful differences in the

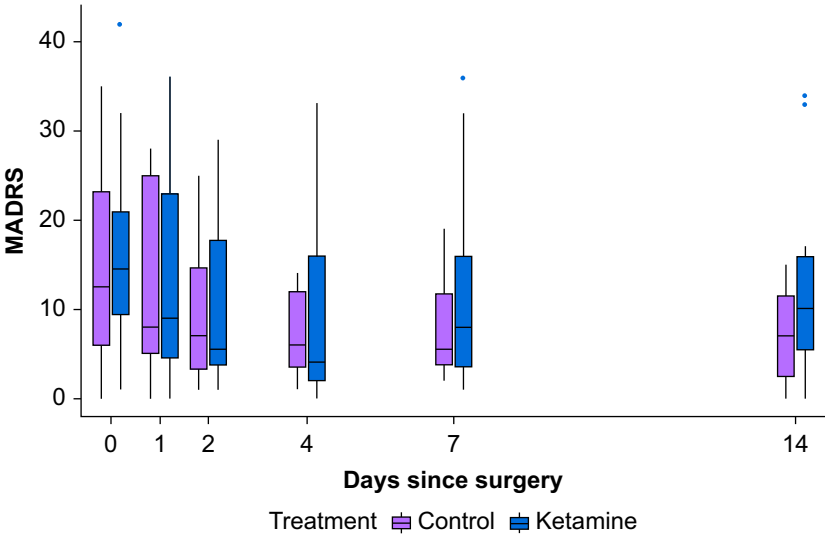

Fig 4. Depressive symptoms in the two treatment groups over time. Horizontal black lines show the median value for each group. Edges of the box represent the upper and lower bounds of the inter-quartile range. Whiskers extend to the minimum and maximum non-outlier values. Dots represent outlier values whose distance from the box edge is more than 1.5 times the group's inter-quartile range. MADRS, Montgomery–Asberg Depression Rating Scale.

depressive symptoms between the two groups. A larger, adequately powered study would be needed to perform that comparison. Second, only one ketamine dosing regimen was evaluated, which prevents evaluation of a dose–response relationship between ketamine and depressive symptoms. Third, details about intraoperative anaesthetic medication selection and dosing were not collected. Fourth, female patients and younger patients were more likely to consent compared with male patients and older patients. Future studies will need to use strategies to ensure all groups of eligible patients are equally represented in the study population. Fifth, this was a single-centre study, which may limit the generalisability of the findings to institutions that have different characteristics.

In conclusion, this study demonstrates that it is feasible to recruit patients with a history of depression undergoing major surgery, to safely administer a sustained infusion of sub-anaesthetic dose ketamine after surgery, and to assess participants for depressive symptoms and pain up to 2 weeks after surgery. Postoperative administration, with a long duration of ketamine exposure and without concurrent use of medications with $GABA_A$ receptor agonist activity, is hypothesised to produce long-lasting reduction in postoperative depressive symptoms. Based on these results, a properly powered clinical trial testing this hypothesis may be warranted.

Authors' contributions

Study conception: BAJ, BRTP, BJAP, JTW, NBF
Study design: BAJ, BRTP, BJAP, JAS, JTW, NBF
Data acquisition: BAF, CD, CH, JAS, LG, WT
Data analysis: BAF, CD, JAS
Initial drafting of the manuscript: BAF
Data interpretation; critical revision for important intellectual content: all authors

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Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2023.100245.

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