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ORIGINAL REPORT

Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain

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ABSTRACT

Purpose
The anesthetic ketamine is widely used for pain related to cancer, but the evidence to support its use in this setting is weak. This study aimed to determine whether ketamine is more effective than placebo when used in conjunction with opioids and standard adjuvant therapy in the management of chronic uncontrolled cancer pain. Ketamine would be considered of net benefit if it provided clinically relevant improvement in pain with limited breakthrough analgesia and acceptable toxicity.

Patients and Methods
In this multisite, dose-escalation, double-blind, randomized, placebo-controlled phase III trial, ketamine or placebo was delivered subcutaneously over 3 to 5 days.

Results
In all, 185 participants were included in the primary analysis. There was no significant difference between the proportion of positive outcomes (0.04; 95% CI, −0.10 to 0.18; $P = .55$) in the placebo and intervention arms (response rates, 27% [25 of 92] and 31% [29 of 93]). Pain type (nociceptive *v* neuropathic) was not a predictor of response. There was almost twice the incidence of adverse events worse than baseline in the ketamine group after day 1 (incidence rate ratio, 1.95; 95% CI, 1.46 to 2.61; $P < .001$) and throughout the study. Those receiving ketamine were more likely to experience a more severe grade of adverse event per day (odds ratio, 1.09; 95% CI, 1.00 to 1.18; $P = .039$). The number of patients needed to treat for one additional patient to have a positive outcome from ketamine was 25 (95% CI, six to ∞). The number needed to harm, because of toxicity-related withdrawal, was six (95% CI, four to 13).

Conclusion
Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard coanalgesics in cancer pain.

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INTRODUCTION

Pain management is a major problem in cancer care,[1] even in developed countries with access to a range of opioids and adjuvant therapies. Analgesic agents must provide net clinical benefit—good pain relief with acceptable levels of toxicity in a defined target population.

The dissociative anesthetic agent ketamine is widely used off label at subanesthetic doses for cancer pain, usually in conjunction with opioids. As a noncompetitive antagonist, ketamine interacts with N-methyl-D-aspartate receptor complexes, interrupts cholinergic transmission, and inhibits the reuptake of noradrenaline and 5-hydroxytryptamine. Evidence to support the use of ketamine in chronic cancer pain has been extrapolated from other settings and has been justified primarily from case series and uncontrolled studies.[2-4]

Cardiac and neurologic toxicities, including emergent phenomena (eg, hallucinations, a sense of disconnection, vivid dreams), have been reported.[5] There is also emerging evidence on the deleterious effect of ketamine on bladder function.[6] In light of these toxicities, definite evidence of clinically significant pain improvement is necessary for ketamine to have sufficient net health and economic benefits.[7]

The aim of this study was to determine whether ketamine, delivered subcutaneously with dose titration over 5 days has greater clinical benefit than placebo, when used in conjunction with opioids and standard adjuvant therapy, in the management of chronic uncontrolled pain related to cancer or its treatment.

PATIENTS AND METHODS

Eligibility and Enrollment

Participants were recruited from 10 palliative care services in a range of metropolitan settings across Australia.[8] Eligible patients were in-patients age 18 years or older. All met the definition of refractory chronic pain secondary to cancer or its treatment[9] with a Brief Pain Inventory (BPI)[10] average pain score of ≥ 3 despite ongoing treatment with opioids and coanalgesics at predefined dose levels (Appendix Table A1, online only). Patients were excluded if they had received ketamine for chronic pain within 6 months, radiotherapy to a site of pain within 2 weeks, any other procedure or therapy likely to affect pain during the trial period, or comorbidities contraindicating the use of ketamine.[11] All participants were formally assessed for cognitive ability to undertake trial requirements (Fig 1).

Interventions

No change in baseline opioid dose or coanalgesia was allowed in the 48 hours before study commencement. No increase in baseline opioid dose was allowed during the study, but participants had access to breakthrough analgesia. Opioid dose reduction was allowed for pain response or opioid toxicity. Total daily opioid dose and number of breakthrough analgesic doses were recorded.

Subcutaneous infusions of placebo (normal saline) or ketamine at three dose levels (100, 300, or 500 mg) were prepared by diluting ketamine hydrochloride 200 mg/2 mL in normal saline to a set volume. Participants received either ketamine or placebo in a 5-day schedule, starting at the first dose level (100 mg/24 hours; Fig 2). Pain and toxicity assessments were undertaken every 24 hours by trained research staff. Least, average, and worst pain over the preceding 24 hours were assessed by using the BPI. If 80% of study drug had been delivered, and average pain improved by ≥ 2 BPI units with no more than four breakthrough doses, the dose remained the same. If not, the dose was increased to the next level. Any psychomimetic toxicity was treated promptly with haloperidol or midazolam at specified doses. Dose reduction to the previous level was allowed in the case of unacceptable toxicity. Study drug was discontinued before 5 days if toxicity was intolerable or if there was no response after 24 hours at 500 mg.

Randomization and Masking

Each site pharmacy used randomization tables from an independent central registry. Stratification was by pain type (neuropathic or nociceptive), according to the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale.[12] Randomization was double blinded, allocated by blocks of four in a 1:1 ratio for each strata by site. All nonpharmacy study staff, treating clinicians, investigators, and participants were unaware of treatment allocation until completion of all data collection and analysis.

Definition of a Clinically Relevant Improvement in Pain

A clinically relevant improvement in pain was defined as a reduction in BPI average pain score by ≥ 2 points from baseline in the absence of more than four breakthrough doses of analgesia over the previous 24 hours.[13]

Completion

Participants were defined as having completed the study if they had received study drug for 5 days, or received 24 hours of study drug at maximum

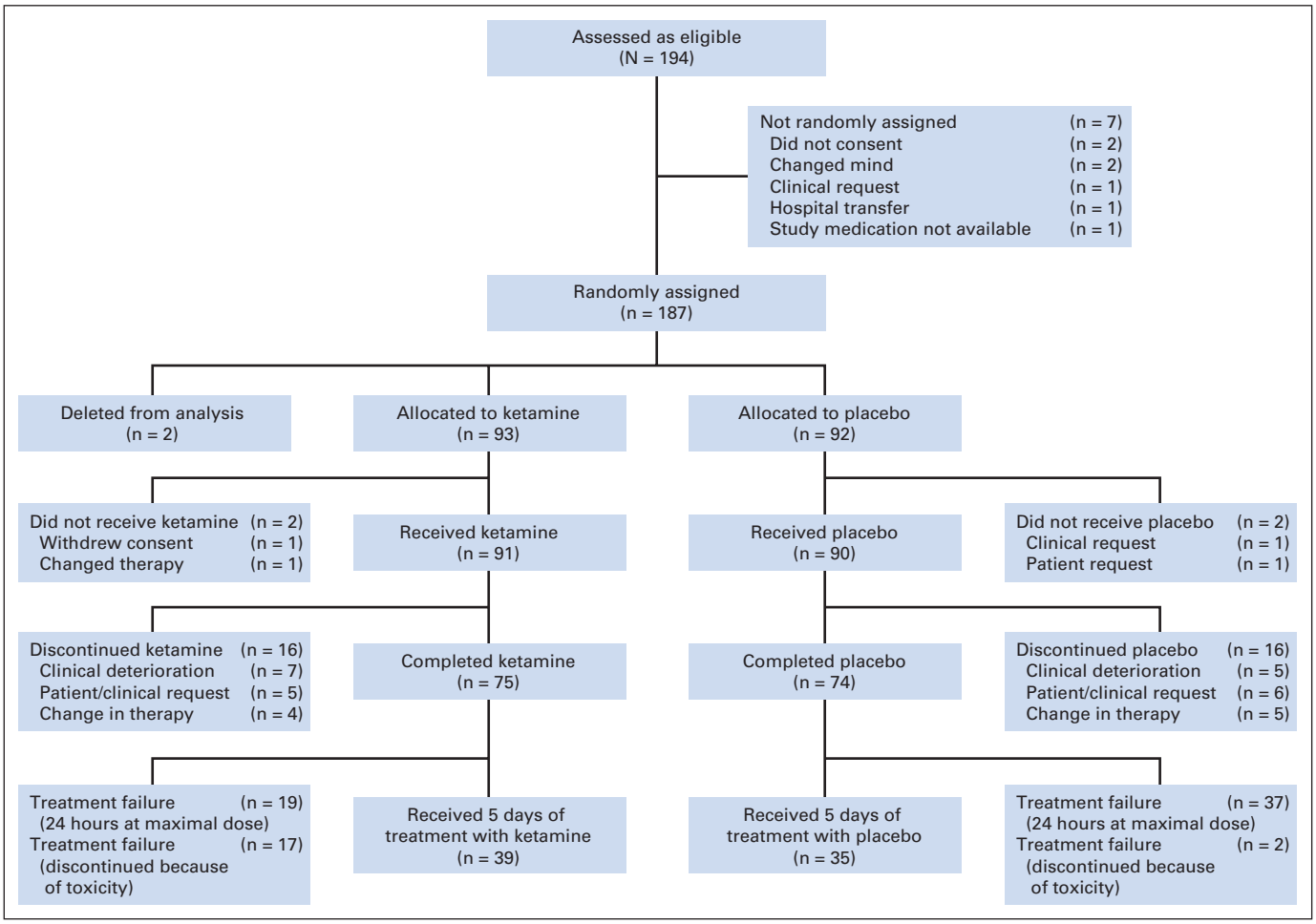

Fig 1. CONSORT diagram.

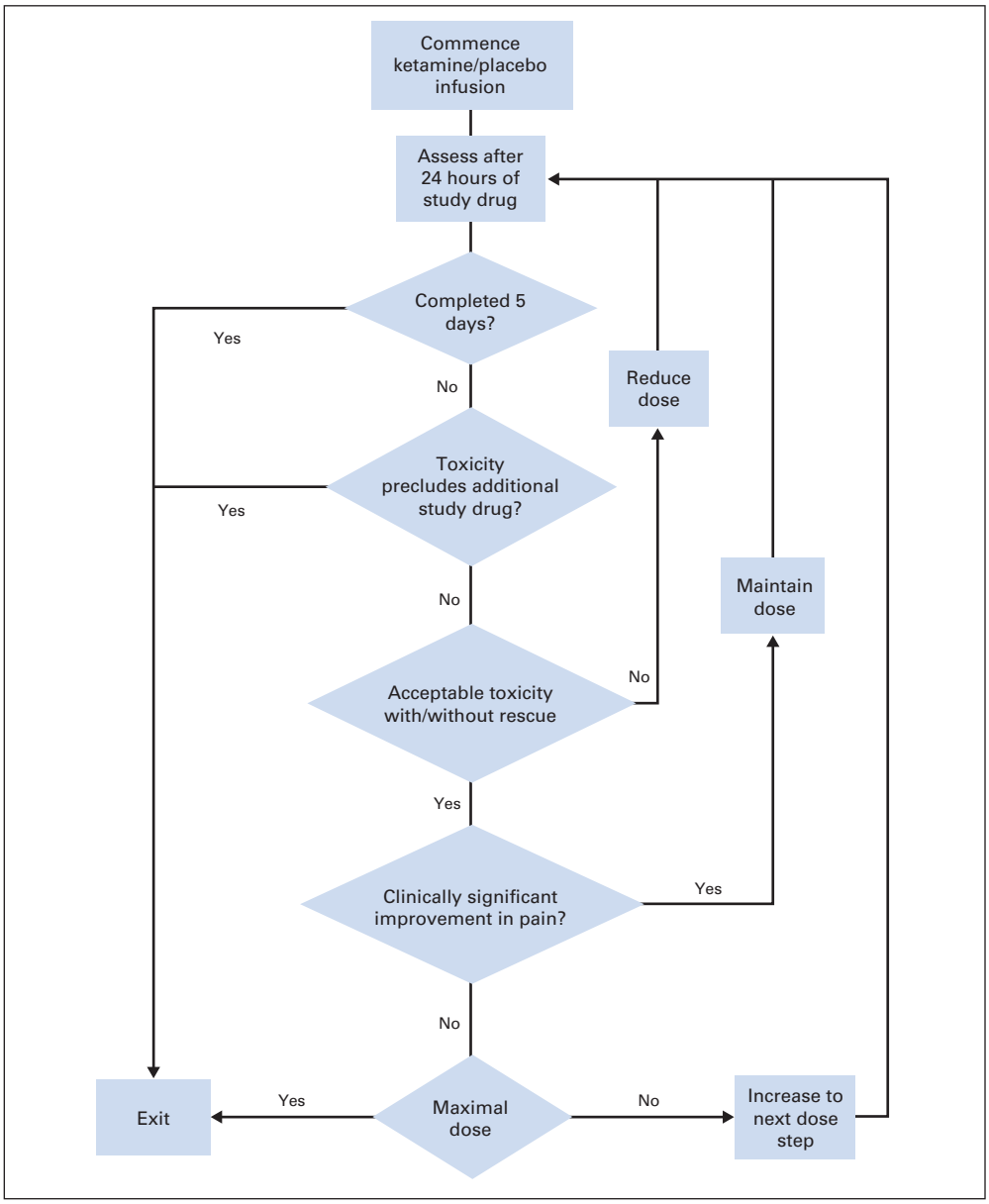

Fig 2. Study diagram.

dose (500 mg) with no clinically relevant improvement in pain, or if study drug was withdrawn because of unacceptable toxicity at any dose level.

Outcomes

The primary outcome measure was a positive response, defined as a clinically relevant improvement in pain at the end of the 5-day study period. Other outcomes were considered to be a negative response.

Secondary outcome measures included pain assessments at days 2 to 5 and adverse events graded according to the National Institutes of Health Common Terminology Criteria for Adverse Events, version 3.0.[14] Psychomimetic-specific events were assessed daily using the Clinician-Administered Dissociative States Scale (CADSS).[15]

Sample Size

A total of 150 participants who met the definition of completion were required to provide 85% power to detect a 25% absolute difference in response rate with a two-tailed type I error of 0.05. This assumed a positive response rate of 30% in the placebo arm. A response rate of at least 55% in the active arm was required to show net clinical benefit, given the expected ketamine toxicity.

Statistical Methods

The primary analysis was an intention-to-treat analysis. The response for participants stopping study drug before day 5 for reasons unrelated to the intervention was imputed from the last recorded assessment of pain. For the primary analysis, the proportions of patients having a positive response in the ketamine and placebo groups were compared by using a χ^2 test. Possible differential response rates in neuropathic and non-neuropathic pain and predictors of toxicity were examined by using mixed effects logistic regression. All longitudinal outcomes, pain (least, average, and worst), severity and incidence of adverse events, and psychotoxicity were analyzed as three-level random effects models (readings nested within participants nested within sites) by using generalized linear latent and mixed models with robust SEs and the appropriate distribution and link. Log time or time squared was added as appropriate (by minimizing Akaike information criterion and/or Bayesian information criterion) to improve model fit. All models were fitted with adaptive quadrature and eight numerical integration points and then refitted with 16 numerical integration points with almost identical estimates in all

cases. A Cox proportional hazards frailty model was used to assess the association between survival and treatment. The covariates, link, and distribution that comprise the model type are summarized in Appendix Table A2 (online only). Regression results are reported as odds ratios (ORs), incidence rate ratios, or β coefficients as appropriate with 95% CIs.

The number needed to treat for clinically relevant pain response and number needed to harm for toxicity resulting from the use of ketamine are reported with 95% CIs, truncated at ∞ when the result is not significant.

Ethical and Safety Oversight

The study was approved by ethics committees at all sites and monitored by a safety monitoring committee. All participants provided written informed consent. A blinded interim analysis was undertaken for safety only. The study was publically registered (ANZCTR [Australian New Zealand Clinical Trials Registry] 12607000501448). The Australian Government funded the study but had no role in trial design, data analysis, or writing of the report, apart from delegated oversight of the Palliative Care Clinical Studies Collaborative (PaCCSC) Management Advisory Board.

RESULTS

Baseline Data

There was no significant association between intervention and control arms and any observed covariate in baseline demographic or clinical characteristics (Table 1).

Table 1. Baseline Demographics*

Characteristic	Ketamine (n = 93)				Placebo (n = 92)			
	No.	%	Mean	SD	No.	%	Mean	SD
Age, years			63.0	13.7			64.3	9.9
Male sex	50	55.0			53	58.2		
Site of cancer diagnosis								
Lung	22	24.2			18	19.8		
Prostate	13	14.3			11	12.1		
Colorectal	8	8.8			14	15.6		
Gynecologic	8	8.8			3	3.3		
Breast	6	6.6			11	12.1		
Bone/soft tissue	5	5.6			2	2.2		
Pancreas	5	5.5			5	5.5		
Other	26	28.6			26	28.9		
Performance status (AKPS)								
Median		60				60		
Interquartile range		50-60				50-60		
Background opioid dose OME, mg								
Median		300				410		
Interquartile range		160-480				258-700		
BPI pain score								
Average			5.43	1.3			5.21	1.4
Worst			8.08	1.5			7.64	1.6
Least			2.47	1.7			2.37	1.9
LANSS score $\geq$ 12	28	30.1			28	30.4		
CADSS score								
0	55	59.8			54	60.4		
1-2	19	20.7			14	15.4		
3-8	12	13.0			14	15.4		
9+	6	6.5			8	8.8		
Concomitant medications								
Antipsychotics	1	1.1			3	3.3		
Benzodiazepines	9	9.7			15	16.3		
Adverse events†								
Somnolence	39	45.4			32	35.2		
Constipation	37	44.1			42	46.7		
Nausea/vomiting	26	28.3			21	22.6		
Dizziness	14	16.3			21	23.1		
Cognitive disturbance/confusion	9	9.7			9	9.8		
Hypertension	7	8.1			4	4.4		
Cardiac arrhythmia	6	6.9			4	4.6		
Hypoxia	6	7.1			11	12.4		
Site irritation	5	5.9			5	5.49		
Other	2	2.2			6	6.5		

Abbreviations: AKPS, Australian-modified Karnofsky performance status scale; BPI, Brief Pain Inventory; CADSS, Clinician-Administered Dissociative States Scale; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; OME, oral morphine equivalents; SD, standard deviation.

*All P values $> .05$; no allowance was made for missing data.

†Any grade.

CONSORT Recruitment and Participant Flow

There were 187 participants randomly assigned over 3 years (March 2008 to February 2011). One participant was recruited twice, and the second set of observations was deleted from the data set. The other was randomly assigned but did not meet eligibility criteria. The intention-to-treat sample therefore comprised 185 patients (ketamine, 93; placebo, 92). Of these, 149 met the definition of completion. Seventy-four participants received study drug on all 5 days.

Primary Analysis

Four of the 185 randomly assigned participants who withdrew before the commencement of study drug were deemed to have a negative response. The response was 27% (25 of 92) in the placebo and 31% (29 of 93) in the intervention arm with no difference ($P = .55$) between the proportion of positive outcomes in each group (0.04; 95% CI, −0.10 to 0.18).

There was no difference in outcome in participants who met the definition of completion (n = 149; 33% *v* 26%; $P = .231$), in the subgroup that received 5 days of study drug (n = 74; 64% *v* 54%; $P = .39$), or when all participants with baseline pain scores were included (n = 181; 32% *v* 28%; $P = .55$). When the primary analysis was completed by using worst pain but not average pain, the placebo response was 23% (21 of 92) and the intervention response was 27% (25 of 93; $P = .52$). The corresponding sensitivity analysis also remained nonsignificant. When the definition of positive response was varied by requiring average pain to improve by ≥ 3 BPI units, no significant difference was found between arms for any level of pain improvement.

The number needed to treat for one additional patient to get a positive outcome from ketamine was 25 (95% CI, six to ∞). The number needed to harm measured by actual withdrawal because of unacceptable toxicity was six (95% CI, 4 to 13).

Secondary Analyses

Baseline data were provided by 181 participants. The number of participants and responders by group and baseline average pain score is shown in Figure 3. There was no difference in response between arms and baseline pain ($P = .15$). Pain type (nociceptive *v* neuropathic) was not a statistically significant predictor of response.

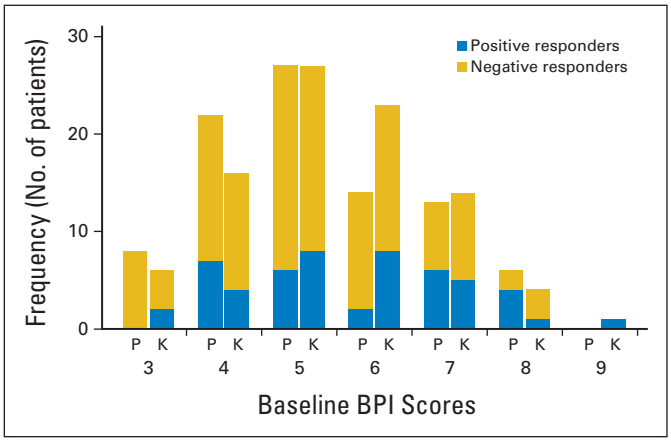

Fig 3. Response by baseline pain score (n= 181). Blue bars represent positive responders within each baseline pain category. Gold bars represent negative responders within each baseline pain category. BPI, Brief Pain Inventory; K, ketamine group; P, placebo group.

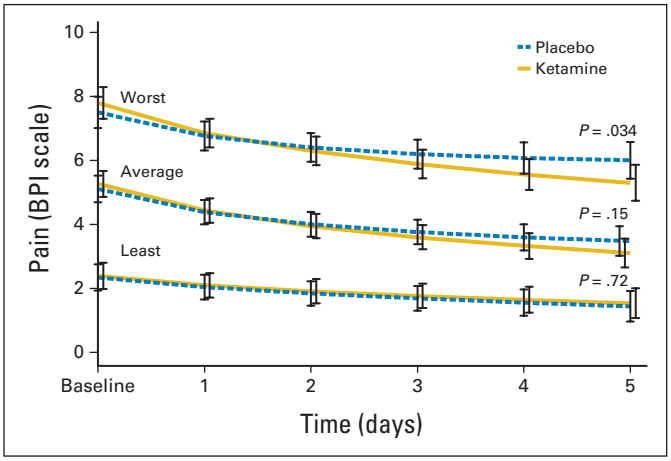

Fig 4. Mean pain scores over time (adjusted for arm, time, arm × time, ln[time], background opioid dose, age, sex, and pain type [n = 181]). *P* values are differences between arms at study end. Error bars represent 95% CIs. BPI, Brief Pain Inventory.

Multivariable analyses of pain scores were conducted, with pain as a continuous outcome. The mean difference in pain between arms/day was greatest for worst pain. By study end, mean worst pain score was 6.01 (95% CI, 5.44 to 6.59) for placebo and 5.30 (95% CI, 4.74 to 5.86) for ketamine ($P = .034$). The difference in absolute terms is small (0.71) and was not clinically significant because the difference was not ≥ 2 BPI units. For average pain, there was no difference in mean pain levels between arms by study end (placebo, 3.49 [95% CI, 3.02 to 3.95] *v* ketamine, 3.11 [95% CI, 2.65 to 3.57)]; $P = .15$). There were no differences between groups at any time for least pain. The trajectory of pain scores over time is modeled in Figure 4 for each pain category. Corresponding sensitivity analyses were conducted for the 74 participants who received study drug over 5 days and the 149 who met the definition of completion. In the former, there was no difference in pain between arms at study end, and in the latter, the results were almost identical to the analysis for 181 patients. When pain was treated as an ordinal outcome, compared with baseline, both arms were less likely to report a higher pain score by day 3 until the end of study period, with no significant differences between groups on any day ($P > .08$). The maximum dose received by participants (Table 2)

Table 2. Maximum Dose Received by Participants in Each Arm

Ketamine/Placebo Dose (mg)*	No. of Patients Who Received Ketamine	No. of Patients Who Received Placebo
< 100	6†	7‡
100	16	12
300	35	19
500	36	54

*Participants were required to have received at least 80% of planned dose to complete that dose level.
†Two patients withdrew before start of treatment, and four withdrew during day 1 before 80% of dose step 1.
‡Two patients withdrew before start of treatment, and five withdrew during day 1 before 80% of dose step 1.

Table 3. Number of Adverse Events That Occurred During the Trial for Which the Grade Was Worse Than at Baseline

Adverse Event	Ketamine	Placebo
Cardiac arrhythmia	2	3
Cognitive disturbance	17	8
Confusion	13	9
Constipation	13	7
Dizziness	17	10
Hypertension	3	8
Hypoxia	7	8
Site irritation	31	4
Somnolence	24	17
Nausea	15	8
Vomiting	10	9
Other	20	12

differed between arms ($P = .03$). Proportionally more participants in the ketamine arm compared with the placebo arm withdrew from the study at 300 mg ($P = .005$).

The median number of breakthrough analgesic doses given on day 1 to the placebo arm was three (interquartile range, one to four) and to the intervention arm was two (interquartile range, one to four; range, zero to 10 in both groups). This remained similar throughout, with no difference between arms on any day ($P > .18$). For each pain category, participants were more likely to receive breakthrough doses with each BPI unit increase in pain: OR for least pain, 1.22 (95% CI, 1.11 to 1.33), OR for average pain, 1.59 (95% CI, 1.45 to 1.74), and OR for worst pain, 1.61 (95% CI, 1.46 to 1.78).

Adverse event scores recorded as worse than those at baseline are shown in Table 3. There was almost twice the incidence of adverse events graded worse than baseline in the ketamine arm compared with the placebo arm at the end of day 1 (incidence rate ratio, 1.95; 95% CI, 1.46 to 2.61; $P < .001$) and throughout the study. Participants receiving ketamine were more likely to experience a more severe grade of adverse event per day (OR, 1.09; 95% CI, 1.00 to 1.18; $P = .039$). Injection site reactions were nearly three times more likely each day in the ketamine group (OR, 2.85; 95% CI, 1.77 to 4.73; $P < .001$). There were relatively few adverse events higher than grade 3 in severity and worse than baseline (14 for ketamine; 16 for placebo). The most common were light-headedness (five cases), hypoxia (five cases), and somnolence (nine cases). Seven serious adverse events were reported, two of which (bradyarrhythmia and cardiac arrest, both in patients receiving ketamine) were thought to be possibly related to study drug.

There was no difference in psychotoxicity at baseline, with approximately 40% of all participants having a positive CADSS score. Because the distribution of CADSS scores was exponential (skewed toward zero), a two-stage analysis was conducted. Compared with the odds of the placebo group, the odds of the ketamine group experiencing psychotoxicity increased each day, becoming significant after day 3 (OR, 2.53; 95% CI, 1.11 to 5.78; $P = .027$). For those with toxicity, when the level of toxicity between arms was compared, the ketamine group was more likely to report higher scores each day ($P = .093$). By study end, the difference between groups was significant ($\beta = 0.46$; 95% CI, 0.4 to 0.88; $P = .034$).

DISCUSSION

This large randomized controlled trial (RCT) demonstrated a strong placebo effect and failed to show any additional clinical benefit for ketamine when delivered subcutaneously in a dose-escalating regimen over 5 days, while significantly increasing toxicity. Mean pain scores in this study improved over time for all participants irrespective of allocation, with no difference between arms. Although there was a greater improvement per day in the ketamine group in worst and average pain scores, this never reached a level that would be considered clinically relevant. The consistency of the results across secondary outcomes and the fact that the study was adequately powered to detect our prespecified differences in response, suggests that type II error is not a factor.

Ketamine is commonly used for the management of pain related to cancer. Although there are many anecdotal reports of efficacy in the literature, the RCT evidence to support the use of ketamine in this patient group to date has been limited to two underpowered trials.[16] There is considerable variation in dose, route of delivery, and frequency of use of ketamine with no standard regimen to guide clinical practice or research. The method of delivery—subcutaneously in a dose-escalating regimen over 5 days—chosen for this trial came from the largest case series in the literature.[3]

The high placebo response rate (27%) has been demonstrated before, especially in neuropathic pain trials.[17-19] Possible explanations for placebo responses of this order of magnitude include regression to the mean (ie, patients are generally enrolled onto trials when their pain is worst, and some will improve over time without treatment), patient expectation of benefit, and the extra care and attention given to patients participating in trials.[20] Of note, there was no difference in the number of participants in each arm who had marked improvements in pain.

The frequency of adverse events at baseline, before the initiation of any study drug, reflects the toxicity of other medications or the disease process itself. The adverse events seen in the placebo arm reflect either a nocebo effect[21] or the cumulative toxicity of concomitant medications. Previous studies in this population group have pointed to the large number of medications per patient and the frequency of drug-related adverse events.[22] The greater incidence of adverse events in the ketamine arm compared with the placebo arm is consistent with the finding that significantly more participants receiving ketamine withdrew because of toxicity. This difference persisted for 5 days, despite the fact that many participants had withdrawn because of toxicity. Despite no difference between arms at baseline in the use of drugs commonly used to treat ketamine toxicity (benzodiazepines and antipsychotics), there was more psychotoxicity in the ketamine arm. The CADSS was developed to measure present-state dissociative symptoms and has been used as a measure of perceptual, behavioral, and attention alterations occurring during dissociative experiences in normal volunteers given ketamine.[15,23] Both the presence and level of psychotoxicity was significantly greater in the ketamine arm compared with the placebo arm by study end. Although CADSS scores were relatively low in the majority of participants, the results were driven by a subgroup in the ketamine arm with high scores. Irritation at subcutaneous infusion sites was also significantly more frequent in those receiving ketamine but was not sufficient to unblind the study. Importantly, for each person observed to achieve a

benefit in pain control from ketamine, four people suffered enough from toxicity to cause them to withdraw.

This study may be criticized in that the population was heterogeneous. The study group is typical, however, of those patients commonly referred to a palliative care service and who receive ketamine for pain. The participants were unwell, with multiple comorbidities and comedications. The median survival was 2 months in both groups (data not shown). A median performance status of 60 at baseline indicates the need for some assistance with activities of daily living. All had chronic refractory pain with defined prior treatment to which there had been an incomplete response. A baseline median oral morphine dose of more than 300 mg/d suggests that most patients had been taking opioids for some time. In addition, we imputed pain scores at study end for missing data by using the last available score. Although multiple imputation could alternatively be applied,[24] this study would have required, at a minimum, imputation of pain scores and the number of breakthrough analgesic doses for each day of absent data, resulting in considerable random variation by study end.

RCTs in patients with life-limiting disease are challenging and are considered by some to be inappropriate and/or unfeasible.[25] This study demonstrates that it is possible to undertake high-quality studies in patients with life-limiting disease and that placebo arms are essential in the absence of a comparator of proven benefit. In many uncontrolled studies, impressive response rates are little different from the placebo response demonstrated in this trial.[26]

In conclusion, this adequately powered RCT fails to support the current widespread practice of using subcutaneous ketamine as an adjuvant to opioids in the management of refractory pain in patients with advanced cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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