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ORIGINAL

Association of low-dose ketamine with hallucinations in critically ill patients: a target trial emulation

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Abstract

Purpose: Ketamine use is a potentially modifiable risk factor for hallucinations. We aimed to use target trial emulation to investigate the association between low-dose ketamine and development of hallucinations in critically ill patients in the intensive care unit (ICU).

Methods: Retrospective study using data from a university affiliated ICU in Melbourne, Australia. Application of marginal structural models and parametric g-formulas to assess the impact of low-dose ketamine on the development of hallucinations.

Results: We studied 7514 patients from June 2016 to April 2021. Of these, 625 patients (8%) received low-dose ketamine, beginning at a median of 0 (0–1) days from ICU admission and at a mean daily dose of 0.11 (0.08–0.15) mg/kg/h. Low-dose ketamine treated patients had a higher rate of hallucinations within 30 days of ICU admission (26% vs. 7%; $p < 0.001$) and the first episode of hallucination occurred earlier than in unexposed patient (2 [1–3] vs. 3 [1–7] days from ICU admission; $p < 0.001$). After adjustment for baseline and time-dependent confounders, low-dose ketamine was associated with a higher risk of hallucinations within 30 days (OR, 6.46 [95% CI 5.17–8.07]; $p < 0.001$). These findings were confirmed with parametric g-formulas.

Conclusions: In ICU patients, low-dose ketamine was strongly associated with an increased risk of hallucinations. However, these findings should be interpreted with caution due to the observational nature of the study and the risk of residual confounding.

Keywords: Ketamine, Hallucination, Analgesia, Delirium, Sedation

Introduction

Ketamine is an intravenous agent with a variety of applications, including sedation, analgesia, bronchodilation, and sympathetic nervous system stimulation [1]. Because of its hemodynamically stable profile, along with its beneficial respiratory properties and analgesic potency [1, 2], it is useful as a procedural sedative, induction agent, and in the treatment of respiratory and/or neurologic clinical conditions, such as asthma and status epilepticus [3]. Moreover, at low dose (< 0.2 mg/kg/h), ketamine is now an option for the adjunctive treatment of pain [4].

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Analgesia with low-dose ketamine is considered safe, with few adverse effects [3, 4]. In contrast, at higher dose (0.5–1.5 mg/kg), ketamine is associated with increased catecholamine release, elevated heart rate and systemic blood pressure, as well as functional and electrophysiological dissociation between limbic systems and the thalamo-neocortical pathway, an effect that underlies both its anaesthetic properties and potential for perceptual disturbances. This presents mainly as dysphoria, disorientation, vivid dreams, sensory and/or perceptual illusions [2–4]. A recent clinical trial in patients receiving procedural sedation found a 12% rate of hallucination with higher doses of ketamine (bolus of 1 mg/kg and 0.5 mg/kg as needed) [5]. In this regard, irrespective of ketamine administration, hallucinations affect one in 12 critically ill patients and are strongly associated with disturbed behaviour, and the use of antipsychotic medications [6].

In critically ill patients, outside of its use to facilitate endotracheal intubation, ketamine is typically given at low dose with the goal of delivering analgesia [3, 7–9]. This therapy may affect the risk of hallucinations. However, the impact of low-dose ketamine on the occurrence of hallucinations in critically ill patients is unknown. In this regard, emulating a target trial using routinely collected clinical data is a well-established methodological approach to estimate the potential causal effects of specific treatments on patient-important outcomes in an uncontrolled setting and under "real-world" conditions [10, 11]. In the absence of a randomized clinical trial, target trial emulation represents the least biased observational approach to addressing this question. Accordingly, we applied this method to investigate whether low-dose ketamine is associated with an increased the occurrence of hallucinations in critically ill patients compared to usual care without ketamine.

Methods

Study design

We performed a retrospective study using data from electronic medical records (EMR) of a university affiliated medical-surgical ICU in Melbourne, Australia. This study was approved by the Austin Hospital Human Research Ethics Committee, with a waiver of informed consent.

All adult patients (≥ 18 years old) admitted to the ICUs between June 2016 and April 2021 were eligible for inclusion. If a patient had multiple admissions only the first admission was considered for inclusion. Patients who developed hallucination before the start of ketamine and patients with missing data for ICU length of stay, time until ketamine use or time until hallucinations were excluded. Details of the statistical approach to target trial emulation using observational data are presented in electronic supplementary table S1.

Take-home message

In ICU patients, after adjustment for baseline and time-dependent confounders, low-dose ketamine was associated with a higher risk of hallucination within 30 days

Data collection and manipulation

All baseline and outcome data were collected from the Australian and New Zealand Intensive Care Society Adult ICU Patient Database run by the Centre for Outcome and Resource Evaluation [12]. During the study period, by ICU policy, patients received general care aimed at decreasing the risk of delirium, including frequent family visits, dimmed lights at night, minimal interaction to facilitate nighttime sleep cycling, and ensuring use of spectacles and hearing aids as necessary. As per unit policy, CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments were assessed by nursing staff during every 8-h shift.

Natural language processing (NLP) of caregiver notes was used to extract the details of the assessments. The clinical progress notes of all caregivers were analysed using NLP tokenizing techniques as previously described (natural language toolkit; NLTK 3.5) [13–15]. Each note was then searched for the presence of words, terms, or expressions, suggestive of hallucination, delirium or behavioural disturbance in accordance with terms selected in a previously published survey of clinical staff [16]. Data on medications, including ketamine, dexmedetomidine, benzodiazepine and antipsychotic drugs (haloperidol, olanzapine, quetiapine, and risperidone) were obtained from the hospital EMR. Data for antipsychotics and benzodiazepines were available only for 2019 and 2020. Thus, all analyses considering these medications were sensitivity analyses in a nested cohort of patients. All notes and medications were time stamped.

Data definition

Hallucinations were identified when the word 'hallucinating/hallucination/hallucinations' and/or variations were present in at least one progress note. This approach was used in a recent study [6]. In a quality check, we performed a direct human assessment of 50 random notes used to identify hallucinations to confirm the performance of the model. Delirium was diagnosed when the word 'delirium' or 'delirious' was present in at least one progress note and also based on reported CAM-ICU assessments. NLP diagnosed behaviour

disturbance (NLP-Dx-BD) was diagnosed when, in at least one progress note, a word indicative of behavioural disturbance was found, as previously described [13, 17].

Outcome and exposure

The primary outcome was the occurrence of hallucinations up to 30 days. Discharge from ICU or death were considered competing events for hallucinations, because they precluded the later occurrence of the primary outcome. Patients were followed from the ICU admission (day 0) until either the first episode of hallucinations, ICU discharge, death, or day 30 in the ICU, whichever occurred first. In patients receiving low-dose ketamine, only episodes of hallucinations starting on the day of the first dose of ketamine or later were considered.

The use of low-dose ketamine within 30 days of ICU admission was the exposure of interest. In all analyses, time zero was the day of ICU admission and the maximum follow-up time was 30 days from ICU admission. The 30 days period was considered because more than 99% of the patients had less than 30 days of ICU length of stay.

The following secondary outcomes were reported for cohort description: (1) delirium within 30 days; (2) NLP-Dx-BD within 30 days; (3) duration of ventilation in ventilated patients; (4) ICU length of stay; and (5) 30-day ICU mortality.

Low-dose ketamine protocol

Patients in the study received low-dose ketamine mainly for analgesic purposes. The dose was in accordance with the local protocol, at doses of 0.1–0.3 mg/kg/h and titrated according to response and side effects. Boluses were not used. All patients received intravenous ketamine prepared in a solution of 200 mg of ketamine diluted in 100 mL of normal saline (final concentration 2 mg/mL). The documentation of the cumulative dose of ketamine used had to be validated by two different nurses.

Statistical analysis

All continuous data are reported as medians (quartile 25%–quartile 75%) and categorical data as numbers and percentages. Clinical characteristics of the patients were compared among the groups using Fisher exact test and the Wilcoxon rank-sum test.

The use of low-dose ketamine is a time-dependent exposure since its use was documented at multiple times until day 30. In addition, there are time-dependent confounders affected by prior treatment that predict future treatment with ketamine and future outcome, conditional on past treatment. The use of standard regression methods in this situation result in biased estimates [18, 19]. Marginal structural models can be used to estimate the possible causal effect of a time-dependent exposure in the presence of time-dependent confounders that are themselves affected by previous treatment [18, 19].

In the present analysis, an extension of marginal structural models called marginal structural Cox proportional hazards model was used [18]. First, four pooled logistic regression models were fitted, two for the probability of remaining off ketamine and two for the probability of remaining free of competing event, and their predicted values were obtained. Second, the weights for each patient-day were calculated from the predicted values of the previous four models. Last, a final weighted pooled logistic regression model using generalized estimating equations was fitted to estimate the causal parameter and its robust standard error. Stabilized weights were used because they generally yield 95% confidence intervals (CI) that are narrower and have actual coverages rates that are closer to 95% [18]. A more detailed description of the model is in the electronic supplementary material.

All models were adjusted for the following baseline covariates: age, sex, type of admission (medical or surgical), planned or unplanned admission, the Australian and New Zealand Risk of Death (ANZROD) after log transformation, admission after medical emergency team call, cardiac arrest in the first 24 h, acute kidney injury at ICU admission, admission diagnosis, ICU source of admission, chronic cardiovascular disease, hepatic failure, metastatic cancer, leukemia, use of renal replacement therapy, use of vasopressor/inotropes and use of mechanical ventilation. ANZROD is a validated and accurate predictor of mortality in ICUs in Australia and New Zealand [20, 21]. All baseline variables were selected based on clinical relevance, previous evidence and when different between groups. The following time-dependent variables were included: delirium, use of dexmedetomidine and NLP-Dx-BD. All models included the day, and the time-dependent intercept was estimated by a smooth function of the day since beginning of follow-up using natural cubic splines with five knots. The effect of ketamine on 30-day ICU mortality (with ICU discharge before day 30 treated as competing event) and ICU length of stay (time until ICU discharge alive with 30-day ICU mortality treated as competing event) were assessed using the same strategy described above.

Missing data are reported in electronic supplementary table S2 and imputation strategy is described in the electronic supplementary material. Subgroup analyses were performed according to subgroups described in the electronic supplementary material. Sensitivity analyses were performed as described in the Online Supplement.

The g-formula was used to confirm the findings from the main model and to assess the impact of different timing and duration of the intervention [22]. Finally, the E-value was calculated to measure the robustness of our findings [23]. The E-value quantifies the minimum strength of association an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away the observed effect. A higher E-value suggests that substantial unmeasured confounding would be required to negate the observed association.

All analyses were performed in R Version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and a $p < 0.05$ was considered significant.

Results

Patients

From June 2016 till April 2021, 7525 patients were available for inclusion. After exclusion of 11 patients, 7514 patients were included in the present study (electronic supplementary figure S1). Baseline characteristics of the included patients are shown in Table 1.

Ketamine infusion characteristics

The median days between ICU admission and low-dose ketamine start was 0 (0–1) days (electronic supplementary figure S2), the mean daily dose of ketamine was 8 (6–12) mg/h (0.11 [0.08–0.15] mg/kg/h) and the median total dose of ketamine used per patient was 208 (104–438) mg (electronic supplementary table S3 and electronic supplementary figure S3). Patients used ketamine for a median duration of 1.2 (0.6–2.2) days.

Outcomes

Outcomes are reported in Table 2. Patients who received low dose ketamine had a higher rate of hallucinations within 30 days (26% vs. 7%; $p < 0.001$) and the first episode of hallucinations occurred earlier than in patient who did not receive ketamine (2 [1–3] vs. 3 [1–7]; $p < 0.001$) (electronic supplementary figure S4). The median number of days between the start of low-dose ketamine infusion and development of the first episode of hallucination was 1 (0–2) (electronic supplementary figure S5). A direct human assessment of 50 random notes used to identify hallucinations did not identify any false positive.

While the occurrence of delirium within 30 days was similar between the group (13% vs. 14%; $p = 0.433$), patient who received low-dose ketamine had a higher incidence of NLP-Dx-BD (63% vs. 50%; $p < 0.001$) mainly due to a higher incidence of hypoactive NLP-Dx-BD (52% vs. 39%; $p < 0.001$) (Table 2 and electronic supplementary figure S4). ICU length of stay was longer in patients who received low dose ketamine but 30-day ICU mortality was lower (3% vs. 7%; $p < 0.001$). After adjustment for confounders in the marginal structural Cox proportional hazards model, there was no association of low dose ketamine with 30-day ICU mortality (odds ratio [OR], 0.42 [95% CI 0.15–1.14]; $p = 0.088$) but the use of low-dose ketamine was associated with longer time alive and in ICU (OR, 0.56 [95% CI 0.49–0.64]; $p < 0.001$).

Association of ketamine and hallucination

After adjustment for baseline and time-dependent confounders, the use of low dose ketamine was associated with a higher risk of hallucinations within 30 days (OR, 6.46 [95% CI 5.17–8.07]; $p < 0.001$) (Table 3). The full multivariable model is described in electronic supplementary table S4. The strength of the association was confirmed assessing the E-value of this effect estimate, which was 12.39 (electronic supplementary figure S6). This indicates that a confounder, or set of confounders, would have to be associated with a 12-fold increase in the risk of outcome, and must be 12 times more prevalent in exposed than non-exposed patients, to explain the observed risk ratio.

Subgroup and sensitivity analyses

There was no heterogeneity of treatment effect according to the subgroup assessed (Table 3). The model considering only patients with available data (complete case analysis), the model adjusting for RASS as a time-dependent confounder, the model including daily use of antipsychotics and benzodiazepines, and additional sensitivity analyses all resulted in similar findings (Table 3).

In the parametric g-formula analysis, the estimated risk of hallucinations within 30 days was 7.4% (95% CI 6.8–8.1%) under natural course (usual care), 6.3% (5.7–6.9%) under a strategy that never used low dose ketamine during follow-up and 26.6% (22.6–30.6%) under a strategy that always used low dose ketamine during follow-up (risk difference, 19.2% [95% CI 15.4–22.9%] and risk ratio, 3.60 [95% CI, 3.07 to 4.14] for always treated vs. natural course) (Table 3, Figs. 1, 2, eTable 5 and electronic supplementary table S5 and electronic supplementary figure S7).

The impact of the treatment strategy on development of hallucinations within 30 days was consistent independently of the timing of initiation and duration of the strategy (Table 3, Figs. 1, 2, electronic supplementary table S5 and electronic supplementary figure S8). However, a late strategy of starting the use of low-dose ketamine at day 10 resulted in a lower risk than an early strategy starting low-dose ketamine earlier during the course of ICU stay.

Table 1 Baseline characteristics of the included patients

	Overall ($n=7514$)	Low-dose ketamine ($n=625$)	No ketamine ($n=6889$)	p value
Age, years	63.7 (51.1–74.0)	58.9 (46.9–68.0)	64.3 (51.7–74.5)	< 0.001
Male gender—no. (%)	4610 (61.4)	407 (65.1)	4203 (61.1)	0.115
Weight, kilograms	78.5 (65.2–93.0)	82.0 (68.2–98.0)	78.0 (65.0–92.0)	0.040
Body mass index, kg/m^2	27.7 (24.0–32.2)	27.9 (24.3–32.5)	27.7 (24.0–32.1)	0.583
APACHE III	48.0 (35.0–64.0)	42.0 (31.0–55.0)	48.0 (35.0–65.0)	< 0.001
ANZROD	2.4 (0.7–10.0)	1.4 (0.6–4.2)	2.6 (0.7–10.9)	< 0.001
Type of admission—no. (%)				< 0.001
Medical	3849 (51.2)	161 (25.8)	3688 (53.6)	
Surgical	3662 (48.8)	464 (74.2)	3198 (46.4)	
Unplanned admission—no. (%)	5263 (70.0)	316 (50.6)	4947 (71.8)	< 0.001
MET call admission—no. (%)	1300 (17.3)	63 (10.1)	1237 (18.0)	< 0.001
Cardiac arrest—no. (%)	198 (2.6)	6 (1.0)	192 (2.8)	0.004
Acute renal failure—no. (%)	214 (2.9)	7 (1.1)	207 (3.0)	0.004
Admission diagnosis—no. (%)				< 0.001
Cardiovascular	2488 (33.1)	167 (26.7)	2321 (33.7)	
Gastrointestinal	1277 (17.0)	199 (31.8)	1078 (15.7)	
Gynaecological	14 (0.2)	2 (0.3)	12 (0.2)	
Haematological	68 (0.9)	0 (0.0)	68 (1.0)	
Metabolic	459 (6.1)	8 (1.3)	451 (6.5)	
Musculoskeletal/skin	159 (2.2)	22 (3.5)	137 (2.0)	
Neurological	642 (8.5)	35 (5.6)	607 (8.8)	
Renal/genitourinary	361 (4.8)	42 (6.7)	319 (4.6)	
Respiratory	1077 (14.3)	80 (12.8)	997 (14.5)	
Sepsis	706 (9.4)	24 (3.8)	682 (9.9)	
Trauma	260 (3.5)	46 (7.4)	214 (3.1)	
ICU source of admission—no. (%)				< 0.001
Emergency department	1779 (23.7)	45 (7.2)	1734 (25.2)	
Operating room	3638 (48.4)	459 (73.4)	3179 (46.1)	
Ward	1215 (16.2)	65 (10.4)	1150 (16.7)	
ICU other hospital	148 (2.0)	18 (2.9)	130 (1.9)	
Other hospital	721 (9.6)	38 (6.1)	683 (9.9)	
ICU same hospital	6 (0.1)	0 (0.0)	6 (0.1)	
Other	7 (0.1)	0 (0.0)	7 (0.1)	
Co-existing disorders—no. (%)				
Diabetes	1059 (78.9)	80 (71.4)	979 (79.5)	0.053
Chronic lung disease	736 (9.8)	66 (10.6)	670 (9.7)	0.483
Chronic cardiovascular disease	338 (4.5)	15 (2.4)	323 (4.7)	0.006
Cirrhosis	560 (7.5)	48 (7.7)	512 (7.4)	0.811
Chronic kidney disease	679 (9.0)	46 (7.4)	633 (9.2)	0.145
Chronic immune disease	191 (2.5)	20 (3.2)	171 (2.5)	0.287
Immunosuppression	584 (7.8)	47 (7.5)	537 (7.8)	0.876
Hepatic failure	103 (1.4)	2 (0.3)	101 (1.5)	0.011
Lymphoma	83 (1.1)	4 (0.6)	79 (1.1)	0.318
Metastatic cancer	329 (4.4)	46 (7.4)	283 (4.1)	< 0.001
Leukemia	153 (2.0)	3 (0.5)	150 (2.2)	0.002
Organ support—no. (%)				
ECMO	17 (0.3)	0 (0.0)	17 (0.4)	0.392
Vasopressor or inotropes	2691 (51.9)	244 (53.2)	2447 (51.8)	0.591
Invasive ventilation	3900 (61.7)	347 (64.6)	3553 (61.4)	0.150

Table 1 (continued)

	Overall ($n=7514$)	Low-dose ketamine ($n=625$)	No ketamine ($n=6889$)	p value
Non-invasive ventilation	342 (6.6)	39 (8.4)	303 (6.4)	0.094
Renal replacement therapy	487 (9.2)	30 (6.5)	457 (9.4)	0.035
Laboratory tests				
pH	7.38 (7.32–7.43)	7.36 (7.31–7.40)	7.38 (7.32–7.43)	< 0.001
PaO_2/FiO_2	305 (212–400)	305 (222–390)	305 (211–402)	0.952
$PaCO_2$, mmHg	40.0 (35.0–45.0)	41.5 (37.2–47.0)	40.0 (35.0–45.0)	< 0.001
Lactate, mmol/L	2.1 (1.5–3.2)	1.9 (1.3–2.9)	2.1 (1.5–3.2)	< 0.001
Highest creatinine, µmol/L	91.0 (69.0–138.0)	86.5 (68.0–121.8)	92.0 (69.0–140.0)	0.011
Lowest platelet, $\times 10^9$/L	176 (125–239)	180 (135–239)	175 (124–239)	0.120
Vital signs				
Lowest MAP, mmHg	65.0 (59.0–72.0)	66.0 (60.0–73.0)	65.0 (59.0–72.0)	0.057
Highest RR, breaths/min	20.0 (15.0–25.0)	20.0 (15.0–24.2)	20.0 (15.0–25.0)	0.195
Highest temperature, °C	37.2 (36.7–37.6)	37.4 (36.8–37.8)	37.2 (36.6–37.5)	< 0.001
Urine output, mL	1509 (1085–2140)	1500 (1040–2020)	1512 (1090–2150)	0.167

Data are median (IQR) or *N* (%)

APACHE Acute Physiology and Chronic Health Evaluation, *ANZROD* Australian and New Zealand Risk of Death, *MET* medical emergency team, *ICU* intensive care unit, *ECMO* extracorporeal membrane oxygenation, *MAP* mean arterial pressure, *RR* respiratory rate

Table 2 Clinical outcomes in included patients

	Overall ($n=7514$)	Low dose ketamine ($n=625$)	No ketamine ($n=6889$)	p value
Primary outcome				
Hallucination within 30 days—no. (%)	616/7514 (8.2)	162/625 (25.9)	454/6889 (6.6)	< 0.001
Days until first episode	2 (1–6)	2 (1–3)	3 (1–7)	< 0.001
Secondary outcomes				
Delirium within 30 days—no. (%)	1048/7506 (14.0)	80/624 (12.8)	968/6882 (14.1)	0.433
Days until first episode	2 (1–5)	2 (1–6)	2 (1–5)	0.435
NLP-Dx-BD within 30 days—no. (%)	3873/7506 (51.6)	396/624 (63.5)	3477/6882 (50.5)	< 0.001
Days until first episode	1 (0–2)	1 (0–2)	1 (0–2)	< 0.001
Hyperactive	2166/7506 (28.9)	189/624 (30.3)	1977/6882 (28.7)	0.407
Days until first episode	1 (0–2)	1 (0–2)	1 (0–2)	0.454
Hypoactive	3029/7506 (40.4)	323/624 (51.8)	2706/6882 (39.3)	< 0.001
Days until first episode	1 (1–2)	1 (1–2)	1 (0–2)	0.070
Mixed	1091/7506 (14.5)	79/624 (12.7)	1012/6882 (14.7)	0.173
Days until first episode	2 (1–4)	2 (1–5)	2 (1–4)	0.013
Clinical outcomes				
Duration of ventilation, days[a]	1.0 (0.4–3.6)	0.7 (0.4–2.5)	1.1 (0.5–3.7)	0.074
ICU length of stay, days	2.0 (1.0–4.0)	3.0 (2.0–5.0)	2.0 (1.0–4.0)	< 0.001
30-day ICU mortality—no. (%)	474/7511 (6.3)	18/625 (2.9)	456/6886 (6.6)	< 0.001

Data are median (quartile 25th–quartile 75th) or *N* (%)

ICU intensive care unit, *NLP-Dx-BD* natural language process diagnosed behavior disturbance

[a] Duration of ventilation reported only in patients who received ventilation

Discussion

Key findings

This large observational study is the first to investigate the impact of low dose ketamine on the development of hallucinations in critically ill patients. We found that one in four patients receiving low-dose ketamine developed hallucinations compared with one in fourteen of those who did not receive the drug. The finding of increased

Table 3 Multivariable association of use of low-dose ketamine and hallucination within 30 days

	Effect estimate (95% CI)	*p* value
Main model	OR, 6.46 (5.17–8.07)	< 0.001
Subgroup analyses		
Age		0.560*
< 50 years (*n* = 1765)	OR, 7.83 (5.09–12.04)	
50–65 years (*n* = 2226)	OR, 6.91 (4.74–10.09)	
≥ 65 years (*n* = 3523)	OR, 5.70 (3.83–8.48)	
Type of admission		0.763*
Medical (*n* = 3849)	OR, 5.95 (4.06–8.71)	
Surgical (*n* = 3662)	OR, 7.03 (5.23–9.44)	
Use of mechanical ventilation		0.960*
Yes (*n* = 3900)	OR, 6.18 (4.72–8.10)	
No (*n* = 2424)	OR, 7.34 (4.74–11.37)	
APACHE III		0.798*
< 48 (*n* = 3743)	OR, 6.70 (4.83–9.31)	
≥ 48 (*n* = 3771)	OR, 6.29 (4.59–8.62)	
Sensitivity analyses		
Complete case analysis	OR, 6.77 (5.23–8.75)	< 0.001
Cohort including other medications[c]		
Imputed cohort	OR, 8.16 (5.67–11.73)	< 0.001
Complete case analysis	OR, 7.51 (5.20–10.86)	< 0.001
Including daily RASS as a time-dependent confounder	OR, 6.56 (5.25–8.20)	< 0.001
Considering only patients who had at least one assessable day (RASS − 1 to 1)[a]	OR, 6.64 (5.28–8.36)	< 0.001
Analysis restricted to patient-days with RASS − 1 to 1[b]	OR, 6.56 (5.24–8.19)	< 0.001
Parametric g-formula		
Full course of follow-up		
Never received low dose ketamine	RR, 0.85 (0.82–0.88)	
Always received low dose ketamine	RR, 3.60 (3.07–4.14)	
Treatment from day 1–5		
Never received low dose ketamine	RR, 0.88 (0.85–0.91)	
Always received low dose ketamine	RR, 2.92 (2.52–3.33)	
Treatment from day 5–10		
Never received low dose ketamine	RR, 0.98 (0.98–0.99)	
Always received low dose ketamine	RR, 1.72 (1.60–1.87)	
Treatment from day 10–15		
Never received low dose ketamine	RR, 1.00 (0.99–1.00)	
Always received low dose ketamine	RR, 1.20 (1.16–1.25)	

All models adjusted for age, sex, type of admission (medical or surgical), planned or unplanned admission, the Australian and New Zealand Risk of Death (ANZROD) after log transformation, admission after medical emergency team call, cardiac arrest in the first 24 h, acute kidney injury at ICU admission, admission diagnosis, ICU source of admission, chronic cardiovascular disease, hepatic failure, metastatic cancer, leukemia, use of renal replacement therapy, use of vasopressor/inotropes and use of mechanical ventilation. The following time-dependent variables were included: delirium, use of dexmedetomidine and NLP-Dx-BD. All models included the day, and the time-dependent intercept was estimated by a smooth function of the day since beginning of follow-up using natural cubic splines with five knots

OR odds ratio, *RR* risk ratio, *CI* confidence interval, *RASS* Richmond Agitation and Sedation Scale

**p* value for the interaction between subgroup and use of low dose ketamine

[a] 7086 patients (94.3%) included

[b] 23,746 days (73.6% of all assessable days) were classified as a RASS − 1 to 1

[c] Daily use of antipsychotics and benzodiazepines included as additional daily confounders

risk of hallucinations with low dose ketamine was consistent in different sensitivity analyses and remained statistically significant in different statistical methods used to adjust for time-dependent confounders. The increase in hallucinations was consistent independent of the timing of initiation or duration of treatment. Even only one

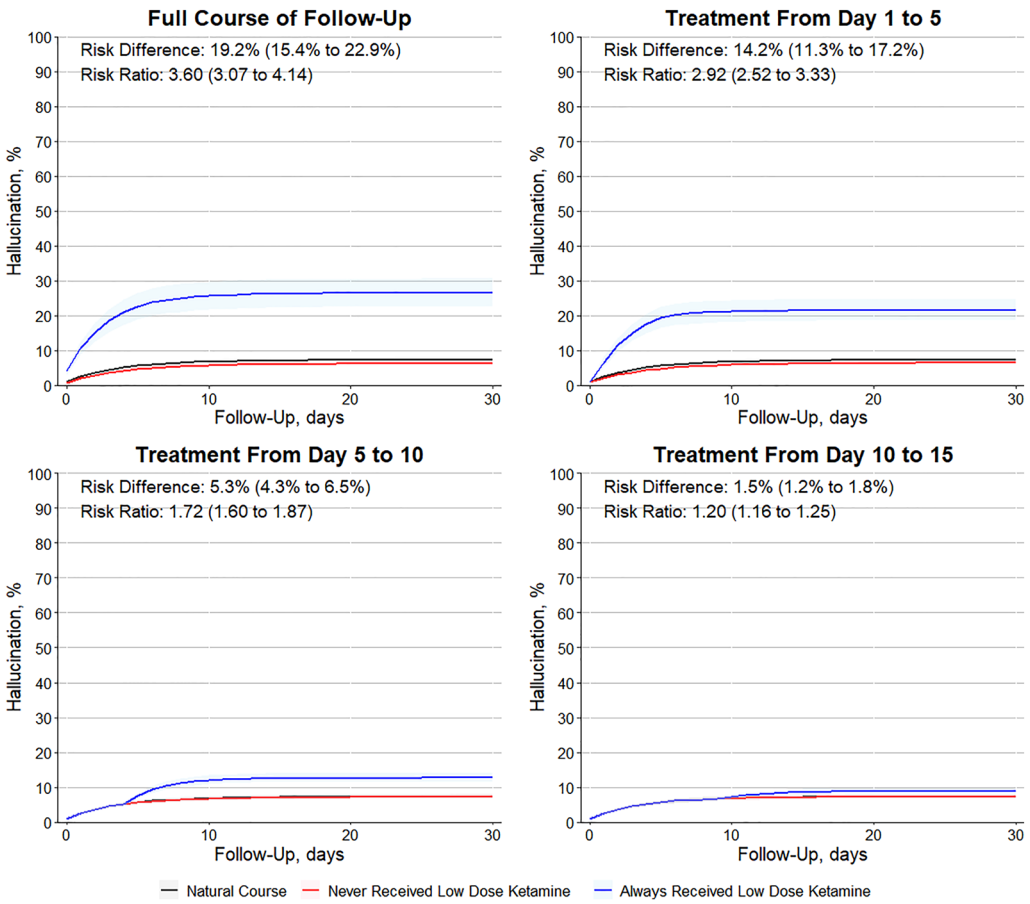

Fig. 1 Estimated risk of hallucinations within 30 days under different treatment strategies with varying initiation timing of treatment. Estimates from parametric g-formula. Reported estimates are for the 'Always Received low dose ketamine' group compared with 'Natural course'. Shaded areas are 95% confidence interval. RD is risk difference and RR is risk ratio

day of use of low-dose ketamine was associated with a 2.5-fold increase in the risk of hallucination. Finally, a late strategy starting the use of low-dose ketamine at day 10 resulted in a lower risk than a strategy of starting low-dose ketamine earlier during ICU stay.

Relationship to previous studies

There are very few studies reporting on hallucinations and their causes in critically ill patients. Observational studies involving critically ill patients have reported a prevalence of hallucinations varying from 7% [6, 24] to 24% [25, 26]. The most recent observational study assessing hallucination in a large cohort of critically ill patients found that hallucinations affected one in 12 ICU patients (a rate broadly aligned with our control population). Such hallucinations were strongly associated with disturbed behaviour, delirium, and the use of antipsychotic medications [6]. A recent trial assessing the impact of haloperidol on patients with delirium reported that 80% of patients receiving haloperidol experienced hallucinations [27].

A recent systematic review found that high dose ketamine provides rapid sedation for undifferentiated agitated patients and is associated with higher intubation rates in the prehospital and emergency setting [3]. The incidence of hallucinations in non-critically ill patients receiving high-dose ketamine as bolus in the emergency department for procedural sedation was 12% [5]. However, the impact of low-dose ketamine on hallucinations in critically ill patients has never been reported. Finally, previous evidence restricted to acute pain management did not find consistent increase in the incidence of hallucination with the use of ketamine in the perioperative setting and in non-critically ill patients [28, 29].

While our study focuses on racemic ketamine, esketamine is another option in critically ill patients. Esketamine is the S-enantiomer of ketamine, with greater NMDA receptor affinity, potentially providing similar

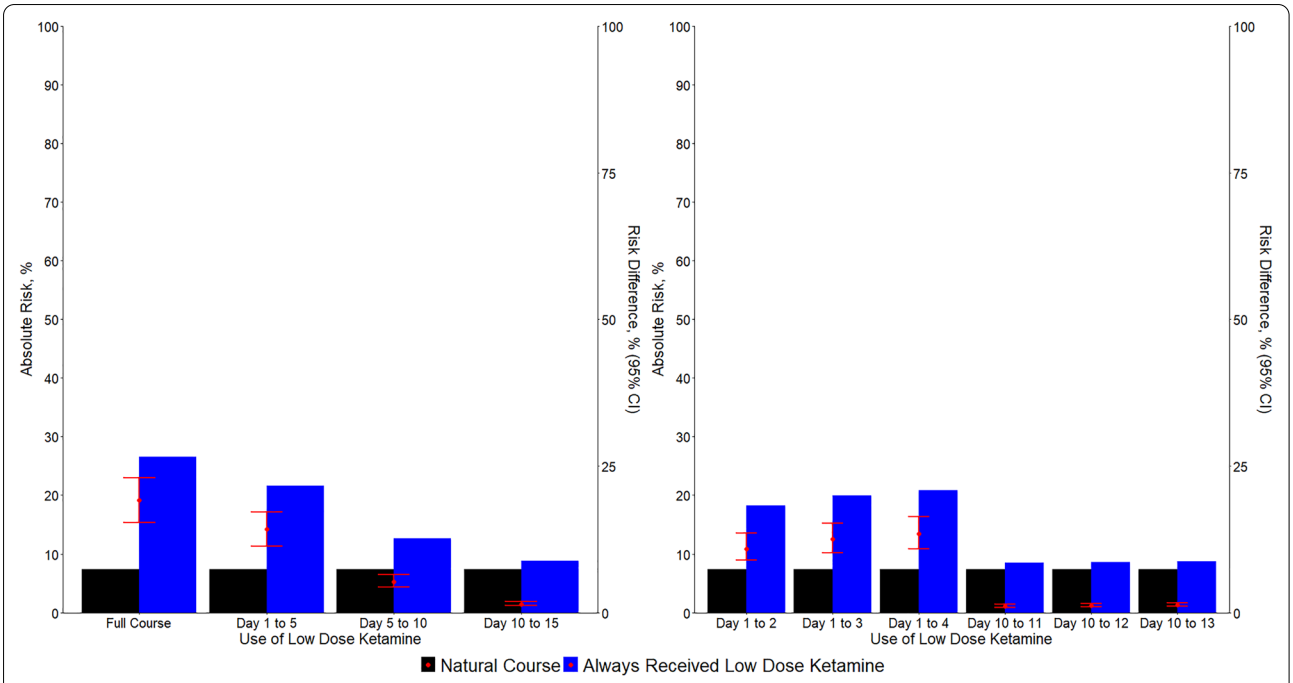

Fig. 2 Risk of hallucinations according to timing and duration of treatment with low-dose ketamine. Left panel, risk of hallucinations within 30 days and risk difference between natural course (black bars) and use of low-dose ketamine (blue bars) according to timing of initiation of ketamine. Right panel, risk of hallucinations within 30 days and risk difference between natural course (black bars) and use of low-dose ketamine (blue bars) according to duration of treatment with ketamine. The superimposed circles are the risk difference and bars are the 95% confidence interval of this difference. Risk difference calculated as the difference in risk between a strategy always using low dose ketamine and the natural course (usual care)

analgesic and sedative effects at lower doses while minimizing psychotropic side effects such as hallucinations [30]. However, data in critically ill patients remain very limited, and further research is required to determine whether esketamine could offer a safer alternative in ICU sedation and analgesia strategies.

Implications of study findings

The present study is the first study to directly to report the impact of low dose ketamine on hallucinations in critically ill patients. As hallucinations can be frightening and distressing to patients, lead to time-consuming interventions such as bedside assistance, verbal reassurance, medications, prolonged monitoring, and may predispose to delirium [2–5, 31], their prevention seems desirable. Moreover, a recent study reported that hallucinations in critically ill patients are associated with more treatment with antipsychotic medications and with the occurrence of other disturbances like delirium [6], highlighting the importance of this complication. In addition, a recent clinical trial in the emergency department found hallucinations increased the amount of clinical and pharmacologic interventions [5]. Hallucinations can also be highly distressing, and negatively impact mental health and social functioning [32], potentially leading to worse long-term cognitive outcomes. Finally, hallucinations can worsen the psychological experience and comfort of critically ill patients. Given all the above concerns, our findings are clinically important because they imply that low-dose ketamine is a significant independent modifiable risk factor for hallucinations in ICU patients.

Strengths and limitations

The use of a marginal structural Cox proportional hazards model and parametric g-formula allows the estimate of causal effect of treatment strategies in the presence of time-dependent and time-varying confounders, which themselves might be influenced by previous treatment and of competing events [18, 22]. In addition, the association of low-dose ketamine with hallucinations was consistent in different sensitivity analyses, subgroup analyses and clinical scenarios. Hallucinations were identified using contemporaneously documented caregiver observations rather than post hoc interviews, with their attendant inaccuracies and biases [6, 15]. Finally, the use of low-dose ketamine was based on the local protocol and the dose range was fixed, reducing heterogeneity of treatment.

We acknowledge several limitations. First, despite the use of a robust marginal structural Cox model, residual confounding remains a limitation, particularly due to the retrospective nature of the study and the potential omission of important baseline and time-dependent confounders that were not available in the study dataset. Second, the study was undertaken in the ICU of a university affiliated tertiary hospital in a resource-rich country. Therefore, the findings may not apply to other ICUs in low- or middle-income countries. However, the study ICUs are typical of other ICUs in resource-rich countries. Also, other ICUs may use strategies for managing hallucinations that result in different rates and outcomes. In the present study, patients were not assessed independently for the presence of hallucinations. However, the terms used to identify episodes of hallucinations were unbiased, highly specific, and more likely to underestimate than overestimate their prevalence. Our NLP approach relied on predefined terms primarily derived from prior studies on delirium and hallucinations [6, 13, 16, 17] and was not validated against a gold standard. As such, some hallucination-related terms may not have been captured, and differences in documentation practices across caregiver categories could influence the recorded frequency of hallucinations. Future studies should refine and validate term selection through expert consensus or additional validation methods, such as surveys, and focus on external validation and interobserver agreement assessments. A key limitation is that the ability to assess hallucinations depends on the patient's level of consciousness, which may be influenced by sedation and mechanical ventilation. While we accounted for this through subgroup and sensitivity analyses, and reporting sedation levels, missing data in this regard remain a limitation. An additional limitation was the lack of information on height in some patients which made calculation of BMI impossible in the full cohort. Our analysis assumes that competing events are independent of the risk of hallucinations given the baseline variables in the model. While this is a standard assumption in survival analysis, it may not fully hold in practice, potentially introducing bias in the estimated effect sizes.

Conclusion

In a study involving more than 7000 critically ill patients, we found that, compared with usual care without ketamine, use of low-dose ketamine was associated with an increased risk of in ICU hallucinations within 30 days of admission. This association was consistent across different sensitivity and subgroup analyses and remained statistically significant using various methods to adjust for time-dependent confounders. However, this study was based on a dataset that was not originally designed to evaluate this specific question, and several proxy measures were required to approximate key variables. Therefore, despite the robustness of the observed association, these findings should be interpreted with caution and considered hypothesis-generating. Further prospective studies specifically designed to address this question are needed to validate our findings and clarify the clinical implications of ketamine use in this population.

Supplementary Information
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Data availability
Data will be made available on request.

Declarations

Conflicts of interest
All other authors declare no competing interests.

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