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PII: S0104-0014(22)00134-8
DOI: https://doi.org/10.1016/j.bjane.2022.10.002
Reference: BJANE 744414

To appear in: *Brazilian Journal of Anesthesiology (English edition)*

Received date: 18 July 2022
Accepted date: 9 October 2022

Please cite this article as: Hélder David Ribeiro Pereira , Maria Vaz Antunes , Daniel Teles , Luís Guimarães Pereira , Fernando Abelha , Association between intraoperative ketamine and the incidence of emergence delirium in laparoscopic surgeries: an observational study, *Brazilian Journal of Anesthesiology (English edition)* (2022), doi: https://doi.org/10.1016/j.bjane.2022.10.002

BJAN-D-22-00267 – Original Investigation

Association between intraoperative ketamine and the incidence of emergence delirium in laparoscopic surgeries: an observational study

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Received 18 July 2022; accepted 9 October 2022

KEYWORDS

Analgesia;

Emergence *delirium*;

Ketamine;

Laparoscopic surgery

Abstract

Background: Emergence *Delirium* (ED) is an essential condition in the immediate postoperative period. Systematic review and meta-analysis of randomized controlled trials have concluded that the effect of ketamine on postoperative delirium remains unclear. The present study sought to evaluate if the intraoperative use of ketamine for postoperative analgesia is associated with postoperative ED in laparoscopic surgeries.

Methods: A prospective observational study was performed in the PostAnesthetic Care Unit (PACU) to evaluate patients who had undergone laparoscopic surgery under a rigid intraoperative anesthesia protocol from July 2018 to January 2019. Patients submitted to laparoscopic surgery for

cholecystectomy, oophorectomy, or salpingectomy with a score ≥1 on the Richmond Assessment Sedation Scale (RASS) or ≥2 on the Nursing Delirium Screening Scale (Nu-DESC) were considered to have ED. *t*-test, Chi-Square test or Fisher's exact tests were used for comparison.

Results: One hundred and fifteen patients were studied after laparoscopic surgery. Seventeen patients (14.8%) developed ED, and the incidence of ED in patients who received ketamine was not different from that of other patients (18.3% vs. 10.6%, $p = 0.262$). Patients with ED had more postoperative pain and morphine requirement at the PACU ($p = 0.005$ and $p = 0.025$, respectively). Type of surgery (general surgery, OR = 6.4, 95% CI 1.2–35.2) and postoperative pain (OR = 3.7, 95% CI 1.2–11.4) were risk factors for ED.

Conclusion: In this study, no association was found between ED and intraoperative administration of ketamine in laparoscopic surgeries. Type of surgery and postoperative pain were risk factors for ED.

Introduction

Delirium is described as a common and multifactorial syndrome manifested by decreased attention and perception of the surrounding environment. It can also be accompanied by hallucinations, disorientation, and temporary memory loss.[1] Emergence *Delirium* (ED) is an abnormal mental state that develops after the administration of anesthesia (during the transition from unconsciousness to complete wakefulness), usually limited in time. It is characterized by agitation, irritability, hypervigilance, and hyperactivity.[2,3] It is a condition that occurs in the first 30 minutes of anesthetic recovery, with symptomatic fluctuation or lucid intervals, which often reverses in one hour. Therefore, it is crucial to distinguish ED from postoperative delirium (occurring for days) and from postoperative cognitive dysfunction (which consists of a prolonged post-surgical state of mental disorder and cognitive deterioration).[3,4]

The incidence of ED varies between 5% and 10%, reaching 20% in specific subgroups, such as pediatric age and the elderly, being more prevalent when associated with major surgery, general anesthesia, and in the presence of postoperative pain.[5] Among the variables related to anesthesia, risk factors identified for developing ED are type of anesthesia, orotracheal intubation and volatile anesthetics. Other risk factors are the type of surgery, male gender, cerebral disease, and drug addiction.[4] In adults, ED is difficult to predict, thus anesthesiologists should remain alert to this possibility by appropriately monitoring the state of consciousness of the patients using valid and reproducible scales, such as the Richmond Agitation Sedation Scale (RASS) and the Nursing Delirium Screening Scale (Nu-DESC).[6-8]

Some anesthetic agents, such as ketamine, have an unclear effect on postoperative ED. Ketamine is a potent inhibitor of the NMDA [N-methyl-D-aspartate], and also an effective analgesic

due to its affinity for μ opioid receptors.[9,10] It is widely applied in perioperative clinical practice to induce general anesthesia, sedation or reduce pain and the consumption of more potent opioids or in patients with opioid tolerance.[9,11,12] In lower doses (< 1 $mg.kg^{-1}$), its psychoactive effects, such as visual and auditory hallucinations, depersonalization, changes in body perception and deficits in proprioception, are less evident. There is controversial information related to the implications of ketamine use during anesthesia: some studies suggest a protective effect of ketamine regarding ED, but other studies state that ketamine does not prevent ED or is associated with ED.[13-16] A recent systematic review and meta-analysis of 6 randomized controlled trials concluded that the effect of ketamine on postoperative delirium remains unclear.[17]

Regarding laparoscopic surgeries, the present study aimed to assess whether the occurrence of postoperative ED is associated with the intraoperative use of ketamine for postoperative analgesia.

Methods

Study design

A prospective observational study was performed at the Anesthesiology Department of Centro Hospitalar e Universitário São João (Porto, Portugal) between July 2018 and January 2019 in patients undergoing laparoscopic surgery. The study was conducted following the Declaration of Helsinki and obtained approval from the local ethics committee. All collected data were saved anonymously, and informed consent was requested from all patients. This observational study was performed according to STROBE guidelines.

Sample

Two days a week (Tuesday and Wednesday), during the period of the study, every patient aged between 18 and 65 years with American Society of Anesthesiology (ASA) physical status I or II who underwent laparoscopic surgery for cholecystectomy, oophorectomy, or salpingectomy, and admitted to the PostAnesthesia Care Unity (PACU) at Centro Hospitalar e Universitário São João, were eligible for the study. Exclusion criteria were patient refusal, incapacity to provide informed consent, history of drug addiction or alcohol abuse, pregnancy, urgent surgery, psychiatric pathology, the existence of adverse anesthetic events in the intraoperative or anesthetic recovery, and patients with a Revised Cardiac Risk Index (RCRI) > 1.[18]

Obtaining data and definitions

Anesthesia was provided and monitored according to the criteria of the anesthesiologist in charge, but

this conduct followed minimum departmental standards. These standards include administering drugs adjusted to the patient's ideal body weight, namely propofol, fentanyl, rocuronium and dexamethasone, and using inhalational anesthetic sevoflurane for maintenance. All patients had Bispectral® index (BIS) or state entropy monitored, and a deep neuromuscular block guided by Post-Tetanic Count (PTC). Analgesia was provided with fentanyl 3–5 $g.kg^{-1}$ (up to 30 minutes to the end of surgery) and maintenance of normothermia (guided by esophageal temperature). Administration of maintenance fluids with 0.9% saline solution according to the Holliday-Segar formula. Before the end of the surgery, paracetamol 1000 mg, ketorolac 30 mg, tramadol 2 $mg.kg^{-1}$, morphine 0.5 $mg.kg^{-1}$, and ondansetron 4 mg are usually administrated. Sugammadex (TOF-guided ratio) was used to obtain reversal of muscle relaxation. Patients were usually extubated in the operating room and transferred to the PACU. Criteria for extubation included sustained head lift or hand grip for more than 5 seconds, the ability to follow simple commands, a stable ventilatory pattern with acceptable arterial oxygen saturation (SpO_2 > 95%), and a TOF ratio greater than 0.9. A face mask was used to administer all subjects 100% oxygen after tracheal extubation. The anesthesiologist was free to decide whether to administer oxygen during the transfer from the operating room to the PACU. Upon arrival at the PACU, all subjects were given oxygen by nasal cannula or face mask. The decision to administer ketamine during anesthesia induction was the responsibility of the anesthesiologist in charge. In these cases, a total of 0.5 $mg.kg^{-1}$ of ketamine (considering the patient's ideal body weight) was administrated during anesthesia induction (after propofol administration). Ketamine administration was only considered when used at the above dosage (0.5 $mg.kg^{-1}$).

A standardized data collection sheet was completed for each patient that included age, Body Mass Index (BMI – $kg.m^{-2}$), ASA, RCRI, and usual medication, provided analgesia, immediate postoperative vital signs, including the evaluation of pain (using the NRS – Numerical Rating Scale), and discharge data from PACU, postoperative nausea and vomiting, and antiemetic medication during PACU stay. In addition, the presence of hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, respiratory pathology, depression, hypothyroidism, and benzodiazepines at home were also collected from the patient's medical records.

Adapting a classification scheme developed by Lee et al.,[18] we calculated an RCRI score for each patient. At admission to the PACU, the patients were screened for ED using the Nursing delirium Screening Scale (Nu-DESC)[8] (Supplementary Material S1) and the RASS[19] (Supplementary Material S2). Diagnostic values of ED are defined as a total RASS ≥ 1 or a total Nu-DESC ≥ 2.[8] During the evaluation, patients with a Nu-DESC score of 2 or more points or a score of ≥ 1 on the RASS scale (RASS ≥ 1) were considered ED-positive. This evaluation was performed by the anesthesiologist in charge of the PACU at the patient's arrival.

Statistical analysis

Considering open-source statistics for public health (www.openepi.com/SampleSize/SSPropor.htm), a minimum sample of 107 patients was calculated, using a 95% Confidence Interval, an 80% power, and a frequency of ED in the population of 7.5%.[5] A descriptive analysis of variables was performed to summarize data. Data following nonparametric distribution based on the Kolmogorov-Smirnov test for normality are presented as median and interquartile ranges. Dichotomous categorical variables are presented as relative or absolute frequencies. ED was evaluated as a dichotomous variable (presence or absence of ED). Univariate analyses were performed to identify differences between patients with and without ED using the *t*-test to compare continuous variables and Chi-Square or Fisher's exact test to compare categorical variables. Differences were considered statistically significant when $p < 0.05$. Binary logistic regression was performed with variables considered to be determinants for ED, and an Odds Ratio (OR) and 95% Confidence Interval (95% CI) were calculated. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 26.0.

Results

Of the 123 patients observed, only 115 were enrolled in this study (Fig. 1). The remaining eight patients were excluded due to intraoperative events, namely 4 cases of hemodynamic instability, 2 of bronchospasm, and two due to conversion to laparotomy. Sixty-six per cent were female, the mean (SD) age was 46 (10) years, 72 patients (62.6%) underwent a general surgery procedure, and 43 patients (37.4%) underwent gynecological surgery (Table 1).

Regarding ketamine administration, 60 patients (52.2%) received the drug. When comparing the two groups (ketamine and no ketamine administration) (Table 2), there appeared to be no differences in sex, age, type of surgery, BMI, ASA physical status, hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, respiratory pathology, depression and hypothyroidism, benzodiazepines at home, postoperative pain, and morphine requirement at PACU. Seventeen patients developed ED (14.8%) in the postoperative period, and no differences in ED were observed between groups of ketamine administration ($p = 0.262$).

Analyzing patients' ED characteristics (Table 3), no differences were found regarding sex, age, BMI, ASA, hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, respiratory pathology, depression, hypothyroidism, and use of benzodiazepines at home. Finally, patients with ED more frequently underwent general surgery ($p = 0.018$), had more NRS scores > 3, (64.7% vs. 29.6% for NRS > 3, $p = 0.005$), and higher morphine requirement at the PACU (76.5% vs. 46.9%, $p = 0.025$).

Logistic regression (Table 4) shows that type of surgery (general surgery, $p = 0.033$) and

postoperative pain (as NRS > 3, $p = 0.022$) are independent risk factors for ED.

Discussion

ED is a frequent complication in the postoperative period. Literature is controversial concerning the incidence of ED associated with using some anesthetic agents, mainly intraoperative ketamine, for postoperative analgesia.[17,20] Dissociative characteristics of ketamine could be considered an inducer of ED, being one of the main limitations to its use.[21] However, according to Riddell et al.,[13] using ketamine as adjuvant of anesthesia reduces the risk of ED. Moreover, ketamine can contribute to the symptomatic control of ED. In our study, the incidence of ED (14.8%) was higher than the incidence reported in the literature (5%–10%).[2,4,22] No differences were observed in the incidence of ED when ketamine was administered. These results corroborate several studies,[14,15,23] in which the incidence of ED is not associated with intraoperative administration of ketamine.

Despite these findings, the possible association between ketamine and ED remains not fully understood. Nevertheless, there is evidence that ketamine can be used in the treatment of ED in PACU[14,17] and can also be used intraoperatively to reduce postoperative pain (which is an independent risk factor for ED).[24] According to Hudetz et al.,[15] ketamine prevents ED after cardiac surgery because NDMA receptor antagonism reduces post-ischemic neuronal loss in the cortex. Ketamine-induced neuroprotection can occur through inflammatory suppression. On the other hand, the Podcast trial[20] suggests that administering a subanesthetic dose of ketamine does not help prevent ED or reduce postoperative pain. The net effect of ketamine may be deleterious at the cardiovascular level, by the stimulation of the sympathetic nervous system, and at the psychiatric level with hallucinations and postoperative nocturnal nightmares.[20,25] These controversial results in the literature are probably due to the different intraoperative anesthetic protocols and the different analyses and interpretations of postoperative outcomes. In this study, the adoption of a rigid anesthetic protocol aimed to limit the presence of confounding factors.

Regarding the association between ED and age, we did not find an association, which is most likely because the study protocol excluded patients under 18 or above 65, and the incidence of ED is higher in extreme age groups.[3-5] We also did not find an association between ED and ASA physical status, possibly because we excluded patients with ASA greater than 2.

Regarding the analgesic effect of ketamine, no difference was found between groups. In some studies, using ketamine in laparoscopic cholecystectomy decreased postoperative pain, but these studies compared ketamine with other analgesic drugs.[26] In the present study, the analgesic protocol is largely multimodal (with paracetamol, ketorolac, tramadol, and morphine) and the scope for improving postoperative analgesia when adding ketamine is narrow. Scientific literature reports an

association between ED and the following risk factors: sex, age, type of surgery ASA and postoperative pain.[4,5] In our study, patients who developed ED more frequently underwent general surgery (cholecystectomy), had more postoperative pain (NRS higher than 3), and needed more morphine for analgesia at PACU.

The present results must be analyzed and interpreted recognizing the study's limitations, namely the fact that it encompasses different types of laparoscopic surgeries (cholecystectomy, oophorectomy, or salpingectomy). Another limitation is that the study excluded patients older than 65 years of age, who are more susceptible to developing ED. Furthermore, the study only considered a standard dose of ketamine (0.5 $mg.kg^{-1}$ of the patient's ideal body weight). Ketamine also has a wide therapeutic interval (from 0.25 $mg.kg^{-1}$ to 4 $mg.kg^{-1}$ intravenously), and it is reasonable to expect that different doses may lead to different results. The lack of association in this study with certain ED risk factors already described in the literature may result from a rigid intraoperative anesthetic protocol and exclusion criteria. The exclusion of patients with an ASA physical status higher than II (patients with more comorbidities and more susceptible to developing ED) probably affects the external validity of this study. The rigid protocol used in this study (exclusion of patients over 65 and with an ASA higher than II) was a methodological strategy to minimize risk factors for ED other than ketamine administration.

Conclusion

Recognition and, if possible, avoidance of ED risk factors is essential to minimize the incidence of ED. Regarding the intraoperative administration of ketamine for postoperative analgesia in laparoscopic surgery, no association was found with ED. Type of surgery and postoperative pain were found as risk factors for developing ED. Despite the controversial literature, this study may help identify subtypes of surgery (in this case, laparoscopic surgeries) where ketamine administration does not result in the development of ED.

Authors' contributions

Study concept and design: HP. Literature search: HP, MVA, DT. Acquisition, analysis, and interpretation of data: HP, MVA, DT. Writing of manuscript: HP, MVA. Critical review and approval of manuscript: all authors. LGP, FA guarantee the integrity of the work.

Funding

No sources of funding.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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Table 1 Patient baseline characteristics.

Variable	**Total (n = 115)**
Sex, n (%)	
Male	39 (33.9)
Female	76 (66.1)
Age, μ (SD)	46.6 (10.1)
Surgery, n (%)	
General	72 (62.6)
Gynecology	43 (37.4)
BMI ($kg.m^{-2}$), μ (SD)	28.2 (7.5)
ASA Physical status, n (%)	
I	33 (28.7)
II	82 (71.3)
Associated pathology, n (%)	
Obesity	47 (40.9)
Hypertension	33 (28.7)
Dyslipidemia	20 (17.4)
Type 2 diabetes mellitus	14 (12.2)
Respiratory pathology	9 (7.8)
Depression	8 (7)
Hypothyroidism	7 (6.1)
Benzodiazepines at home, n (%)	21 (18.3)
Emergence *Delirium*, n (%)	17 (14.8)
Intraoperative use of ketamine, n (%)	60 (52.2)
Without intraoperative ketamine, n (%)	55 (47.8)

μ, mean; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status.

Table 2 Ketamine comparison between patients (n = 115).

Variable	**Ketamine (n = 60)**	**No Ketamine (n = 55)**	***p*-value**
Sex, n (%)			0.515[a]
Male	22 (36.7)	17 (30.9)	
Female	38 (63.3)	38 (69.1)	
Age, μ (SD)	46.2 (9)	47 (11.1)	0.665[b]
Surgery, n (%)			0.580[a]
General	39 (65)	33 (60)	
Gynecology	21 (35)	22 (40)	
BMI ($kg.m^{-2}$), μ (SD)	29.2 (8.9)	27.2 (5.5)	0.151[b]
Physical status ASA, n (%)			0.615[a]
I	16 (26.7)	17 (30.9)	
II	44 (73.3)	38 (69.1)	
Associated pathology, n (%)			
Hypertension	19 (31.7)	14 (25.5)	0.462[a]
Type 2 diabetes mellitus	9 (15)	5 (9.1)	0.333[a]
Obesity	27 (45)	20 (36.4)	0.347[a]
Dyslipidemia	11 (18.3)	9 (16.4)	0.781[a]
Respiratory pathology	4 (6.7)	5 (9.1)	0.735[c]
Depression	4 (6.7)	4 (7.3)	1.000[c]
Hypothyroidism	2 (3.3)	5 (9.1)	0.257[c]
Benzodiazepines at home, n (%)	14 (23.3)	7 (12.7)	0.141[a]
Emergence *Delirium*, n (%)	11 (18.3)	6 (10.9)	0,262[a]
Pain after surgery, n (%)			0.959[a]
NRS ≤ 3	39 (65)	36 (65.5)	
NRS > 3	21 (35)	19 (34.5)	
Morphine requirement at PACU	27 (45)	32 (58.2)	0.158[a]

[a] Chi-square test; [b] *t*-Test; [c]Fisher's exact test.

μ, mean; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status; NRS, Numerical Rating Scale; PACU, PostAnesthetic Care Unit.

Table 3 Emergence delirium comparison between patients (n = 115).

Variable	Emergence *delirium* (n = 17)	Without Emergence, *delirium* (n = 98)	*p*-value
Sex, n (%)			0.493[a]
Male	7 (41.2)	32 (32.7)	
Female	10 (58.8)	66 (67.3)	
Age, μ (SD)	45.6 (11)	46.8 (10)	0.672[b]
Surgery, n (%)			0.018[a]
General	15 (88.2)	57 (58.2)	
Gynecology	2 (11.8)	41 (41.8)	
BMI ($kg.m^{-2}$), μ (SD)	27.5 (5.8)	28.3 (7.8)	0.686[b]
Physical status ASA, n (%)			0.388[c]
I	3 (17.6)	30 (30.6)	
II	14 (82.4)	68 (69.4)	
Associated pathology, n (%)			
Hypertension	5 (29.4)	28 (28.6)	1.000[c]
Type 2 diabetes mellitus	4 (23.5)	10 (10.2)	0.219[c]
Obesity	4 (23.5)	43 (43.9)	0.115[a]
Dyslipidemia	3 (17.6)	17 (17.3)	1.000[c]
Respiratory pathology	3 (17.6)	6 (6.1)	0.128[c]
Depression	1 (5.9)	7 (7.1)	1.000[c]
Hypothyroidism	2 (11.8)	5 (5.1)	0.276[c]
Benzodiazepines at home, n (%)	4 (23.5)	17 (17.3)	0.511[c]
With Ketamine, n (%)	11 (64.7)	49 (50)	0.262[a]
Without Ketamine, n (%)	6 (35.3)	49 (50)	
Pain after surgery, n (%)			
NRS ≤ 3	6 (35.3)	69 (70.4)	
NRS > 3	11 (64.7)	29 (29.6)	0.005[a]
Morphine requirement at PACU	13 (76.5)	46 (46.9)	0.025[a]

[a] Chi-square test; [b] *t*-Test; [c] Fisher's exact test.

μ, mean; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status; NRS, Numerical Rating Scale; PACU, PostAnesthetic Care Unit.

Table 4 Logistic Regression analysis for predictors of ED.

Variable	OR	OR (95% CI)	*p*-value[a]
Type of Surgery (general)	6.40	(1.2–35.2)	0.033
Sex (male)	1.41	(0.43–4.65)	-
Age	0.99	–	-
Benzodiazepines at home	0.76	–	-
Pain after surgery, (NRS > 3)	3.70	(1.2–11.3)	0.022

[a] Logistic regression analysis, with variables considered to be determinants for ED.

OR, Odds Ratio; CI, Confidence Interval; NRS, Numerical Rating Scale.

Figure 1 Flow chart of recruitable and included patients.