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REPORTS OF ORIGINAL INVESTIGATIONS

A prospective observational study of the efficacy of ketamine for rescue analgesia in the postanesthesia recovery unit

Une étude observationnelle prospective sur l'efficacité de la kétamine pour l'analgésie de secours en salle de réveil

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Abstract

Background *Early severe postoperative pain is frequently resistant to management with opioid analgesia alone. Perioperative low-dose ketamine as an analgesia adjunct has been studied extensively. Its efficacy as a rescue analgesic in the postanesthesia care unit (PACU) has not been determined. The objective of this study was to evaluate the analgesic efficacy of low-dose bolus ketamine for opioid-resistant pain in the PACU by measuring its effect on numerical rating scale (NRS) pain scores and opioid requirement.*

Methods *This was a prospective observational study of adult noncardiac surgery patients with significant postoperative pain in the PACU. Patients were administered bolus doses of intravenous ketamine in 10-mg increments, repeated two to three times to an approximate maximum dose of 0.25 mg·kg^{-1}. Primary outcomes were resting pain score reduction and opioid use from time of bolus ketamine administration to 30 min after administration of final ketamine bolus. The secondary outcome was incidence of side effects from ketamine administration.*

Results *A convenience sample of 100 patients was chosen. The mean (standard deviation) NRS resting pain score reduction 30 min after iv ketamine administration was 2.7 (1.8) ($P < 0.001$). Patients with a history of previous opioid use or chronic pain were not more responsive to the effects of low-dose bolus ketamine. There were no ketamine-related adverse effects in any of the study patients.*

Conclusion *Administration of low-dose bolus ketamine in the PACU for severe opioid-resistant pain was associated with a significant improvement in analgesia in this observational study.*

Résumé

Contexte *La douleur postopératoire sévère précoce est souvent résistante à une prise en charge par analgésie opioïde seule. La kétamine périopératoire à faible dose en tant qu'analgésie adjuvante a fait l'objet d'études approfondies. Son efficacité en tant qu'analgésie de secours en salle de réveil est encore mal déterminée. L'objectif de cette étude était d'évaluer l'efficacité analgésique d'un bolus de kétamine à faible dose pour soulager la douleur résistante aux opioïdes en salle de réveil en mesurant son effet sur les scores de douleur sur une échelle d'évaluation numérique (EEN) et sur les besoins en opioïdes.*

Méthode *Il s'agissait d'une étude observationnelle prospective auprès de patients adultes ayant bénéficié d'une chirurgie non cardiaque et présentant une douleur postopératoire importante en salle de réveil. Les patients ont reçu des bolus de kétamine intraveineuse par tranches de 10 mg, répétés deux à trois fois jusqu'à une dose maximale approximative de 0,25 mg·kg^{-1}. Les critères d'évaluation principaux étaient la réduction du score de douleur au repos et la consommation d'opioïdes à partir du moment de l'administration de kétamine en bolus jusqu'à*

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30 minutes après l'administration du bolus final de kétamine. Le critère d'évaluation secondaire était l'incidence d'effets secondaires liés à l'administration de kétamine.

Résultats *Un échantillon de commodité de 100 patients a été choisi. La réduction moyenne (écart type) du score de douleur au repos sur l'EEN 30 min après l'administration de kétamine iv était de 2,7 (1,8) (P < 0,001). Les patients ayant des antécédents de consommation antérieure d'opioïdes ou de douleur chronique n'étaient pas plus sensibles aux effets de la kétamine en bolus à faible dose. Il n'y a eu aucun effet indésirable lié à la kétamine chez aucun des patients de l'étude.*

Conclusion *L'administration de kétamine en bolus à faible dose en salle de réveil pour soulager la douleur sévère résistante aux opioïdes a été associée à une amélioration significative de l'analgésie dans cette étude observationnelle.*

Keywords ketamine · opioid-resistant pain · PACU · postsurgical pain

Early postoperative pain control in the postanesthesia care unit (PACU) can be challenging. Opioid analgesia is the predominant treatment modality. Nevertheless, repeat dosing and escalating doses are frequently inadequate. In addition, opioid analgesia can be associated with unwanted adverse events such as respiratory depression, sedation, nausea, and vomiting. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has analgesic properties at subanesthetic doses (< 0.2 mg·kg^{-1}). It acts in a noncompetitive manner by binding to the phencyclidine receptor site and has previously been noted to have a marked hypoalgesic effect on high-intensity nociceptive stimuli.[1,2] This may explain why it has a more marked analgesic effect on high-intensity opioid-resistant postoperative pain.

Perioperative use of ketamine as an analgesia adjunct has been studied extensively. A 2018 Cochrane review of 130 studies with 8,341 participants concluded that perioperative intravenous ketamine reduces postoperative opioid consumption and pain intensity after thoracic surgery, major orthopedic surgery, and major abdominal surgery.[3] Most of the studies in this review evaluated a peri-incisional ketamine bolus,[4] an intraoperative or postoperative ketamine infusion,[5] or a postoperative ketamine dose as part of patient-controlled opioid analgesia.[6] At our institution, it is common practice to administer a bolus of low-dose ketamine in the PACU for patients with pain that is not responding to conventional doses of opioid analgesia. Evidence supporting this practice is sparse and nonconvergent. In a randomized controlled trial (RCT), Gillies *et al*. found no benefit with respect to pain score or morphine consumption when ketamine 0.25 mg·kg^{-1} was coadministered with morphine in the recovery room.[1] In this study, ketamine was administered as an infusion over ten minutes. Conversely, in an RCT of 245 patients undergoing abdominal surgery, orthopedic surgery, or lung wedge resection, Weinbroum reported significantly lower pain scores in patients who were coadministered ketamine 0.25 mg·kg^{-1} with morphine 15 μg·kg^{-1} as rescue analgesia for opioid-resistant immediate postoperative pain.[7]

There are no studies evaluating the efficacy of a subanesthetic bolus of ketamine as a sole rescue analgesic agent in the PACU. The objective of this study was to evaluate the analgesic efficacy of low-dose bolus ketamine for opioid-resistant pain in the PACU after noncardiac surgery by measuring its effect on NRS pain scores and opioid requirement after ketamine administration.

Methods

This prospective observational study was approved by the institutional review board of the University of Alberta (protocol number 00102967) and registered at ClinicalTrials.gov (NCT04701008). Need for consent was waived by the institutional review board as this was an observational study and did not involve an intervention that differed from institutional standard of care for management of opioid-resistant pain in the PACU.

From 14 September 2020 to 10 June 2021, patients who were 18 yr and older and having elective or emergency noncardiac surgery at the University of Alberta Hospital were included in the study if they were having significant postoperative pain in PACU, as determined by the PACU nurse, despite having received 0.1 mg·kg^{-1} or more of *iv* morphine equivalents (*iv* MoEq). Exclusion criteria were refusal to receive ketamine, undergoing cardiac surgery, not receiving opioids in the PACU, and a contraindication for receiving ketamine. Having satisfied inclusion and exclusion criteria, patients were administered a bolus dose of *iv* ketamine 10 mg. In the event of an inadequate response to the initial bolus as determined by the PACU nurse, further 10-mg increments were administered to an approximate maximum dose of 0.25 mg·kg^{-1}, until such time as pain was well controlled and tolerable. Midazolam 1 mg *iv* was coadministered as a premedication at the PACU nurse's discretion to prevent psychomimetic effects. This was repeated after 15 min if necessary. Opioid administration continued after ketamine administration on an "as required" basis. Primary outcomes were resting pain

score reduction and opioid use from time of bolus ketamine administration to 30 min after administration of final ketamine bolus. Pain scores were measured using a numerical rating scale (NRS) from 0 to 10. The secondary outcome was incidence of adverse events related to ketamine administration. The following adverse effects were sought: visual disturbances, hallucinations, nightmares, dysphoria, disorientation, and sedation.

Statistical analysis

A convenience sample was chosen of patients who matched inclusion criteria within one year from the start of enrollment, or 100 patients who matched all inclusion criteria, should this occur first.

An *a priori* statistical analysis plan was developed and finalized prior to study commencement.

Analysis was performed using R 3.4.0 (R Foundation of Statistical Computing, Vienna, Austria) and SAS 9.4 software (SAS Institute, Cary, NC, USA). Participants were included only if they received the intended intervention in accordance with the study protocol. Patients' demographic information and clinical characteristics were examined with descriptive statistics, using frequency (percentage) for categorical variables and mean (standard derivation [SD]) for continuous variables. The primary outcome, pain score reduction 30 min after ketamine administration, was analyzed using a paired *t* test. Regression analysis was performed to evaluate the impact of demographic variables, history of chronic pain, regular opioid use or substance abuse, and administration of intraoperative opioids, PACU opioids, and midazolam on pain reduction. Univariable regression was performed using linear regression. Variables that were significant (statistically $P < 0.05$, or clinically as identified by the research team) at the univariate level were moved into the multivariate regression model. Multivariable regression was performed using linear regression. The pattern of multicollinearity was assessed using variable inflation factors (VIF) (which determine the strength of the correlation between the independent variables). This test showed no issue of multicollinearity (VIFs < 10). For all the statistical tests, a P value < 0.05 was considered statistically significant.

Results

One hundred and forty-three patients were included in the initial analysis. Forty-three patients were excluded because ketamine was administered before administration of 0.1 $mg{\cdot}kg^{-1}$ of *iv* MoEq. Of the remaining one hundred patients, data were not available regarding the presence of pre-existing chronic pain and preoperative opioid use in one patient. The mean (SD) age was 50.5 (16.5) yr, 41% of patients were male, 84% of patients had an American Society of Anesthesiologists Physical Status of II or III, and the commonest surgery subtype was general surgery (27%) (Table 1). Almost a third of the patients (32%) were regular opioid users preoperatively, 15% described a history of substance abuse, and 30% had a history of chronic pain. All patients received general anesthesia; one patient had an attempted spinal anesthetic that required conversion to general anesthesia. Three patients received preoperative nerve blocks for postoperative analgesia—a continuous interscalene brachial plexus block, a continuous femoral block, and a single-shot femoral block. Total intraoperative remifentanil use was low, with a mean (SD) of 207 (510) μg and a median [interquartile range] of 0 [0–100] μg

The mean (SD) NRS resting pain score reduced from 7.9 (1.5) before ketamine administration to 5.2 (2.4) 30 min after ketamine administration ($P < 0.001$) (Table 2). The mean (SD) reduction in NRS pain score was 2.7 (1.8) 30 min after *iv* ketamine administration ($P < 0.001$) (Table 2). The mean (SD) ketamine dose in the recovery room was 0.24 (0.11) $mg{\cdot}kg^{-1}$ (Table 3). In the PACU, patients received a mean (SD) *iv* MoEq dose of 0.14 (0.05) $mg{\cdot}kg^{-1}$ before receiving ketamine and a dose of 0.04 (0.07) $mg{\cdot}kg^{-1}$ after receiving ketamine. Patients with a history of previous opioid use, substance abuse, or chronic pain were not more responsive to the effects of low-dose bolus ketamine. There were no reported ketamine-related adverse events in any of the study patients (Table 4).

A multivariable linear regression model with pain score reduction at 30 min as the dependent variable found a positive association with ketamine administration in the PACU ($P = 0.04$). No association was found between pain score reduction at 30 min after ketamine administration and *iv* MoEq dose in the PACU after ketamine in the PACU ($P = 0.08$), intraoperative remifentanil administration ($P = 0.15$), midazolam coadministration with ketamine in the PACU ($P = 0.37$), substance abuse preoperatively ($P = 0.16$), history of chronic pain ($P = 0.70$), and regular opioid use preoperatively ($P = 0.48$).

Discussion

In this observational study, low-dose bolus ketamine was found to be of benefit for the management of opioid-resistant pain in the PACU. The mean (SD) reduction in NRS resting pain score 30 min after *iv* ketamine administration was 2.7 (1.8) ($P < 0.001$). This represents a greater than 25% reduction, which we deem to be clinically significant. We did not find an association

Table 1 Characteristics of patients who received bolus ketamine for rescue analgesia in the PACU

ASA Physical Status score, mean (SD)		2.3 (0.7)
	I, *n*/total *N* (%)	12/100 (12%)
	II, *n*/total *N* (%)	47/100 (47%)
	III, *n*/total *N* (%)	37/100 (37%)
	IV, *n*/total *N* (%)	4/100 (4%)
Age (yr), mean (SD)		50.5 (16.4)
Sex, *n*/total *N* (%)	Male	41/100 (41%)
Weight (kg), mean (SD)		77.8 (15.2)
Surgery type, *n*/total *N* (%)	ENT	5/100 (5%)
	General surgery	27/100 (27%)
	Neurosurgery	1/100 (1%)
	Orthopedic surgery	23/100 (23%)
	Plastic surgery	13/100 (13%)
	Spine	8/100 (8%)
	Urology	23/100 (23%)

ASA = American Society of Anesthesiologists; ENT = ear, nose, and throat; SD = standard deviation

Table 2 Univariate analysis of pain scores and pain score reduction related to ketamine use for rescue analgesia in the PACU

Variable	Before ketamine	30 min after ketamine	*P* value
NRS pain score, mean (SD)	7.9 (1.5)	5.2 (2.4)	< 0.001
NRS pain score reduction 30 min after ketamine administration, mean (SD)		2.7 (1.8)	< 0.001

NRS = numerical rating scale; PACU = postanesthesia care unit; SD = standard deviation

Table 3 Descriptive analysis of ketamine and opioid doses in the OR and PACU

Ketamine in the PACU ($mg \cdot kg^{-1}$), mean (SD)	0.24 (0.11)
iv MoEq in the OR (mg), mean (SD)	19.0 (11.0)
iv MoEq in the OR ($mg \cdot kg^{-1}$), mean (SD)	0.25 (0.15)
iv MoEq in the PACU before ketamine (mg), mean (SD)	10.6 (3.8)
iv MoEq in the PACU before ketamine ($mg \cdot kg^{-1}$), mean (SD)	0.14 (0.05)
IV MoEq after ketamine (mg), mean (SD)	3.3 (5.4)
IV MoEq after ketamine ($mg \cdot kg^{-1}$), mean (SD)	0.04 (0.07)
Rescue regional anesthesia, *n*/total *N* (%)	11/100 (11%)
Midazolam in the PACU, *n*/total *N* (%)	45/100 (45%)

iv MoEq = *iv* morphine equivalents; OR = operating room; PACU = postanesthesia care unit; SD = standard deviation

between analgesic efficacy of ketamine and a history of regular opioid use or chronic pain. This is notable in the context of previous findings in favor of ketamine as an adjunct for postoperative pain management in opioid-tolerant patients.[8] Nevertheless, this study is most likely underpowered to detect such a differential effect and these findings must be interpreted with caution.

Perioperative ketamine for analgesia has been studied extensively, most commonly as an intraoperative or postoperative continuous infusion, or as a peri-incisional bolus.[3,4] A 2018 Cochrane review found that, when administered in this fashion, ketamine was associated with modest reductions in resting pain scores at 24 and 48 postoperative hr (5/100 mm at both junctures) and had

Table 4 Multivariable linear regression model with pain score reduction at 30 min as the dependent variable

	Coefficient (SE)	95% CI	*P* value
Ketamine in PACU (mg·kg^{-1})	-3.68 (1.82)	-7.31 to -0.04	0.04
Intraoperative remifentanil	-0.53 (0.36)	-1.26 to 0.20	0.15
iv MoEq in PACU after ketamine (mg)	-0.66 (0.37)	-1.40 to 0.08	0.08
Midazolam in PACU (mg)	0.35 (0.39)	-0.42 to 1.13	0.37
Substance abuse preoperatively	-0.71 (0.50)	-1.71 to 0.28	0.16
History of chronic pain	-0.23 (0.62)	-1.48 to 1.00	0.70
Regular opioid use preoperatively	-0.40 (0.57)	-1.54 to 0.73	0.48

CI = confidence interval; *iv* MoEq = *iv* morphine equivalents; PACU = postanesthesia care unit; SE = standard error

opioid-sparing properties.[3] Both studies that investigated the use of bolus low-dose ketamine as a rescue analgesic in the PACU were excluded from this Cochrane review.[1,7]

The analgesic effect of ketamine is most likely mediated via inhibition of NMDA receptors in nociceptive neurons and activation of descending inhibitory monoaminergic pathways.[9] It may also attenuate the wind-up of dorsal horn neurons that results from repetitive, constant-intensity C-fiber stimuli. Finally, ketamine may offset opioid-induced hyperalgesia, once thought to require months to develop but now known to occur in the intraoperative and early postoperative periods in response to high-dose remifentanil and fentanyl.[10,11]

The immediate postoperative period is unique regarding pain and its treatment because onset is abrupt, and pain is frequently severe in nature. The mean (SD) resting NRS pain score prior to ketamine administration in our study was 7.9 (1.5). This represents severe, opioid-resistant pain at baseline. Subtherapeutic ketamine as a sole agent has weak analgesic properties. Nevertheless, when used for severe pain, or when coadministered with an opioid, our study findings are in line with earlier investigations showing its efficacy in these circumstances. It is notable that we found a greater pain score reduction compared with what was reported in the Cochrane review.[3] This may be because of the more intense nature of immediate postoperative pain in addition to the fact that ketamine was administered as a bolus.

A closer look at the mechanism of action of ketamine at the NMDA receptor may help elucidate its specificity for severe pain. The NMDA receptor, a ligand-gated ion channel, is found peripherally in deep tissue and centrally in dorsal horn neurons.[2,12,13] Its associated ion channel must be in an open state to allow passage of Ca^{2+} and Na^{+} ions. The excitatory amino acid glutamate, released in response to nociceptive stimulation, opens the NMDA ion channel thereby allowing ion influx, depolarization, and neuronal activation. Ketamine acts as a noncompetitive antagonist at the NMDA receptor, but the channel must be in an open state for ketamine to bind to it. It is possible that the nociceptive stimulation of severe early postoperative pain provides a substrate for ketamine, which in less painful circumstances is not as effective an analgesic. A prolonged effect associated with ketamine-induced analgesia, extending beyond five half-lives ($t_{½\alpha}$ ketamine, 11–17 min), might be explained by the noncompetitive nature of its antagonism, i.e., an increased concentration of glutamate cannot overcome the ketamine block in the ion channel.[1]

We did not find an association between intraoperative remifentanil administration and pain score reduction after ketamine administration in the PACU. Intraoperative remifentanil use has previously been associated with development of acute opioid tolerance and opioid-induced hyperalgesia (OIH).[14,15] Indeed, ketamine has been shown to attenuate remifentanil-induced postoperative hyperalgesia.[15] Total intraoperative remifentanil use in our patient population was low. A meta-analysis of RCTs investigating an association between intraoperative opioid use and acute OIH found that OIH was not seen below a cumulative mean (SD) remifentanil dose of 2,297 (1,890) μg.[11]

Our study has limitations. It is not an RCT and without a comparator group, several confounding factors may have contributed to the observed pain reduction. This prevents us from drawing strong conclusions regarding the effect of low-dose ketamine on opioid-resistant pain in the PACU. Convenience sampling is a relatively quick and inexpensive methodology. An RCT would have necessitated recruiting and obtaining consent from all surgical patients as it is not possible to determine with reasonable accuracy before surgery which population will have opioid-resistant immediate postoperative pain. The scarcity of previous studies to inform anticipated effect size also contributed to our decision to choose nonprobabilistic convenience sampling. Nevertheless, we acknowledge that

the data are subject to sampling and selection bias, which limit its generalizability and external validity. Secondly, we did not control for which patients were coadministered midazolam with ketamine. A large proportion of patients (45%) received midazolam. Though univariable and multivariable linear regression models failed to show an association between midazolam administration and pain score reduction 30 min after ketamine administration, these analyses may not have been powered to detect such an association. Finally, 11/100 patients received a rescue regional block more than 30 min after ketamine administration. The mean (SD) resting pain score in these eleven patients 30 min after ketamine administration was 6.7 (2.8), showing failure of low-dose bolus ketamine in these patients and the need for further analgesia.

Conclusion

Administration of low-dose bolus ketamine in the PACU for severe opioid-resistant pain was associated with a significant improvement in analgesia in this observational study. Randomized controlled trials in selected surgical subgroups are required to further investigate this effect.

Author contributions *Carole-Anne Potvin* contributed to study design and data collection. *James Green* contributed to study design and manuscript writing. *Bo Pan* contributed to statistical planning, analysis, and reviewing the manuscript. *Yazid N. Al Hamarneh* contributed to statistical planning, analysis, and reviewing the manuscript. *Derek Dillane* contributed to study design, data collection, and manuscript writing.

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