Lack of a pre-emptive effect of low-dose ketamine on postoperative pain following oral surgery

[Absence d'effet préventif de faibles doses de kétamine sur la douleur postopératoire en chirurgie buccale]

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Purpose: The aim of this study was to assess the effect of pre- *vs* postincisional low-dose *iv* ketamine on postoperative pain in outpatients scheduled for oral surgery under general anesthesia.

Methods: Eighty-four patients were randomly assigned to receive intravenously saline before and after surgery in Group 1, ketamine 300 $\mu g \cdot kg^{-1}$ *iv* before and saline after surgery in Group 2, saline before and ketamine 300 $\mu g \cdot kg^{-1}$ *iv* after surgery in Group 3. Postoperative analgesia consisted of *iv* proparacetamol and ketoprofen. Rescue analgesia consisted of nalbuphine 200 $\mu g \cdot kg^{-1}$ *iv*. Analgesia at home consisted of oral ketoprofen, and acetaminophen with codeine as rescue analgesia. A telephone interview was conducted on the first and second postoperative days.

Results: There were no significant differences between groups with respect to pain scores, the number of patients requiring nalbuphine in the postanesthesia care unit (PACU), (36.7%, 38.7%, and 39.5% for Groups 1, 2, and 3 respectively), or nalbuphine consumption in the PACU (66.5 $\mu g \cdot kg^{-1}$ ± 16.8, 75.9 $\mu g \cdot kg^{-1}$ ± 17.5, 66.7 $\mu g \cdot kg^{-1}$ ± 21.6 for Groups 1, 2, and 3 respectively). The number of rescue analgesic tablets taken at home, and time to first request for rescue analgesia, sedation scores, or side-effects were similar amongst groups. No patient required nalbuphine in the ambulatory care unit.

Conclusions: There was no benefit to pre-emptive administration of ketamine 300 $\mu g \cdot kg^{-1}$ *iv* whether administered pre- or postoperatively.

Objectif *: Le but de cette étude était de tester l'efficacité sur la douleur postopératoire de faibles doses iv de kétamine préopératoires vs postopératoires en chirurgie buccale ambulatoire.*

Méthode *: Quatre-vingt-quatre patients étaient répartis au hasard pour recevoir par voie iv respectivement avant et après la chirurgie : une solution salée dans le Groupe 1, 300 $\mu g \cdot kg^{-1}$ de kétamine et une solution salée dans le Groupe 2, une solution salée et 300 $\mu g \cdot kg^{-1}$ de kétamine dans le Groupe 3. L'analgésie postopératoire était assurée systématiquement par du propara-cétamol et du kétoprofène en hospitalisation, et du kétoprofène à domicile. L'analgésie de complément était assurée par 200 $\mu g \cdot kg^{-1}$ de nalbuphine en hospitalisation, et par du paracétamol-codéine po à domicile. Un interview téléphonique était effectué les premier et second jours postopératoires.*

Résultats *: Aucune différence significative n'a été retrouvée entre les groupes concernant les scores de douleur, le nombre de patients ayant reçu de la nalbuphine (36,7 %, 38,7 %, et 39,5 % respectivement pour les Groupes 1, 2 et 3), la consommation de nalbuphine (66,5 $\mu g \cdot kg^{-1}$ ± 16,8, 75,9 $\mu g \cdot kg^{-1}$ ± 17,5, 66,7 $\mu g \cdot kg^{-1}$ ± 21,6 respectivement pour les Groupes 1, 2 et 3), le nombre de comprimés de secours à domicile : 6 (2,13), 7 (2,20), et 7 (1,12) respectivement pour les Groupes 1, 2 et 3, la première demande d'analgésique de secours, les scores de sédation ou les effets secondaires.*

Conclusion *: Cette étude n'a démontré aucun effet préventif sur la douleur postopératoire de 300 $\mu g \cdot kg^{-1}$ de kétamine iv administrée avant ou après l'opération.*

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Assessed February 17, 2005.
Revision accepted July 2, 2005.
Final revision accepted September 1, 2005.

SURGICAL removal of third molars is a common procedure that is well suited for outpatient surgery. However, tissue trauma during surgery modifies the central processing pathway for pain perception. These changes lead to central sensitization with increased sensitivity to painful stimuli (mechanical hyperalgesia).[1] Consequently, pain may delay time for discharge from the outpatient surgery unit and may last for several days after oral surgery. Central sensitization involves activation of the N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord.[2] The NMDA receptor antagonist ketamine may therefore be appropriate for preventing postoperative hyperalgesia and for improving postoperative pain relief.[3] There are controversial results concerning the pre-emptive effect of ketamine on postoperative pain. Some studies have documented an opioid sparing effect of perioperative *iv* low-dose ketamine[4–8] and others have not.[9–14] These discrepancies may be due to the large interstudy variability in surgical procedures, patient population, dose of ketamine administered, timing of administration, and study design.[15,16]

In studies that fail to demonstrate a preventive effect of a low-dose ketamine on postoperative pain, the question of whether a lack of efficacy on central sensitization is linked to insufficient pre- or postoperative blockade remains unresolved. Pre-emptive analgesia requires that a preoperative analgesic intervention reduce pain or analgesic consumption to a greater extent than the identical intervention administered after surgery. This is distinct from the broader concept of preventive analgesia that does not require inclusion of a preoperative analgesic intervention. We therefore conducted a prospective, randomized, double-blind, placebo-controlled study to assess the pre-emptive effect of low-dose *iv* ketamine administered before surgical incision or at the end of surgery on postoperative pain, in outpatients scheduled for third molar surgical removal under standardized general anesthesia.

Material and methods

This study received Institutional Review Board approval for clinical research and all patients gave informed consent. Outpatients of American Society of Anesthesiologists physical status I or II scheduled for third molar surgical removal (three to four teeth) performed by the same surgeon under general anesthesia were eligible for the study if they suffered moderate to severe pain (assessed on a four-point scale: 0 = no pain at all, 1 = moderate pain, 2 = severe but bearable pain, 3 = severe unbearable pain) within four hours of surgery, for better assessment of rescue analgesia. The surgeon did not perform local infiltration of the surgical field. Patients with a history of substance abuse, chronic analgesic use, intake of any analgesic drug within one week before surgery, cardiovascular, hepatic, renal or psychiatric disease, were excluded from the study. All patients were instructed preoperatively in the use of a ten–step visual analogue scale (VAS; 0 = no pain, 100 = worst pain imaginable).

Patients were premedicated with oral hydroxyzine 1 $mg \cdot kg^{-1}$ 90 min before surgery. Intraoperative monitoring included electrocardiogram, non-invasive blood pressure and pulse oximetry. Standard recording of heart rate (HR) and mean arterial pressure (MAP) was performed before induction of anesthesia, and were considered as baseline values.

After three minutes of preoxygenation, (FiO_2 = 1.0) anesthesia was induced with propofol 2 $mg \cdot kg^{-1}$ *iv*, lidocaine 1.5 $mg \cdot kg^{-1}$ *iv*, and alfentanil 30 $\mu g \cdot kg^{-1}$ *iv*. Tracheal intubation was performed two minutes after induction without the use of a neuromuscular blocking drug. Lungs were mechanically ventilated (end-tidal CO_2 35–40 mmHg) with sevoflurane 3 to 4% in an oxygen-air mixture (FiO_2 = 0.33). Mean arterial pressure and HR were measured preoperatively and every five minutes intraoperatively. In response to bradycardia, defined as a 20% decrease in HR compared with preoperative value, atropine 20 $\mu g \cdot kg^{-1}$ *iv* was administered. In response to tachycardia, defined as a 20% increase in HR compared with preoperative value, alfentanil 10 $\mu g \cdot kg^{-1}$ *iv* was administered. Finally, in response to hypotension defined as a 20% decrease, or hypertension defined as a 20% increase in MAP compared with the preoperative value, sevoflurane end-tidal concentration was decreased or increased 0.5% respectively.

Patients were randomly assigned, in a double-blind fashion, to one of three groups using a table of computer-generated random numbers. Patients in Group 1 (n = 30) received *iv* isotonic saline at induction of anesthesia and *iv* isotonic saline at the end of surgery. Patients in Group 2 (n = 31) received 300 $\mu g \cdot kg^{-1}$ *iv* ketamine at induction of anesthesia and *iv* isotonic saline at the end of surgery. Patients in Group 3 (n = 23) received *iv* isotonic saline at induction of anesthesia and 300 $\mu g \cdot kg^{-1}$ *iv* ketamine at the end of surgery.

Before induction of anesthesia, a research nurse not involved in the perioperative care of the patient prepared and labelled two syringes with a capacity of 10 mL. The syringe contained either 3 $mg \cdot mL^{-1}$ of ketamine diluted in isotonic saline or isotonic saline alone, according to the randomization schedule.

At induction of anesthesia, 0.1 $mL \cdot kg^{-1}$ of the first 10 mL syringe was administered intravenously. In

Group 2, this volume corresponded to a bolus dose of 300 $\mu g \cdot kg^{-1}$ *iv* of ketamine. At the end of surgery, 0.1 $mL \cdot kg^{-1}$ *iv* of the second 10 mL syringe was administered. In Group 3, this volume corresponded to a bolus dose of 300 $\mu g \cdot kg^{-1}$ *iv* of ketamine. Patients and personnel involved in patient management were unaware of study group assignment, as were those involved in data collection.

After emergence from anesthesia, patients were transferred to the postanesthesia care unit (PACU) until they achieved a modified Aldrete score of 9 on two sequential measurements.[17] They were then transferred to the ambulatory care unit. They were discharged six hours later if they met home-readiness criteria that included orientation to time and place, stable vital signs, absence of nausea, control of pain, and ability to void and ambulate.

Analgesia in the PACU consisted of proparacetamol 15 $mg \cdot kg^{-1}$ *iv* and ketoprofen 1 $mg \cdot kg^{-1}$ *iv*. Pain scores were assessed at 15, 30, 45, 60, 90 min after arrival in the PACU. Nalbuphine 200 $\mu g \cdot kg^{-1}$ bolus dose was given intravenously if VAS pain score was > 30 mm. If VAS pain score remained > 30 mm after nalbuphine administration, morphine was administered using a patient controlled analgesia (PCA) device, and the patient was withdrawn from the outpatient surgery schedule and excluded from the study. Pain scores were assessed in the ambulatory care unit at two, four, and six hours after the completion of surgery. Analgesia in the ambulatory care unit consisted of nalbuphine 200 $\mu g \cdot kg^{-1}$ *iv* if the VAS pain score was > 30 mm. If the VAS pain score remained > 30 mm after nalbuphine administration, morphine was administered using a PCA device and the patient was withdrawn from the outpatient surgery schedule and excluded from the study. The following postoperative complications were recorded in the PACU and in the ambulatory care unit: nausea and vomiting, sedation (assessed on a four-point categorical scale as follows: 0 = alert, aware; 1 = drowsy, not sleeping; 2 = asleep, arousable by verbal contact; 3 = asleep, not arousable by verbal contact), pruritus, urinary retention, and psychodysleptic disorders (hallucinations, dreams, nightmares) and diplopia.

Before discharge from the ambulatory care unit,patients were instructed to take one oral ketoprofen 100 mg tablet twice daily. Rescue analgesic medication at home consisted of oral acetaminophen (400 mg) and codeine (30 mg) every four hours as needed. Patients were instructed to note time to first request rescue analgesic medication and requirement for pain tablets during the first two postoperative days.

A research assistant, also blinded to the group assignment, recorded data on postoperative pain, analgesic consumption at home, time to first request for rescue analgesic medication, and occurrence of side effects during a telephone interview on the first and second postoperative days.

Statistics

All analyses were conducted on an "intention-to-treat" basis. The sample size estimate indicated that at least 23 patients per group were required to show a difference between groups of 25 mm on a 100-mm VAS, assuming a standard deviation (SD) of 30 mm, risk of a type I error of 0.05, and a power of 0.8. Patient characteristics were analyzed by two-way analysis of variance (ANOVA) and unpaired Student's t test. Nominal data were analyzed using the Chi-square test. The mean time that the patients first required postoperative analgesia was calculated using the Kaplan-Meier survival analysis and was compared among groups using the log-rank test. Pain intensity scores were analyzed by using two-way repeated-measures ANOVA. Bonferroni correction was applied when multiple comparisons were made. If data failed requirements for parametric analysis including normality and equal variance, then non-parametric tests were used for comparison between groups. Data are reported as mean ± SD for parametric data or median with a 25% and a 75% range for non-parametric data. Gender data were analysed by a test of proportion. A value of $P < 0.05$ was considered significant. All analyses were performed using the statistical package Statview (Statview for Windows and Macintosh, version 5, SAS Institute Inc., Cary, NC, USA) on Mac OS 9.2.

Results

Of the 117 patients who underwent surgery, 95 (81.2%) experienced moderate or severe pain intensity during the first four hours after the procedure and were enrolled in the study. Eleven patients were excluded from analysis because of protocol violations due to data collection failure (four in Group 1, three in Group 2 and four in Group 3): the data sheets of six patients were incompletely filled, four patients could not be interviewed on rescue analgesia at home, and one patient was administered sufentanil instead of alfentanil intraoperatively. No patient was withdrawn from the outpatient schedule because of postoperative pain requiring morphine administration. The groups were similar with respect to demographic characteristics, duration of surgery, duration of anesthesia, and intraoperative analgesic consumption (Table I).

The median time spent in the PACU was 60 min in the three treatment groups. The groups were similar with respect to the number of patients who

TABLE I Demographic variables, operative times, and intraoperative analgesics

Measure	*Group 1 (placebo)* (*n* = 30)	*Group 2 (preoperative ketamine)* (*n* = 31)	*Group 3 (postoperative ketamine)* (*n* = 23)
Age (yr)	20.7 ± 8.7	18.8 ± 6.7	19.2 ± 6.9
Gender (m/f)	17/13	19/12	13/10
Weight (kg)	60.1 ± 11.9	59.2 ± 12.1	58.6 ± 12.9
Height (cm)	169.2 ± 7.2	170 ± 8.8	168.8 ± 10.5
Duration of			
surgery (min)	20.5 ± 6.7	21.6 ± 8.5	19.4 ± 8.4
anesthesia (min)	29.8 ± 8	30.8 ± 10.5	21.6 ± 8.5
Intraoperative			
alfentanil ($\mu g \cdot kg^{-1}$)	36.7 ± 9.1	44 ± 14.5	37.6 ± 14.5

Mean ± standard deviation for parametric data; no statistical differences among groups.

TABLE II Patient sedation in the PACU and in the ambulatory care unit

Location	*Time*	*Group 1*	*Group 2*	*Group 3*	*P*
PACU	Arrival	2 (1,3)	2 (1,3)	2 (1,3)	NS
PACU	15 min	2 (1,3)	1 (1,3)	2 (1,3)	NS
PACU	30 min	1 (1,3)	1 (1,3)	2 (1,3)	NS
PACU	60 min	1 (1,3)	1 (1,3)	1 (1,3)	NS
PACU	90 min	0 (0,2)	0 (0,2)	1 (0,2)	NS
ACU	3 hr	0 (0,1)	0 (0,1)	0 (0,1)	NS
ACU	Discharge	0 (0,0)	0 (0,0)	0 (0,0)	NS

PACU = postanesthesia care unit; ACU = ambulatory care unit; Median = 25% and 75% range; NS = non significant. Numerical data represent sedation levels: 0 = alert, aware; 1 = drowsy, not sleeping; 2 = asleep, arousable by verbal contact; 3 = asleep, not arousable by verbal contact.

required nalbuphine in the PACU (36.7%, 38.7%, and 39.5% for Groups 1, 2, and 3 respectively). There was no statistical difference in nalbuphine consumption between the three groups in the PACU (66.5 $\mu g \cdot kg^{-1}$ ± 16.8, 75.9 $\mu g \cdot kg^{-1}$ ± 17.5, 66.7 $\mu g \cdot kg^{-1}$ ± 21.6 for Groups 1, 2, and 3 respectively). No patient required nalbuphine in the ambulatory care unit. There was no difference between groups with respect to the number of rescue analgesic tablets required at home: 6 (2,13), 7 (2,20), and 7 (1,12) for Groups 1, 2, and 3 respectively. The mean times to first request for rescue analgesic medication were similar amongst groups (Figure 1), as were VAS pain scores measured in the PACU and in the ambulatory care unit (Figure 2).

No differences were found between groups with respect to sedation scores (Table II). No patient reported hallucinations, nightmares, dysphoria or diplopia after the operation, and no patient required bladder catheterization or reported pruritus.

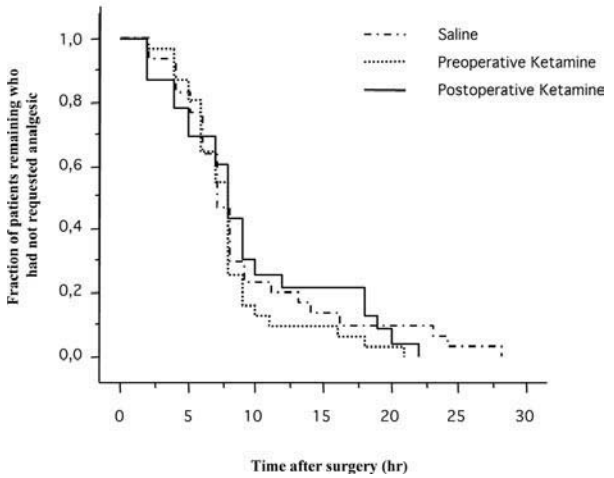

FIGURE 1 Kaplan-Meier survival curve describing the fraction of patients remaining who did not require analgesic after surgery. There were no significant differences between groups ($P > 0.05$).

Discussion

Although prevention of NMDA receptor activation and subsequent central sensitization following tissue damage is involved in prevention of postoperative pain,[2–18] 300 $\mu g \cdot kg^{-1}$ of the non-competitive NMDA receptor antagonist ketamine, given in our study either before or after surgery, did not show any pre-emptive effect in outpatients undergoing third molar surgical removal under general anesthesia. Postoperative pain after surgical removal of third molar was selected because it is a robust and reliable pain model that has been widely used by investigators,[19,20] and because it is widely performed in our institution on an outpatient basis with adequate pain control.

These findings are consistent with those of recent studies that failed to demonstrate any pre-emptive analgesic effect of low-dose *iv* ketamine, with no significant benefit of postincisional *vs* preincisional administration. In the studies of Adam *et al.*,[9] Dahl *et al.*,[11] and Mathisen *et al.*,[12] a single dose of *iv* ketamine was administered either before surgery, or after surgery. There was no evidence of a pre-emptive effect when ketamine was administered before surgery, and the analgesic effect of ketamine when administered at the end of surgery was short-lasting and failed to produce a significant opioid-sparing effect. In the study of Katz *et al.*[21] an *iv* infusion of ketamine was administered after a 200 $\mu g \cdot kg^{-1}$ *iv* bolus dose in patients undergoing radical prostatectomy, either before incision or 70 min after incision. Preincisional

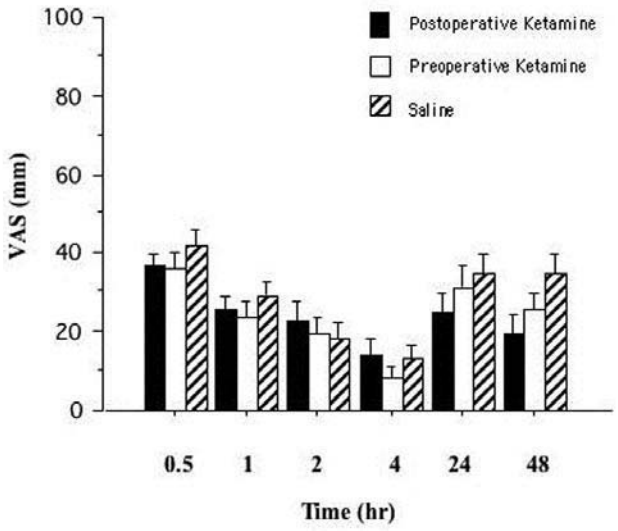

FIGURE 2 Visual analogue scale (VAS) in the postoperative period. There were no significant differences between groups ($P > 0.05$).

low-dose ketamine did not result in a clinically meaningful reduction in pain or morphine consumption when compared with postincisional administration of ketamine or a saline control condition.

Interestingly, Kwok *et al.* showed recently that ketamine 150 $\mu g \cdot kg^{-1}$ *iv* given before skin incision has a pre-emptive effect on postoperative pain after laparoscopic gynecologic surgery, whereas postoperative analgesia is not improved in patients receiving ketamine after skin closure.[22] This may be explained by the minimally invasive procedure with a subsequent minimal inflammatory process in the postoperative period, and therefore limited subsequent central sensitization.

Several possibilities may explain the lack of a clinically significant preventive effect of ketamine on postoperative pain in our study. Firstly, the timing of administration of ketamine may have been suboptimal. It is known that central sensitization is induced during surgery and postoperatively by inflammatory inputs.[18] In the group receiving a bolus dose of ketamine before surgery without subsequent perioperative infusion, prevention of central sensitization due to postoperative inflammatory inputs may not be prevented. In the group receiving a bolus dose of ketamine at the end of surgery without subsequent postoperative infusion, NMDA receptors were likely to have been activated by noxious surgical stimuli, and we might have expected a positive action of ketamine. However, the efficacy of ketamine is linked to activation of NMDA receptors. In case of adequate perioperative analgesia, NMDA receptor activation is likely to be suppressed, and the effect of ketamine administration hence limited. In our study, adequate administration of intraoperative alfentanil might therefore have prevented NMDA receptor activation and subsequent demonstration of a positive action of ketamine, whereas central sensitization due to postoperative inflammatory inputs was not prevented.

Secondly, the dose of ketamine could have been inadequate. In the study of Adam *et al.*, a bolus dose of 150 $\mu g \cdot kg^{-1}$ ketamine induced in the postincisional group a short-lasting analgesic effect without significant opioid-sparing effect after mastectomy.[9] We used a ketamine dose two times larger than that used by Adam *et al.* without a positive effect. On the other hand, in the study of Dahl *et al.*,[11] the ketamine dose after hysterectomy was 400 $\mu g \cdot kg^{-1}$, almost three times larger than in the study of Adams *et al.* with a subsequent similar pre-emptive effect.[9] Although a larger dose of ketamine might have produced a clinically important analgesic effect, the well known dose-related psychomimetic effects of ketamine limit its clinical usefulness at higher doses.[23]

Thirdly, Hoffmann *et al.* have recently suggested that liposolubility could be a factor influencing the efficacy of ketamine on postoperative pain when concomitantly administered with opioids.[24] This is in accordance with the findings of Aida *et al.* who have shown a significant reduction of postoperative pain compared with a control group when ketamine was administered in combination with morphine,[25] whereas other studies combining ketamine with sufentanil,[9] or alfentanil[11] did not show a preventive effect on postoperative pain. A possible explanation is competition for active blood barrier transport proteins due to lipophilicity of ketamine and alfentanil or sufentanil, or intracellular differences in phosphorylation associated with specific opioid-ketamine combination.[21,24]

A fourth possible reason for the lack of pre-emptive effect of ketamine in our study may be pre-emptive effects in all the groups from some of the other drugs used as part of the anesthetic technique. Administration of analgesic agents (i.e., acetaminophen, non-inflammatory analgesic drugs) may have attenuated sensitization induced by surgery, thereby blunting the effect size between the groups, and leading to a possible type II statistical error. On the other hand, no patient experienced severe pain. This suggests that this pain model may not have been powerful enough to detect a difference.

Finally, a pronociceptive effect induced by opioids has been demonstrated in recent studies.[26] This pronociceptive effect leads to opioid-induced hyperalgesia mediated by NMDA receptors, and shares similar cellular mechanisms to that following tissue injury.[27] Alfentanil might have therefore activated this pronociceptive process, minimizing intergroup differences in postoperative pain.

In conclusion, this study failed to demonstrate a pre-emptive effect on postoperative pain with 300 $\mu g \cdot kg^{-1}$ of *iv* ketamine administered either before or after surgery. It is possible that combination of a continuous *iv* infusion of ketamine covering the intra- and postoperative period would have resulted in a clinically significant effect. Further studies are warranted in this field.

Acknowledgements

The authors thank Research Nurses Valérie Grimaud, Pascale Prudent and Aurore Viraye for their technical assistance.

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