



SCIENTIFIC ARTICLE

## Assessment of the Effect of Ketamine in Combination with Remifentanil on Postoperative Pain

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### Abstract

**Background and objectives:** The combination of ketamine and remifentanil seems to be associated with better analgesia and duration. The aim of this study was to evaluate whether a ketamine-remifentanil combination promotes improved postoperative analgesia.

**Methods:** Prospective, randomized, double blind study of 40 patients undergoing video laparoscopic cholecystectomy. Anesthesia was performed with remifentanil, propofol, atracurium, and 50% oxygen. Group 1 (G1) patients received remifentanil ( $0.4 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and ketamine ( $5 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and Group 2 (G2) received remifentanil ( $0.4 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and saline solution. Morphine  $0.1 \text{ mg} \cdot \text{kg}^{-1}$  was administered at the end of the procedure, and postoperative pain was treated with morphine via PCA. We evaluated the severity of postoperative pain by a numerical scale from zero to 10 during 24 hours. We registered the time to the first analgesic supplementation, amount of morphine used in the first 24 hours, and adverse effects.

**Results:** There was a decrease in pain severity between extubation and other times evaluated in G1 and G2. There was no significant difference in pain intensity between the groups. There was no difference between G1 ( $22 \pm 24.9 \text{ min}$ ) and G2 ( $21.5 \pm 28.1 \text{ min}$ ) regarding time to first dose of morphine and dose supplement of morphine consumed in G1 ( $29 \pm 18.4 \text{ mg}$ ) and G2 ( $25.1 \pm 13.3 \text{ mg}$ ).

**Conclusion:** The combination of ketamine ( $5 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and remifentanil ( $0.4 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) for cholecystectomy did not alter the severity of postoperative pain, time to first analgesic supplementation or dose of morphine in 24 hours.

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## Introduction

Although there have been many advances in the pathophysiology of postoperative pain and emergence of new drugs and analgesic techniques, postoperative pain control remains inadequate<sup>1,2</sup>. About half of patients undergoing surgeries presents with severe pain during hospitalization<sup>3</sup>.

Remifentanil is an opioid with very short action<sup>4</sup>. It is used for analgesia when fast recovery is important<sup>5</sup>. Due to the nonspecific metabolism by plasma and tissue esterases, its clearance is independent from the liver function<sup>4</sup>. In subjects with renal impairment, there was no increased sensitivity to remifentanil<sup>5</sup>. Despite these advantages, there is also a rapid termination of the analgesic effect.

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Moreover, some authors have reported that a factor involved in the hyperalgesia is the short duration of action of opioids, such as remifentanyl<sup>7-10</sup>. The main mechanism of hyperalgesia induced by opioids is the activation of N-methyl-D-aspartate (NMDA) receptors<sup>11-14</sup>.

Ketamine is a NMDA receptor antagonist, which acts by non-competitive blockage, binding itself to the intra-channel phencyclidinic site and changing the channel opening time. S(+) Ketamine affinity for this binding site is three to four times higher compared to isomer R(-). Analgesic potency of S(+) ketamine is two times that of racemic mixture<sup>15</sup>.

We observed preemptive analgesic effect of S(+)ketamine and reduction of the hyperalgesia phenomenon induced by remifentanyl, using low-dose infusion intravenously<sup>7,16,17</sup>. When administered both prior to anesthesia induction and throughout the perioperative period, ketamine is able to promote significant reduction in the consumption of anesthetic agents during surgical anesthetic procedure, exerting an "opioid sparing" effect, aside from promoting adequate postoperative analgesia<sup>18</sup>.

Thus, the combination of ketamine and remifentanyl seems to relate to better analgesia and duration. The aim of this study was to evaluate whether the combination of ketamine and remifentanyl promotes improved postoperative analgesia.

## Method

After approval by the Ethics Committee and signing of informed consent, we conducted a prospective, randomized, double-blind study of 40 patients over 18 years of age, both sexes, ASA I or II, undergoing video laparoscopic cholecystectomy. Patients were allocated into two equal groups. Group allocation was determined by drawing envelopes containing numbers. On the morning of the operation and before starting anesthesia, a nurse or anesthesiologist blind to the patient's group opened this patient's envelope and prepared the syringes with remifentanyl and ketamine or remifentanyl and saline. None of the other researchers involved in the study or collecting data knew which group the patient belonged. In case of an emergency, the anesthesiologist attending the patient could see the group to which he belongs, breaking the protocol. Patients with chronic pain, myocardial ischemia, psychiatric illness, drug user, and those receiving opioids in the previous week were excluded.

Monitoring was performed with cardioscope, capnography, pulse oximetry, noninvasive blood pressure, and thermometer. Infusion was administered with midazolam (3 mg, 30 min), remifentanyl (1 mcg.kg<sup>-1</sup>), propofol (2-4 mg.kg<sup>-1</sup>), and atracurium (0.5 mg.kg<sup>-1</sup>). G1 received remifentanyl (0.4 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) and ketamine (5 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) and G2 received remifentanyl (0.4 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) and saline (0.9%). Remifentanyl was increased or decreased as needed, based on hemodynamic data (hypotension, defined as systolic blood pressure below 80 mm Hg or mean arterial blood pressure below 60 mm Hg). Infusion of solutions was maintained until wound closure. Atracurium doses were titrated to maintain muscle relaxation. Anesthesia was maintained with sevoflurane and 50% oxygen without nitrous oxide. Before extubation, atropine (0.02 mg.kg<sup>-1</sup>), neostigmine

(0.04 mg.kg<sup>-1</sup>), metoclopramide (20 mg), and ondansetron (4 mg) were administered. Morphine (0.1 mg.kg<sup>-1</sup>) was administered at the end of surgery.

Postoperative pain was treated with morphine via patient controlled analgesia (PCA) by intravenous route, with bolus of 2 mg in 3 mL, 10 minutes safety interval (administration blockade), dose limit of 20 mg in four hours, and without infusion.

We registered the total dose of remifentanyl used during operation. To evaluate the severity of postoperative pain, a numerical scale from zero to 10 was used (where zero: no pain and 10: the most severe pain possible; scores between one and four: mild pain; five and six: moderate pain; and seven to 10: severe pain). Evaluations were made every 30 minutes during four hours and six, 12, 18 and 24 hours after awakening. Time to first postoperative analgesic supplementation, amount of analgesic used during 24 hours, and adverse effects were registered.

The statistical program used to calculate the number of patients and analyze the results was the InStat Graph®. A difference of 3 cm in pain intensity was considered clinically significant. Based on preliminary assessment, we estimated a standard deviation (SD) score of pain intensity within group of 2.2<sup>7</sup>. For a power of 80% and a confidence interval of 95%, the sample size for each group was calculated at 15 patients. Data were expressed as mean ± standard deviation. We used the Mann Whitney test for remifentanyl dosage, duration of anesthesia and surgical procedure, time to supplementation need, total dose of morphine used, and pain intensity between groups; the Student's *t*-test for weight, age, height, and body mass index; ANOVA for pain intensity during evolution; and Fisher's exact test for gender, ASA, and adverse effects. We used central tendency, mean, and dispersion (standard deviation) measurements. We set the statistical significance level at 5%.

## Results

Patient's demographic data were similar (Table 1). Duration of operation was 131.2 ± 39.5 min in G1 and 128 ± 57.5 min in G2, with no statistically significant difference between groups (*p* = 0.279, Mann-Whitney). Duration of anesthesia was 173.2 ± 39.9 min in G1 and 175.1 ± 63.8 min in G2, with no statistically significant difference between groups (*p* = 0.250, Mann-Whitney). Remifentanyl dose used was 0.35 ± 0.10 mcg.kg<sup>-1</sup>.min<sup>-1</sup> in G1 and 0.38 ± 0.10 mcg.kg<sup>-1</sup>.min<sup>-1</sup> in G2, with no statistically significant difference between groups (*p* = 0.310, Mann-Whitney).

There was a significant decrease in pain intensity by the verbal numerical scale between the time after awakening and other times evaluated in G1. There was no statistically significant difference in pain intensity between groups at each time evaluated (Table 2).

There was no difference between G1 (22 ± 24.9 min) and G2 (21.5 ± 28.1 min) in time to first dose of postoperative morphine supplementation (*p* = 0.516, Mann-Whitney test). There was no significant difference between groups regarding additional dose of morphine consumed in G1 (29 ± 18.4 mg) and G2 (25.1 ± 13.3 mg) (*p* = 0.598, Mann-Whitney test).

Adverse effects were agitation (G1: 3 and G2: 1, *p* = 0.605), hallucinations (G1: 3, *p* = 0.231), vertigo (G1: 6 and G2: 12; *p* = 0.111), discomfort (G1: 10 and G2: 5; *p* = 0.191),

**Table 1** Demographic Data of Patients.

	G1 (n = 20)	G2 (n = 20)	p
Age (years)	46.0 ± 12.5	45.5 ± 16.1	0.9221*
Weigh (Kg)	76.2 ± 15.3	75.5 ± 15.3	0.8943*
Height (cm)	165.7 ± 9.8	163.3 ± 11.6	0.3247*
BMI (kg.m <sup>-2</sup> )	26.9 ± 4.9	28.1 ± 6.2	0.5241*
Sex (M/F)	4 / 16	3 / 17	1.0000#
ASA (I/II)	8 / 12	11 / 9	0.5272#

G1: Ketamine + Remifentanyl; G2: Remifentanyl; BMI: body mass index; #: Fisher's test; \*: Student's *t*-test.

**Table 2** Pain Intensity upon Awakening.

Times (h)	G1 (n= 20)	G2 (n= 20)	p <sup>1</sup>
1/2	6.1 ± 3.2	6.0 ± 2.3	0.6449
1	4.6 ± 2.8	4.4 ± 2.2	0.8602
1 ½	3.3 ± 2.3	2.7 ± 2.1	0.4004
2	2.0 ± 2.2	1.4 ± 1.5	0.4878
2 ½	1.3 ± 1.7	1.2 ± 1.7	0.7535
3	1.1 ± 1.5	1.1 ± 1.6	0.8161
3 ½	1.1 ± 1.7	1.1 ± 1.4	0.7015
4	1.2 ± 1.9	1.0 ± 1.3	0.8261
6	0.9 ± 1.2	0.5 ± 0.9	0.2224
12	1.7 ± 1.9	1.1 ± 1.2	0.3682
18	1.8 ± 1.9	1.1 ± 1.3	0.3829
24	1.5 ± 1.3	0.5 ± 0.7	0.0510
p <sup>2</sup>	0.0001	0.0001	

G1: Ketamine + Remifentanyl; G2: Remifentanyl; <sup>1</sup>: Mann-Whitney test; <sup>2</sup>: ANOVA.

diplopia (G1: 1,  $p = 1.00$ ), nystagmus (G1: 2,  $p = 0.487$ ), loss of reality perception (G1: 1,  $p = 1.00$ ), change in hearing (G1: 1,  $p = 1.00$ ), reduced visual acuity (G1: 1,  $p = 1.00$ ), malaise (G1: 11 and G2: 7,  $p = 0.341$ ), nausea (G1 18 and G2: 15,  $p = 0.407$ ), vomiting (G1: 12 and G2: 4;  $p = 0.022$ ), and pruritus (G1: 2 and G2: 1;  $p = 1.00$ ).

## Discussion

Cholecystectomy was chosen because it is a procedure that provokes nociceptive stimulus sufficient to cause algogenic substance release, which allows evaluation of the analgesic effect of drugs. The study was conducted only with patients undergoing laparoscopic procedure because the stimulus intensity was similar. Patients' age group was 40-50 years, and females were most affected, as in most studies of patients undergoing cholecystectomy<sup>19,20</sup>. The frequency of gallstones increases with age, more significantly after the age of 40<sup>21</sup>. Females are more predisposed to stone formation due to hormonal factors<sup>21,22</sup>. Patients of this study were overweight, which is a risk factor for gallstone<sup>21,23</sup>.

Dosage of remifentanyl used was based on the ideal weight of patients, as recommended by a study in the literature<sup>24</sup>. This is due to the fact that remifentanyl volume of distribution

is small, limited primarily to central compartment. In one study, the authors recommend using remifentanyl bolus of 1 mcg.kg<sup>-1</sup>, followed by an infusion of 0.5 mcg.kg<sup>-1</sup>.min<sup>-1</sup>, titrated according to surgical stimulation<sup>25</sup>.

The factors that seem to be more associated with severe postoperative pain after the use of remifentanyl are age (over 16 years), duration of surgery (> 2 hours), and high dosage use<sup>26,27</sup>. In this study, the duration of surgery was greater than two hours in both groups and remifentanyl dosage was high and similar between groups (> 0.3 mcg.kg<sup>-1</sup>.min<sup>-1</sup>), which may be associated with more intense postoperative pain.

There is a study that assesses the analgesic effect of ketamine-remifentanyl combination<sup>18</sup>. Several studies of other surgical procedures were conducted using ketamine and remifentanyl<sup>7,28-30</sup>. Due to the effects on NMDA receptors, ketamine can reduce central sensitization and intensity of postoperative pain. The combination of ketamine and remifentanyl may promote prolonged analgesia, since this opioid's great disadvantage of producing no analgesic effect after infusion discontinuation. A study has shown that ketamine administration both before induction of anesthesia and during surgery markedly reduced the need for opioids, in addition to adequate postoperative analgesia<sup>18</sup>.

In some studies that did not assess the combination with remifentanyl administered intravenously during the intraoperative period, ketamine decreased pain intensity and opioid consumption postoperatively<sup>31-34</sup>. From such evidence, protocols were developed to evaluate the combination of ketamine and remifentanyl.

This study used 5 mcg.kg<sup>-1</sup>.min<sup>-1</sup>, without initial bolus dose. This dose, which is considered low, was also used in another study<sup>10</sup>. A dose is considered low when < 1 mg.kg<sup>-1</sup> (intravenous bolus) or ≤ 20 mcg.kg<sup>-1</sup>.min<sup>-1</sup> (infusion)<sup>34</sup>. The doses used for induction were 0.15 mg.kg<sup>-1</sup><sup>30</sup>, 0.3 mg.kg<sup>-1</sup><sup>17</sup>, and 0.5 mg.kg<sup>-1</sup><sup>7,29</sup>. For infusion, the authors used 0.3 mcg.kg<sup>-1</sup>.min<sup>-1</sup><sup>17</sup>, 2 mcg.kg<sup>-1</sup>.min<sup>-1</sup><sup>30</sup>, 4 mcg.kg<sup>-1</sup>.min<sup>-1</sup><sup>29</sup>, and 5 mcg.kg<sup>-1</sup>.min<sup>-1</sup><sup>7</sup>. Moreover, in one study, infusion was maintained with 2 mcg.kg<sup>-1</sup>.min<sup>-1</sup> for the first 48 hours postoperatively<sup>7</sup>. Differences in infusion dosage and use of bolus for induction and postoperative maintenance may modify the results of the studies.

Adverse effects caused by remifentanyl increased as the dose increased. In a multicenter study, during the period of induction or maintenance with remifentanyl, adverse events occurred in about 2% of patients. The most common were hypotension, hypertension, and bradycardia<sup>38</sup>. These effects were not observed in this study. In this study, the most prevalent adverse effects in both groups were nausea and vomiting, despite the use of metoclopramide and ondansetron administered before extubation. Several factors may have contributed to this, such as the use of inhalational anesthetic, laparoscopic procedure, being overweight, female prevalence, and postoperative analgesia with morphine via PCA<sup>39-41</sup>. Other effects (hallucinations, diplopia, nystagmus, loss of reality perception) are related to ketamine. Besides the lack of analgesic effect, there was an increase of adverse effects related to ketamine in G1.

One can conclude that the combination of ketamine (5 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) and remifentanyl (0.4 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) for video laparoscopic cholecystectomy did not alter the intensity of postoperative pain, time to first analgesic supplementation or morphine dose during 24 hours.

The difference in results may be related to surgical stimulation intensity, amount of remifentanyl used during operation, as well as the dose of ketamine used, in addition to the study method, which may modify the response of ketamine-remifentanyl combination.

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