

Analgesia with Low-Dose S(+)-ketamine in Laparoscopic Cholecystectomy: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Florentino Fernandes Mendes*, Ana Luft and Claudio Telöken

Federal University of Health Sciences – UFCSPA, Porto Alegre, Rio Grande do Sul Brazil

Introduction

Because of the development of anesthetic and surgical techniques and the need to reduce costs, surgeries such as laparoscopic cholecystectomy are now performed with minimal hospital stay or in outpatient services. The intensity of postoperative pain and the occurrence of nausea or vomiting are the most important factors causing delayed discharges from hospital, and therefore increase costs [1]. The use of opioids, which provide adequate pain control, is associated with a high incidence of nausea and vomiting, and this association is dose-dependent [2]. Recent analgesic techniques use analgesic with different mechanisms of action to improve postoperative pain relief and reduce opioids requirements, and opioids-related adverse effects [3]. Studies suggest that the use of low dose of S(+)-ketamine, a nonspecific blocker of NMDA receptors, may reduce the need for opioids and opioid-related adverse effects [4,5].

The purpose of this study was to evaluate in a double blind randomized trial the analgesic and adverse effects of S(+)-ketamine in a patients undergoing laparoscopic cholecystectomy.

Methods

This study was conducted in the Anesthesiology Division, Department of Surgery, of Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), after approval by the institutional review board. Patient eligibility was assessed during preanesthetic evaluation and according to the following inclusion criteria: age 18 to 65 years; BMI < 35 kg/m²; capacity to understand the use of the 0-10 visual analog scale to measure pain; ASA I-III physical status. Exclusion criteria were: diagnosis of renal failure (creatinine > 1.5); regular use of anti-inflammatory drugs (NSAIDs), chronic pain syndromes; psychiatric disease; suspected or known history of drug abuse; alcohol consumption; intolerance or allergy to S(+)-ketamine. Eligible patients who provided written informed consent were then randomized by “drawing lots” to one of the four groups: Group 1 – 100 mcg. Kg⁻¹ S(+)-ketamine IV bolus [4] before surgery, and continuous infusion [6] of 20 mcg. Kg⁻¹.min⁻¹ until skin closure; Group 2 – 100 mcg. Kg⁻¹ S(+)-ketamine IV bolus administered before surgery and continuous infusion of placebo until skin closure; Group 3 – IV placebo before the beginning of surgery and continuous infusion of 20 mcg. Kg⁻¹.min⁻¹ until skin closure; Group 4 – IV placebo before the beginning of surgery, and continuous infusion of placebo until skin closure. S(+)-ketamine (Ketamin™, Laboratório Cristália, Brazil; 2 mL ampule, 50mg. mL⁻¹) was diluted in a 10 mL syringe for IV administration and in a bag with 250 mL saline in a closed system at a 0.2 mg:mL concentration for continuous infusion (NIKISO™ pump). The 10 mL syringes were labeled as preoperative, and the solution that they contained was administered after anesthesia induction. The saline bags were labeled as preoperative; infusion was initiated immediately after orotracheal intubation and maintained until skin closure. So that the substance under study was not identified by its color, volume or effect, placebo was saline solution at the same volume and infusion rate of S(+)-ketamine, and IV administration was performed only after the patient was in a state of hypnosis, confirmed by the absence of pupillary reflex. Randomization was based on computer-generated codes that were maintained in sequentially numbered opaque envelopes until just before use. The preparation of the solutions under study was carried out by

one of the authors (FFM), who was not involved in patient's care.

Before surgery, patients were trained and familiarized with the use of the visual analog scale (VAS). No pre-anesthetic medication was used, and all patients received general anesthesia, which was standardized. Induction was performed with IV administration of 2 mg.kg⁻¹ propofol, 3µg.kg⁻¹ fentanyl, and 0.5 mg.kg⁻¹ rocuronium bromide. Anesthesia was maintained with sevoflurane and a mixture of, 50% oxygen and 50% compressed air at a 2 L.min⁻¹ flow, mechanical ventilation with volume cycle ventilation and gas reinhalation system. At the end of the procedure, residual neuromuscular block was antagonized with IV administration of prostigmine (1.5 mg) and atropine (0.75 mg). Patients were monitored using pulse oximetry, ECG derivations DII and V5, noninvasive arterial blood pressures, inspired fraction of oxygen, capnography, and curves of respiratory mechanics measurements.

At the beginning of skin closure, all patients received 30 mg IV ketorolac tromethamine (Toradol™, Laboratório Roche, Brazil; 1mL ampoule, 30mg.mL⁻¹). Pain was assessed at patient arrival at the post-anesthetic care unit (PACU), every 15 minutes in the first hour and every 30 minutes in the following hours until patient discharge from the PACU. Pain was measured using a 0-10 point VAS, in which 0 was “no pain” and 10 “the greatest imaginable pain”. When VAS scale results were greater than 3, pain was treated with intravascular morphine (Dimorf™, Laboratório Cristália, Brazil; 1mL ampoule, 10mg.mL⁻¹), titrated until adequate pain control was achieved. If VAS score surpassed 3 for a second time, a scheme of 3 mg morphine IV every 2 hours was instituted.

The total postoperative opioid dose administered up to discharge from the PACU and in the first 24 postoperative hours was recorded. The use of other anti-inflammatory, analgesic or local anesthetic agents was not allowed. Nausea, vomiting and dizziness were evaluated as present or absent. Sedation was assessed using a sedation scale (grade 1 – patient awake; grade 2 – patient drowsy but awake when called without touching; grade 3 – drowsy but awake when lightly touched; grade 4 – partially awake only when vigorously stimulated). Bad dreams were assessed at discharge from the PACU and 24 hours after discharge from the PACU by means of two questions: Do you remember having any dreams? If yes, do you classify them as bad dreams? Hallucinations were recorded only when reported by the patients. Recovery time was measured in minutes from the end of anesthesia to patient discharge when an index of 10 was reached in the

*Corresponding author: Florentino Fernandes Mendes, Federal University of Health Sciences – UFCSPA, Porto Alegre, Rio Grande do Sul Brazil; E-mail: men.terra.com.br

Received February 23, 2011; Accepted March 31, 2011; Published April 4, 2011

Citation: Mendes FF, Luft A, Telöken C (2011) Analgesia with Low-Dose S(+)-ketamine in Laparoscopic Cholecystectomy: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Anesth Clin Res 2:133. doi:10.4172/2155-6148.1000133

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modified Aldrete-Kroulik scoring system [7]. Data were collected by the authors and by the anesthesiology and nursing teams, blinded to group assignment, at the unit where the study was conducted.

Continuous variables were reported as mean, median and standard deviation (SD); the ANOVA test was used for the comparison between variables. The Kruskal-Wallis test was used for the variables that did not meet the assumptions of the ANOVA test. Categorical variables were reported as absolute and relative frequencies in tables, and the chi-square test was used for the comparisons between groups. In all tested hypotheses, statistical significance was set at $p < 0.05$. Sample size to identify a difference between groups of a least 2 points in the visual analog pain scale, at a standard deviation of 1.8 in each group, was calculated as at least 14 patients

per group for a type I error (alpha) of 5% and a type II error (beta) of 20%. To compensate for probable losses, the required sample size was estimated as 88 patients, with 22 participants in each group.

Pain scores were analyzed as mean and SD of VAS scores. To analyze the degree of satisfaction with anesthesia and analgesia, the grades in the satisfaction scale were grouped as satisfied patients, which included those that were very satisfied and satisfied, and dissatisfied patients, which comprised those that were very dissatisfied and dissatisfied.

Results

Ninety patients consented to participate in the study and were randomized (Figure 1). There were 12 exclusions after group assignments

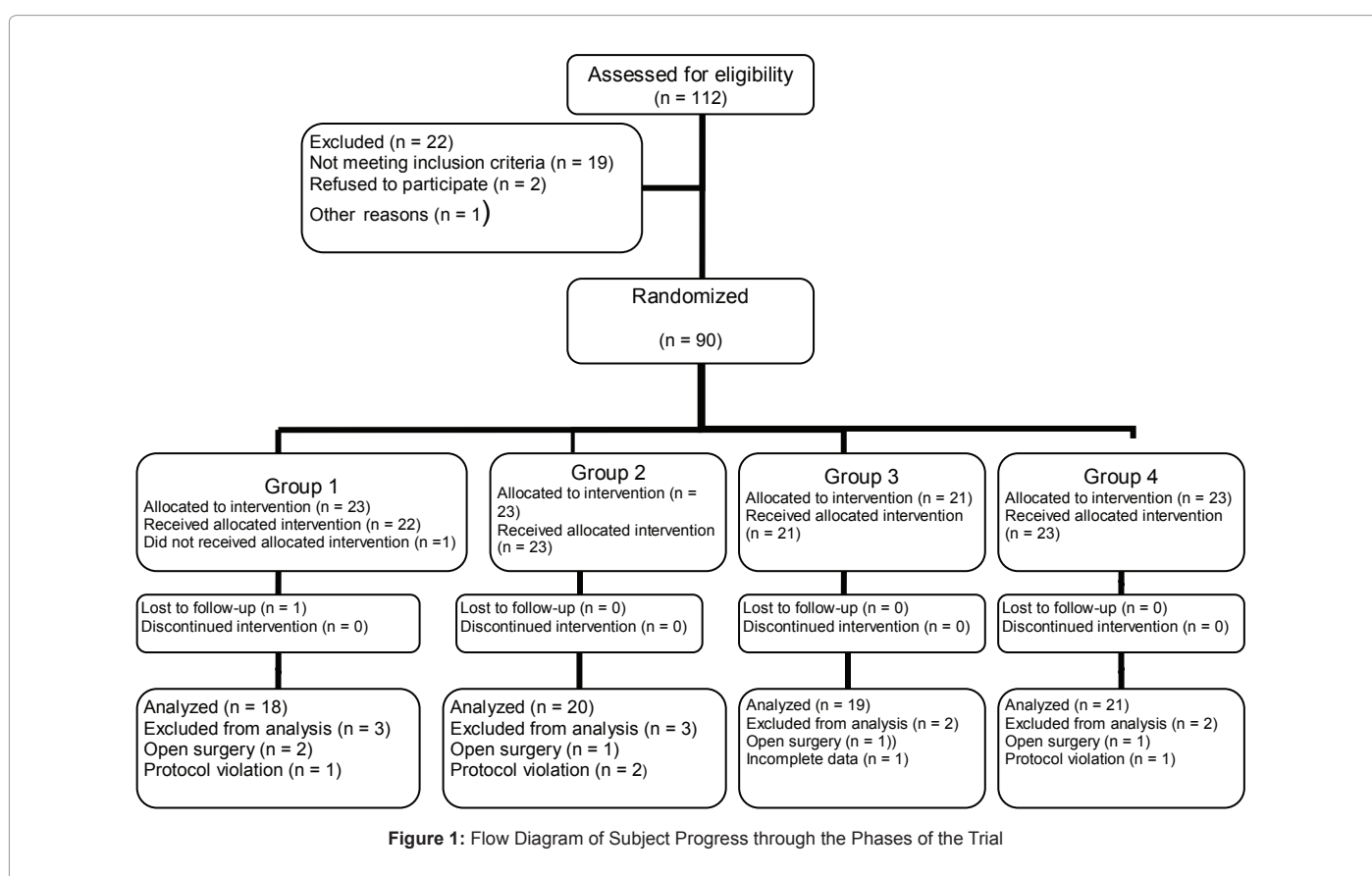


Figure 1: Flow Diagram of Subject Progress through the Phases of the Trial

	Group 1 (n = 18)	Group 2 (n = 20)	Group 3 (n = 19)	Group 4 (n = 21)	P
Age (yr)	45.4 ± 12.5	46.6 ± 13.2	45.9 ± 11.4	41.9 ± 12.0	0.64Δ
Weight (kg)	77.2 ± 15.2	73.4 ± 12.8	69.9 ± 9.9	71.2 ± 11.9	0.23 #
Height (cm)	162.3 ± 6.1	164.1 ± 6.5	164.6 ± 9.2	167.2 ± 8.9	0.24 #
BMI (Kg/m2)	29.3 ± 5.6	27.2 ± 4.5	25.6 ± 2.5	27.6 ± 3.6	0.14 #
Physical status (%)**					
ASA I	27.8	25.0	36.8	35.3	
ASA II	72.2	70.0	63.2	57.2	0.77
ASA III	0.0	5.0	0.0	7.5	
Surgery duration (min)	135.72 ± 42.2	128.5 ± 34.9	122.6 ± 22.9	133.0 ± 29.8	0.49#
Propofol dose (mg)	123.0 ± 30.0	133.0 ± 26.7	115.3 ± 12.8	121.1 ± 29.1	0.11#
Fentanyl dose (mcg)	233.3 ± 37.7	235.8 ± 33.6	238.2 ± 20.7	242.2 ± 26.6	0.87#

Values presented as means ± SD. Δ P calculated using the ANOVA test. # P values according to the Kruskal-Wallis test. BMI – body mass index. ** Values presented as relative frequencies.

Table 1: Anthropometric Data, Physical Status, Surgery Duration and Total Dose of Anesthetics.

	Group 1 (n = 18)	Group 2 (n = 20)	Group 3 (n = 19)	Group 4 (n = 21)	P
Pain VAS scale ¹	1.00 ± 1.71	1.70 ± 2.40	1.74 ± 2.13	2.57 ± 2.67	0.29#
Morphine in PACU (mg) ¹	2.83 ± 0.93	3.55 ± 1.04	3.45 ± 2.77	3.45 ± 2.77	0.76#
Consumption of morphine 24 hrs (mg) ¹	4.5 ± 3.29	5.9 ± 5.81	5.7 ± 3.58	7.87 ± 4.84	0.13#

1 Values presented as means ± SD. # P values according to the Kruskal-Wallis test.

Table 2: Pain and Consumption of Analgesics.

	Group 1 (n = 18)	Group 2 (n = 20)	Group 3 (n = 19)	Group 4 (n = 21)	P
PACU stay ¹	33.3 ± 4.9	27.25 ± 4.3	41.32 ± 9.9	30.18 ± 4.6	0.45#
Nausea at PACU ²					
Yes	6 (33.3%)	7(35.0%)	4 (21.1%)	8 (38.9%)	0.68 Δ
No	12 (66.6%)	13 (65%)	15 (78.9%)	13 (62.9%)	
Vomiting at PACU ²					
Yes	2 (11.1%)	1 (5%)	0 (0.0%)	3 (14.29%)	
No	16 (88.9%)	19 (95.0%)	19 (100%)	18 (85.71%)	0.40 Δ
Sedation in thePACU ²					
Grade 1	16 (88.9%)	19 (95%)	18 (94.7%)	20 (95.2%)	
Grade 2	2 (11.1%)	1 (5.0%)	1 (5.3%)	1 (4.8%)	0.83 Δ
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	
Satisfied with anesthesia ²	16 (88.9%)	20 (100%)	17 (89.5%)	20 (95.2%)	0.44 Δ
Dissatisfied with anesthesia ²	2 (11.1%)	0 (0%)	2 (10.5%)	1 (4.8%)	
Nausea and/or vomiting at 24h ²					
Yes	15 (83.3%)	17 (89.5%)	17 (94.4%)	19 (95.0%)	0.77 Δ
Not	3 (16.7%)	2 (10.5%)	1 (5.6%)	1 (5.0%)	
Satisfied with analgesia	16 (88%)	20 (100%)	18 (100%)	20 (100%)	0.69 Δ
Dissatisfied with analgesia	2 (11.1%)	0 (0%)	0 (0%)	0 (0%)	
Bad dreams ²					
Yes	3 (16.7%)	0 (0%)	2 (11.1%)	0 (0%)	0.06 Δ
No	15 (83.3%)	19 (100%)	16 (88.9%)	20 (100%)	

1 Values presented as means ± SD. 2 Values presented as absolute and relative frequencies.

P values according to the Kruskal-Wallis test. Δ P values according to the chi-square test.

Table 3: Adverse Effects and Satisfaction with Anesthesia and Analgesia.

because of change from laparoscopic to open surgery, incomplete data, or protocol violation. The 4 groups were similar regarding anthropometric data, physical status surgery duration and total anesthetic dose used (Table 1). There was no significant difference in the use of sevoflurane or adverse events during surgery (data not shown).

The analysis of analgesia showed that there was no difference in the classification of pain intensity in the four groups under study (p = 0.29). The consumption of analgesics in the PACU (p = 0.76), and consumption of analgesics in 24 hours postoperation (p = 0.13) were similar in the groups (Table 2).

The analysis of adverse effects showed that there were no differences in time to reach 10 points in the modified Aldrete-Kroulik scoring system (p = 0.45), in incidence of nausea (p = 0.68), vomiting (p = 0.40) or sedation in the PACU (p = 0.83).

Even though no statistically significant difference was found (p = 0.06), only patients from the groups that received continuous infusion of S(+)-ketamine had bad dreams.

Patient satisfaction was high and there were no difference in satisfaction between groups regarding anesthesia (p = 0.44), analgesia received (p = 0.11) or occurrence of nausea and/ or vomiting in 24 hours (p = 0.49) (Table 3).

Discussion

In this study, patients undergoing laparoscopic cholecystectomy received low doses of S(+)-ketamine before, as well as before and during

surgery. When compared with the placebo group, there were no differences in the pain scores, rescue opioids requirements, and opioid-related adverse effects in the PACU and at 24-h postoperatively. Therefore, opioid sparing interventions such as perioperative S(+)-ketamine may not be necessary or appropriate for this type of minimally invasive procedure. These findings differ from those reported in previous studies, which demonstrated the preemptive effect of the administration of low doses of ketamine in abdominal surgeries [8] and in laparoscopic gynecologic surgeries, [9] as well as its preventive effect during the performance of radical prostatectomy [4] and major abdominal surgery, [5] measured as reductions in pain scores, rescue analgesic consumption, or both.

When examining the effect of different analgesic regimens on pain control, it is important to determine whether a statistically significant difference is also clinically meaningful, or even noticeable. Although there is some controversy on the precise “cutoff” for a clinically significant or noticeable difference in patients with acute pain is approximately 1.3-1.4 U (on a numeric rating scale of 0-10) [10]. A difference of approximately 2 – 2.4 U (33% - 35% reduction) on the same scale may correlate to a greater and more meaningful reduction in acute pain, although a percent, rather than an absolute, difference may be more meaningful [11,12]. Despite some evidence suggesting that approximately 20 mm or 30% decrease in visual analog scale (VAS) pain scores (depending in part on the reference point for baseline pain) would be clinically noticeable in acute pain, it is possible that a one-dimensional instrument such as the VAS may not accurately capture the multidimensional complexity of acute pain, which may parallel that seen with chronic pain [11,12]. In addition, there is some controversy

as to the precise statistical properties of the VAS, which may contribute to further confusion. Although the one-dimensional VAS score is easy to administer and almost universally reported in analgesic trials, focusing on the VAS pain score as the most important clinical end-point (e.g., titration of analgesics to a VAS score ≤ 3) may not always be desirable and may even be misleading [13,14].

The analgesic effect of S(+)-ketamine may have been too small to be detected clinically due to the low intensity of pain inflicted by laparoscopic cholecystectomy and, moreover, may have been overshadowed by the use of ketorolac as postoperative analgesic. Ketorolac, administered in its active form, has immediate bioavailability to inhibit cyclooxygenase (COX); it thus regulates the synthesis of prostaglandins and decreases the inflammatory cascade [15]. The analgesic power of ketorolac might have been enough for the adequate control of pain; the use of rescue analgesia was, therefore, unnecessary, and a possible analgesic effect of S(+)-ketamine could not be observed. It is still unclear whether treatment with NMDA receptor antagonists have a role in the control of postoperative pain [16,17]. A review of the literature about laparoscopic cholecystectomy revealed that clinical trials should be conducted before this type of treatment is recommended [18]. The results of our study are clearly against such recommendation.

Perioperative uses of multimodal analgesia with analgesic regimens that contain nonopioids facilitate recovery from outpatient surgery and improve patient satisfaction [3]. The use of low doses of ketamine is associated with a lower incidence of adverse effects and is widely accepted by patients [19]. Therefore, analgesic protocols with fewer adverse effects than those found with the use of opioids should be evaluated [2].

This study did not find any differences between groups in the incidence of nausea and vomiting, sedation, postoperative recovery time, or degree of satisfaction with anesthesia and analgesia. In addition to adequate pain control, a decrease in the incidence of nausea, vomiting and other adverse effects are also important endpoints [20,21]. In this study, the use of S(+)-ketamine was not associated with improvement in this aspect.

Even though no statistically significant difference was reached, bad dreams occurred in groups 1 and 3, which received continuous infusion of S(+)-ketamine until skin closure to the end of surgery, at somewhat higher doses than previously described [6]. Considering that the duration of dreams is about 5 minutes, coinciding with the plasmatic half-life of S(+)-ketamine [22] it can be hypothesized that bad dream may be associated with high plasma concentrations of this drug. To minimize such occurrence, continuous infusion should be discontinued well before the end of surgery. In fact, the incidence of this effect has been previously shown to be associated with ketamine plasma concentrations, and psychedelic effects may be less likely, although still possible, with the use of lower drug concentrations [23].

A possible explanation for the lack of effect of S(+)-ketamine may be the effect of another anesthetic and analgesic drugs used during anesthesia (propofol, sevoflurane, fentanyl, ketorolac) as part of the anesthetic or analgesic technique. These drugs may reduce the sensitization induced by surgery and, therefore, weaken the effect size between groups, which may lead to a possible statistical type II error. At the same time, only 4 patients had intense pain, two in group 2 and two in the placebo group, which suggests that the pain model used in this study might not have the power to detect a difference [24].

In conclusion, the use of S(+)-ketamine did not result in a clinically detectable analgesic effect, was associated with an equal incidence of nausea, vomiting and other adverse effects, and triggered the occurrence of bad dreams. The results of this study do not support the use of S(+)-ketamine for postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

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