

# Ketamine infiltration decreases opioid requirement after thyroid surgery

## Abstract

### Objectives:

Postoperative pain increases the risk of postoperative complications and may predispose to chronic postsurgical pain.

This study aims to evaluate the impact of ketamine wound infiltration versus placebo at the end of thyroid surgery on postoperative pain and analgesic requirements.

### Methods

In this randomized controlled trial, we prospectively studied patients who underwent thyroid surgery. Patients were randomized into two groups: group S, local infiltration was performed using 10 ml of a physiological saline solution; group K, 10 ml of a solution containing 2 mg / kg ketamine was infiltrated. Standardized thyroidectomies were performed in the 2 groups. Pain perception was measured using a visual analog scale (VAS) every 10 minutes in the post-anesthetic care unit (PACU) for 2 hours and every 6 hours during the first 24 hours. The opioids requirement in the PACU was evaluated.

Comparison between the 2 groups was carried out.

### Results

Postoperatively, the mean VAS was higher in group S compared to group K during all PACU stay periods and during the first 24 hours postoperatively without a statistically significant difference between the 2 groups ( $p > 0.05$ ). The median doses received of morphine were 0.71 mg and 0 mg, respectively, for group S and group K ( $p = 0.04$ ). The incidence of nausea and vomiting was similar in both groups.

### Conclusions

Ketamine wound infiltration is an efficient modality to reduce postoperative opioid consumption compared to a placebo after thyroid surgery.

### Keywords:

Ketamine, thyroid surgery, wound infiltration, analgesia

## **Patients and Methods**

### **Selection of patients**

After obtaining the approval of the Institutional Ethics Committee of the Hospital, we conducted a randomized double-blind study. This study was achieved through collaboration between the head and neck surgery department of Otorhinolaryngology and the anesthesia department.

Patients aged 18 to 65 who scheduled thyroid surgery were included in this study if they had an ASA score (American Society of Anesthesiology) of I or II. Patients with unstable diabetes, an allergy to study drugs, a history of previous cervical surgery, or a history of cardiac or respiratory disease, as well as patients on long-term analgesic or corticosteroids, were not included in this study. Patients who had major complications, such as allergic reactions to anesthetic drugs and major bleeding or patients whose surgery duration exceeded 3 hours were excluded from this study. Patients who underwent a neck dissection associated with thyroid surgery were also excluded from the study.

### **Information about the patient and randomization**

The patients were informed about the anesthetic protocols and were educated about the use of the visual analog scale (VAS) to evaluate the severity of the pain. All patients in the study were blinded to the drug they received for postoperative pain.

A complete explanation of the procedure was provided and written informed consent was obtained prior to randomization. These patients were randomized into 2 groups: Group K represents wound infiltration using 10 ml of a solution containing 2 mg kg<sup>-1</sup> of ketamine, Group S represents wound infiltration using 10 ml of normal saline solution.

### **General anesthesia procedure**

After 3 minutes of preoxygenation, anesthesia was induced with injection of 3 µg kg<sup>-1</sup> of Fentanyl followed by 3 mg kg<sup>-1</sup> of Propofol; intubation using a silicone wire reinforced tracheal tube with 0.2 mg kg<sup>-1</sup> Cisatracurium. Anesthesia was maintained using isoflurane with a minimum alveolar concentration (MAC) of 1% in a 50% oxygen/air mixture. A 0.03 mg kg<sup>-1</sup> cisatracurium bolus was administered every 40 min, Fentanyl bolus of 0.1 µg/kg was injected whenever there is an increase of 20% of the base values in heart rate or systolic arterial blood pressure.

Before surgery, an anesthesiologist, not involved in the study, prepared an unlabeled sterile syringe using 10 ml of ketamine (2 mg kg<sup>-1</sup>) or 10 ml of a saline solution. After wound closure, the infiltration was performed by a blinded surgeon. The needle was introduced to a depth of 0.5 cm, an aspiration was then performed to avoid an intravascular injection followed by infiltrating the wound. The

content of the syringe was used for homogenous infiltration of the subcutaneous wound sides by the surgeon.

### **Analgesic protocol**

Thirty minutes before the end of surgery, all patients received 1 g of paracetamol and then were extubated before being moved to the PACU for closely monitoring for 2 hours. In the PACU, intravenous morphine titration (2mg every 5 min) was performed until the VAS value is less than 30. All patients were admitted for at least 24 hours postoperatively in the ENT department. They all received 1g of paracetamol systematically every 6 hours during the first 24 hours. An anesthesiologist blinded to study groups collected intraoperative and postoperative parameters.

### **Evaluation Criteria**

The primary outcomes were to determine the intensity of the pain using VAS in 0-100 in the first 24 hours. The VAS score was assessed every 10 minutes in the PACU for 2 hours and every 6 hours during the first 24 hours after the operation in the ENT department. Nefopam was administrated in the cases where VAS exceeded 30. Opioid requirements were recorded during the PACU admission period. The occurrence of side effects of opioid and ketamine was noted.

### **Statistical analysis**

In each group, a total number of 27 patients was required to obtain a difference on the VAS scale of 20 mm (standard deviation of 25 mm), with a power of 0.9 and an  $\alpha = 0.05$ . We decided to include 32 patients per group. All variables, including basic characteristics, were presented as a number with a percentage for qualitative variables, as an average standard deviation for quantitative variables following a normal distribution, and as a median with an interquartile interval for quantitative variables not following a normal distribution. The normal distribution was evaluated with the Kolmogorov-Smirnov test.  $\chi^2$  test or Fisher statistical tests were used for the analysis of qualitative variables and the Student's T test or Mann-Whitney U test was used for the analysis of quantitative variables. A p-value of 0.05 or less was considered statistically significant. Data entry and statistical analysis of data were performed with the software version 20 of Statistical Package for Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA).

## **1. Results**

### **3.1. Study population:**

The study lasted for a total of 6 months from September 2018 to March 2019. Sixty-four patients were included. Two patients were withdrawn from the study for prolonged surgery (more than 3

hours). A total of 62 patients completed the CONSORT diagram of the study of the patients, which is shown in Figure 1.

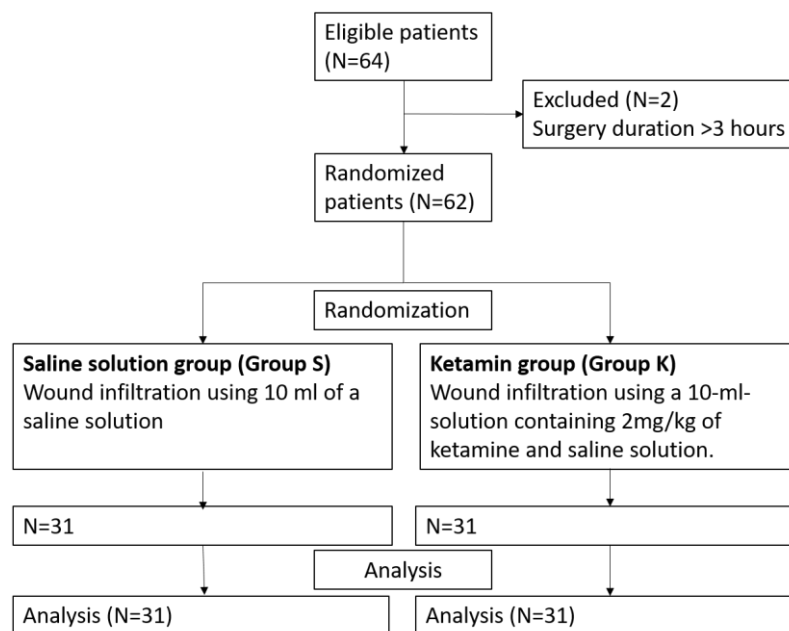


Figure 1: CONSORT 2010 flow chart of patients

We did not find any significant differences in demographic and intraoperative anesthetic parameters and surgery type between the two groups (Table 1).

Table 1: demographic characteristics and intraoperative anesthetic characteristics of both groups

		Group S (N=31)	Group K (N=31)	P value
Demographic characteristics	Age (years)	49 [21-65]	40 [27-64]	0.078 *
	Sex (M/F ratio)	3/28	1/30	0.306 **
	Size (cm)	166 [163-176]	165.5 [162-180]	0.677 *
	Weight (kg)	65 [55-70]	65 [55-70]	0.194 *
The performed thyroid surgery :	Total/ partial thyroidectomy	14 /17	24/7	
Intraoperative anesthetic parameters	HR (bpm)	82.3 (8)	80.7 (8.7)	0.449 *
	SBP (mmHg)	121.4 (13)	121.7 (10)	0.858 *
	MAP (mmHg)	77.33 (13.1)	79.35 (11.5)	0.375 *
	DBP (mmHg)	68.77 (12.1)	66.10 (11.6)	0.349 *
	SpO2 (%)	99.67 (0.5)	99.71 (0.6 )	0.586 *

	PetCO <sub>2</sub> (%)	35.97 (1.6)	35.74 (1.2)	0.222 *
<b>Surgery duration</b>	(minutes)	114.5 (± 29)	106.7 (±13)	0.181 ***

S: physiological Serum, K: ketamine, Cm: centimeters , Kg: kilograms, HR: Hear beat, bpm: beat per minute, SBP: systolic blood pressure, MAP: mean arterial pressure, DBP: diastolic blood pressure, SpO<sub>2</sub>: oxygen saturation, Pet CO<sub>2</sub>: Postapneic end-tidal carbon dioxide pressure. \* Mann-Whitney test, \*\* Fisher exact test, Student T test

### 3.2. Assessment of postoperative pain:

During the PACU admission period, the mean VAS values at rest or during swallowing were higher in Group S compared to Group K, however the difference was not statistically significant  $p>0.05$  (table 2).

**Table 2: Mean VAS values in group S and group K at rest and during swallowing at the PACU admission period**

Timing (minutes)	VAS values at rest during the first 24 hours post operatively			VAS values during swallowing at the first 24 hours post operatively		
	Group S	Group K	P value	Group S	Group K	P value
0	4.52	1.94		6.13	2.58	
10	3.87	1.94		6.45	2.58	
20	3.87	1.94		6.77	2.58	
30	4.52	2.58		7.10	3.23	
40	4.84	2.58		6.13	2.90	
50	4.19	2.58	>0.05	6.13	3.23	>0.05
60	3.87	2.58		5.81	3.23	
70	3.87	2.58		5.81	3.23	
80	4.19	3.23		6.77	3.87	
90	3.87	3.23		6.13	3.87	
100	3.87	3.23		6.13	3.55	
110	4.19	3.23		6.45	3.55	
120	4.19	3.23		6.45	3.55	

Group S: saline solution group, group K: ketamine group, VAS: visual analog scale, PACU: post anesthetic care unit

Regarding the first 24-hour postoperative hospitalization period in the ENT department, the mean VAS values were higher in group S compared to group K; either at rest or during swallowing , but the difference was not statistically significant. ( $p >0, 05$ ) (Table 3 ).

**Table 3: Mean VAS values in group S and group K at rest and during swallowing during the first 24 hours post operatively**

Timing (hours)	VAS values at rest during the first 24 hours post operatively			VAS values during swallowing at the first 24 hours post operatively		
	Group S	Group K	P value	Group S	Group K	P value
6	3.87	2.9	>0.05	4.52	4.52	>0.05
12	3.55	2.9		4.19	4.19	
18	3.55	2.58		4.84	4.19	
24	3.55	2.58		4.84	3.55	

Group S: saline solution group, Group K: ketamine group, VAS: visual analog scale

None of the patients in Group K received morphine while it was administered to four patients in Group S. The mean morphine consumption in the PACU was 0.71 mg and 0 mg in group S and group K, respectively. The difference in morphine consumption between both groups was statistically significant ( $p=0.04$ ). Nefopam was not administered to any of our patients.

No patient presented a hematoma at the injection points of the product. A patient in group K showed hallucinations during the stay in the PACU. Dizziness was recorded in three patients of group K and one patient of group S. No patients presented postoperative shivers.

Respiratory distress was not recorded in any of our patients. Nausea and vomiting were observed in a total of 11 patients, but without significant differences between both groups.