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Efficacy of ketamine for postoperative pain following robotic thyroidectomy: A prospective randomised study

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Abstract

Objective: Although robotic thyroidectomy (RoT) is a minimally invasive surgery, percutaneous tunneling causes moderate to severe pain immediately postoperatively. We evaluated the efficacy of ketamine for postoperative pain management in patients following RoT.

Methods: Sixty-four patients scheduled for RoT were randomly divided into two groups. In the ketamine group (n = 32), ketamine was infused from induction of anaesthesia until the end of the procedure (0.15-mg/kg bolus with continuous infusion at 2 μg/kg/min). In the control group (n = 32), the same volume of saline was infused. Visual analogue scale (VAS) scores for acute and chronic pain, the incidence of hypoesthesia, postoperative analgesic requirements, and complications related to opioids or ketamine were compared between the two groups.

Results: The VAS pain scores were significantly lower in the ketamine group up to 24 h postoperatively. The VAS pain score when coughing was significantly higher in the control group than in the ketamine group at 24 h postoperatively. A significantly greater proportion of patients in the control group required rescue analgesics. Complications were comparable in both groups.

Conclusions: Ketamine infusion decreased pain scores for 24 h postoperatively and reduced analgesic requirements without serious complications in patients following RoT.

Trial Registration: Clinicaltrials.gov Identifier: NCT01997801

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Introduction

Robotic thyroidectomy (RoT) has been widely accepted due to its safety, short learning curve, and cosmetic advantages.[1,2] The bilateral axillo-breast approach (BABA) in RoT requires hydrodissection; *i.e.*, subcutaneous tunneling in the neck and anterior chest. Despite the use of small incisions, RoT using the BABA does not reduce pain in the immediate postoperative period compared with open surgery.[3–5] Appropriate analgesic treatment is necessary after RoT to manage acute and chronic postoperative pain and sensory changes. Paracetamol, bilateral superficial cervical plexus blockade, and gabapentin have been effective for managing postoperative pain in patients undergoing RoT.[6–8]

Ketamine is a noncompetitive N-methyl-D-aspartate receptor blocker and has some advantages in terms of preemptive analgesia.[9] When low-dose ketamine is administered perioperatively, an opioid-sparing effect has been reported during the postoperative period after various surgeries, such as gastrectomy, Caesarean section, and colectomy.[10–12] Low-dose ketamine also reduces immediate postoperative pain in patients undergoing minimally invasive surgery, such as gynaecologic diagnostic laparoscopy.[13] Nevertheless, the efficacy of ketamine infusion following RoT using the BABA remains unclear.

We evaluated the efficacy of intravenous low-dose ketamine during RoT in this prospective randomised study. Our hypothesis was that an intravenous infusion of low-dose ketamine would decrease acute and chronic postoperative pain scores and reduce the number of patients requiring systemic opioids after RoT.

Patients and methods

Study population

The Institutional Review Board of Seoul National University Hospital approved this investigation (Ref: H1311-062-534). This investigation was registered at ClinicalTrials.gov (registration no. NCT01997801). Patients were recruited from April 2014 to December 2014 in the Seoul National University of Hospital by two of the investigators (J.L. and H.P.P.). Patients scheduled for RoT were enrolled after having provided written informed consent. Patients with an American Society of Anesthesiologists physical status of I to III and age of 19 to 80 years were included. The exclusion criteria were as follows: renal, liver function, or neurological disorders; uncontrolled hypertension; heart failure; coronary disease; uncontrolled thyroid disease; pregnancy; pain syndromes; a history of drug or alcohol addiction; acute treatment with corticosteroids; chronic treatment with opioids or beta-blockers; hypersensitivity to ketamine; abnormal intracerebral pressure or intraocular pressure; and risk of aspiration. Before surgery, all patients were educated on the use of a 0- to 10-cm visual analogue scale (VAS) using a ruler (0 cm = no pain, 10 cm = worst possible pain).

Randomisation

The patients were randomly allocated into the control and ketamine groups using

Random Allocation Software, version 1.0.0 (Isfahan University of Medical Sciences, Isfahan, Iran). The randomisation was generated using random blocks of four and six and performed by an investigator who was blind to the study protocol. The assignments were placed in opaque envelopes and managed by anaesthetists who did not participate in either the patient care or the investigation. The group assignment was revealed to the investigator on the morning of the surgery.

Anaesthesia procedure

Patients arrived in the operating room without premedication and were then monitored by noninvasive arterial blood pressure, pulse oximetry, and three-lead electrocardiography. Intravenous access was established using an 18-gauge catheter. General anaesthesia was induced using a target-controlled continuous infusion of 4 μg/mL of propofol and 4 ng/mL of remifentanil (Orchestra® Base Primea; Fresenius Kabi, Brézins, France). Rocuronium (0.8 mg/kg) was administered for tracheal intubation. A Nerve Integrity Monitor electromyographic endotracheal tube (Medtronic Xomed; Jacksonville, FL, USA) was inserted for continuous recurrent laryngeal nerve monitoring. The radial artery was cannulated to monitor the arterial pressure, and an additional peripheral intravenous catheter was inserted.

Patients in the ketamine group received a bolus dose of 0.15 mg/kg of racemic ketamine after anaesthetic induction. Racemic ketamine was also infused continuously until the end of the surgery at a rate of 2 μg/kg/min.[12] Patients in the control group were given an equal volume of saline. A nurse supplied 3- and 50-mL syringes containing the study drug.

Anaesthesia was maintained by continuous infusion of propofol and remifentanil. The propofol and remifentanil concentrations were adjusted to maintain a bispectral index of 40 to 60 and a systolic blood pressure within ±20% of baseline. Additional rocuronium was not injected while the recurrent laryngeal nerve was monitored. The attending anaesthesiologist was blinded to the patient groups.

Surgical procedure

After inducing anaesthesia, the patients were placed in the supine position with slight neck extension using a specially designed pillow under the shoulders. Surgery was aided by the Da Vinci Robot System (Intuitive Surgical, Inc., Mountain View, CA, USA). Dilute epinephrine (1:200,000) in 200 mL was injected along the neck subplatysmal space and anterior chest. For the port sites, two incisions were made in the axillary area (0.8 cm each) and two in the circumareolar area (right, 1.2 cm; left, 0.8 cm). A flap was dissected using endoscopic instruments. The bilateral circumareolar and axillary ports were inserted via a vascular tunneler after the flaps were raised. Carbon dioxide was insufflated at a pressure of 5 to 6 mmHg via the camera port. The flap was dissected to the thyroid cartilage superiorly, 3 cm below the clavicle inferiorly, and laterally from just beyond the lateral border of one sternocleidomastoid muscle to the other. The robotic instruments were docked, and the midline was divided with monopolar electrocautery until the thyroid was recognised. The cricothyroid membrane, the isthmus, and the central group of lymph nodes were visualised. The isthmus was divided to facilitate dissection of the thyroid gland laterally and posteriorly and to optimally visualise the superior thyroid pedicle. The middle thyroid pedicles were ligated and divided. Thyroidectomy was completed with a view of the middle and inferior thyroid pedicles, the recurrent laryngeal nerve, and the superior and inferior parathyroid

glands. The thyroid lobes were resected and pulled out through the axillary incision using an Endopouch (Ethicon, Somerville, NJ, USA).

Postoperative pain management

Patients received pethidine (25 mg) intravenously at the end of the procedure after all of the surgical instruments had been removed. Atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg) were administered intravenously to antagonize the residual neuromuscular blockade. The time from the end of surgery to extubation was recorded. The total amounts of propofol and remifentanil used during surgery and the time from the end of surgery to extubation were recorded.

The VAS pain score was assessed 0, 1, 6, 24, and 48 h postoperatively, both at rest and while coughing, with the patients in a sitting position. Fentanyl (50 μg) in the post-anaesthesia care unit and ketorolac (30 mg) or pethidine (25 mg) on the ward were administered on request. The time to administration of the first analgesic agent and the number of patients who required additional analgesics were recorded. The incidence of chronic pain and hypoesthesia and the VAS pain score were checked 3 months postoperatively in a telephone interview conducted by a blinded investigator.

Postoperative side effects, including nausea, vomiting, dizziness, headache, pruritus, dysphoria, hallucination, diplopia, and nightmares, were assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at 0, 1, 6, 24, and 48 h postoperatively. These side effects were treated on request by the patients. Sedation was assessed on a 5-point scale (1 = completely awake with eyes open, 2 = drowsy, 3 = dozing, 4 = mostly sleeping, and 5 = not responding). Respiratory depression was defined by at least one of the following variables: respiratory rate of <8 breaths/min, blood oxygen saturation of <90%, or partial pressure of carbon dioxide in arterial blood of >70 mmHg. Side effects were recorded and treated by physicians who were blinded to the group assignments. The postoperative variables, including the VAS pain scores, rescue therapy, and opioid-related complications, were recorded by an investigator who was blinded to the group assignments.

Statistical analysis

The primary endpoint of this study was the VAS pain score at 6 h postoperatively. The secondary endpoints were the VAS pain scores at 0, 1, 24, and 48 h postoperatively; the incidence of side effects, including nausea, vomiting, dizziness, headache, pruritus, dysphoria, hallucinations, diplopia, nightmares, sedation, and respiratory depression; and the use of rescue analgesics. The VAS pain scores were compared using multivariate analysis of variance followed by Tukey's post-hoc test. Student's *t*-test or the Mann–Whitney *U*-test was performed to analyse continuous variables after the normality test (Kolmogorov–Smirnov test). The incidence of complications was compared between the two groups using the chi-square test or Fisher's exact test. A *P*-value of <0.05 was considered to indicate a significant difference. Values are presented as mean (standard deviation), median [interquartile range (IQR)], or number (percentage).

The sample size was calculated based on a report by Yoo et al.,[4] in which the mean VAS pain score at 6 h postoperatively was 4.2 (2.1). We considered these values for the control group. We assumed that a 40% reduction in postoperative pain would be clinically relevant. We also assumed that the standard deviation in the ketamine group would be the same as that in the control group. With $\alpha = 0.05$ and a power of 0.8, a minimum sample size of 25 in each

group was necessary. To allow for a possible dropout rate of 20%, 32 patients per group were recruited. The statistical analysis was performed using SPSS software (ver. 19.0; IBM Corp., Armonk, NY, USA). The sample size was calculated using G*power 3 software.[14]

Results

In total, 64 patients scheduled for RoT from April 2014 to December 2014 were included in this study: 32 patients were randomised to the ketamine group and 32 to the control group (Figure 1). The patients were followed until 48 h postoperatively. Eight patients in the control group and seven in the ketamine group were lost to follow-up at 3 months postoperatively and were thus excluded from the analyses. The demographics and preoperative characteristics of the patients were comparable between the two groups (Table 1). After the Kolmogorov–Smirnov test, Student's *t*-test was applied to assess age and intraoperative use of remifentanil. Other continuous variables such as weight, duration of surgery, intraoperative use of propofol, intraoperative fluids, time to extubation, and time to administration of the first

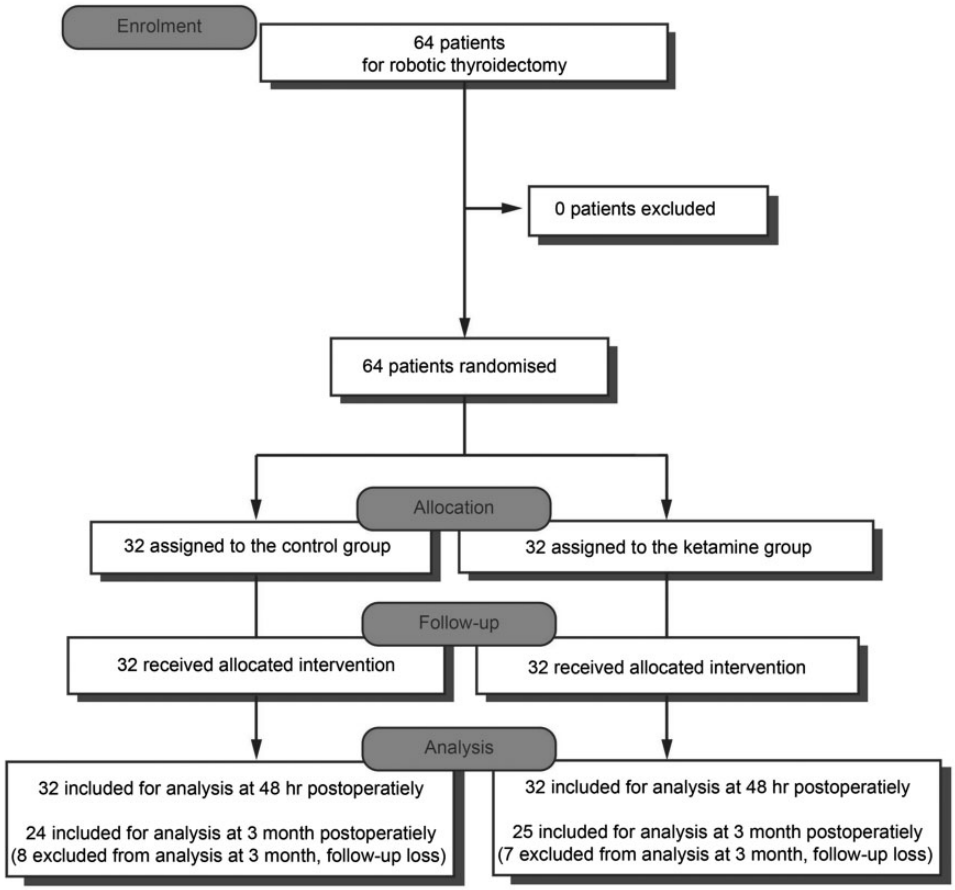

Figure 1. CONSORT diagram.

Table 1. Baseline characteristics of patients

	Control group (n = 32)	Ketamine group (n = 32)
Age (years)	38 (9)	37 (12)
Male/female (n)	2 (6%)/30 (94%)	4 (12%)/28 (88%)
Weight (kg)	60 (10)	60 (8)
Duration of surgery (min)	174 (41)	161 (24)
Intraoperative use of propofol (mg/kg/h)	9.2 (1.9)	8.5 (1.8)
Intraoperative use of remifentanil (μg/kg/h)	10.8 (2.8)	10.0 (3.1)
Intraoperative fluids (ml/kg/h)	5.4 (1.8)	6.0 (2.2)
Time to extubation (min)	10.7 (5.0)	11.7 (6.1)

Data are presented as mean (standard deviation) or n (%).
No statistically significant between-group differences were observed ($P > 0.05$) (Student's *t*-test or Mann–Whitney *U*-test)

analgesic agent were analysed using the Mann–Whitney *U*-test. No differences in surgical or anaesthetic data were observed, including the total amounts of propofol and remifentanil used during surgery and the time to extubation.

There was a statistically significant difference in the VAS pain scores at rest and while coughing until 24 h postoperatively between the two groups ($P = 0.028$ and $P = 0.039$, respectively) (Figure 2). At rest, the VAS pain score at 1 h postoperatively was 5.0 (IQR: 3.0) in the control group and 3.3 (IQR: 2.5) in the ketamine group ($P < 0.01$). At 6 h postoperatively, the VAS pain score at rest was higher in the control group than in the ketamine group [4.0 (IQR: 3.0) *vs.* 2.0 (IQR: 3.0), respectively; $P < 0.01$]. While coughing, the VAS pain score at 1 h postoperatively was higher in the control group than in the ketamine group [6.0 (IQR: 3.0) *vs.* 4.0 (IQR: 2.8), respectively; $P < 0.01$]. At 6 h postoperatively, the VAS pain score while coughing was higher in the control group than in the ketamine group. [5.0 (IQR: 2.0) *vs.* 4.0 (IQR: 3.0), respectively; $P < 0.01$]. The VAS pain scores at rest and while coughing were similar in both groups after the first 24 h postoperatively.

The time to administration of the first rescue analgesics did not differ between the control group and ketamine group [20 (IQR: 40) min *vs.* 25 (IQR: 17) min, respectively; $P = 0.175$] (Table 2). The number of patients who required rescue analgesics was higher in the control group than in the ketamine group [18 (56%) *vs.* 9 (28%), respectively; $P = 0.023$]. The number of patients with chronic pain was comparable in both groups [10 (42%) *vs.* 9 (36%), respectively]. The number of patients with hypoesthesia was also similar in both groups [20 (83%) *vs.* 20 (80%), respectively]. At 3 months postoperatively, the VAS pain scores did not differ between the two groups [0 (IQR: 2.5) *vs.* 0 (IQR: 1.0), respectively].

Nausea and vomiting occurred in 5 (16%) *vs.* 7 (22%) patients and 1 (3%) *vs.* 2 (6%) patients in the control and ketamine groups, respectively, with no significant difference. Severe nausea and vomiting were not reported in either group. No patient experienced respiratory depression. Four patients in the control group and four patients in the ketamine group required 10 mg of metoclopramide for nausea. Dysphoria, hallucinations, diplopia, and nightmares were not reported in either group.

Discussion

In this study, continuous infusion of low-dose ketamine was found to reduce VAS pain scores up to 24 h postoperatively as

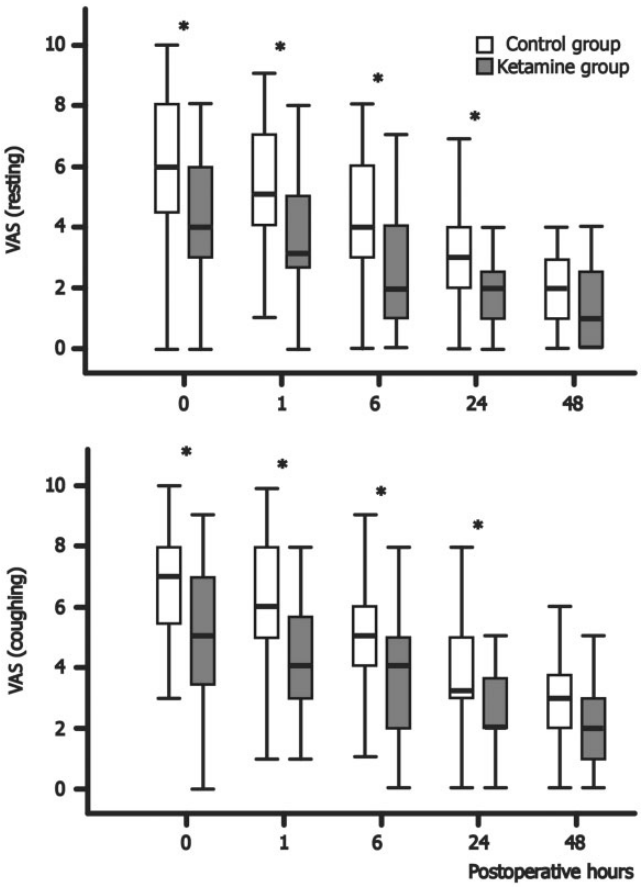

Figure 2. Visual analogue scale pain scores (0 = no pain, 10 = worst imaginable) at rest and on coughing. Visual analogue scale pain scores were significantly higher in the control group up to 24 h postoperatively than in the ketamine group. The box represents the interquartile range, and the line across the box indicates the median. *$P < 0.01$ *vs.* control group (Student's *t*-test or Mann–Whitney *U*-test). VAS, visual analogue scale.

Table 2. Variables related to analgesic use, chronic pain, and hypoesthesia

	Control group (n = 32)	Ketamine group (n = 32)	*P*-value
Time to first analgesic agent (min)	20 (IQR: 40)	25 (IQR: 17)	0.175
Number of patients requiring analgesics	18 (56%)	9 (28%)	0.023
Number of patients with chronic pain at 3 months postoperatively	10/24 (42%)	9/25 (36%)	0.684
Number of patients with hypoesthesia at 3 months postoperatively	20/24 (83%)	20/25 (80%)	1.000

Data are presented as median (IQR) or n (%).
IQR, interquartile range.

well as postoperative rescue analgesic requirements. Although the time to administration of the first analgesic agent was comparable between the two groups, the proportion of patients who requested analgesics was significantly higher in the controls than in the ketamine group. We did not observe any between-group differences in side effects, chronic pain, or hypoesthesia.

Although RoT via the BABA provides an optimal view of the thyroid gland and important structures,[15] it may cause moderate pain and sensory changes due to wide hydrodissection of the skin flaps from the axilla to the anterior neck and forceful lifting of the tissues during the surgery.[5,16] After RoT, patients experience considerable pain for 48 h postoperatively.[5] Patients undergoing RoT often complain of moderate to severe pain especially at 0, 1, and 6 h postoperatively.[5,17] In the present study, the median pain score in the control group at 6 h postoperatively was 4 (IQR: 3), which is consistent with other studies of the BABA approach.[4,5,17] Highly severe pain needs to be managed properly to decrease morbidity and increase quality of life. In the present study, patients in the ketamine group had VAS scores consistent with only mild pain at 6 h postoperatively, which was the primary endpoint of this investigation. A low-dose ketamine infusion decreased the acute postoperative pain scores after RoT in our study, which is consistent with other studies of preemptive analgesia with ketamine infusion.[10,18] As a preemptive analgesia strategy, low-dose ketamine infusion may be appropriate for the acute postoperative pain associated with RoT.

RoT is known to cause chronic pain and hypoesthesia of the anterior chest.[19] A previous study demonstrated that anterior chest discomfort and sensory disturbance were greater after RoT than open thyroidectomy.[20] Subanaesthetic infusion of ketamine decreased chronic residual pain in patients undergoing rectal adenocarcinoma surgery.[21] However, ketamine does not reduce chronic pain in patients undergoing hysterectomy and thoracotomy.[18,22] Acute pain control may affect the development of chronic pain.[23] Despite the superior analgesic effect in the early postoperative period, we observed no difference in chronic pain and hypoesthesia at 3 months between the two groups. Our sample size may have been too small to evaluate the long-term outcome. The low-dose ketamine infusion protocol in our investigation may have decreased the beneficial effect of ketamine on the development of chronic pain. We used a racemic ketamine infusion in the present study. (S)-ketamine is more potent than racemic ketamine.[24] Further investigations should determine the relationships among chronic pain, hypoesthesia, higher-dose infusion of ketamine, and (S)-ketamine.

A previous study by Kim et al.[17] demonstrated the efficacy of ketamine on postoperative pain after robotic or endoscopic thyroidectomy. Our study showed similar results with respect to the reduction in acute pain provided by ketamine. In our study, however, we enrolled only patients undergoing RoT. RoT is associated with higher pain scores on postoperative 1 day than is endoscopic thyroidectomy.[25,26] Our investigation showed that the ketamine infusion decreased the severity of postoperative pain in patients at higher risk of pain after thyroidectomy. We evaluated the pain in the anterior chest area when resting and coughing. Coughing is recommended to prevent postoperative atelectasis.[27] Anterior chest pain induced by hydrodissection in the BABA approach may be increased while coughing. Our study also demonstrated that the ketamine infusion decreased postoperative pain in patients while coughing after RoT. In our protocol, additional muscle relaxation agents were

not used to monitor the integrity of the recurrent laryngeal nerve. Muscle relaxants are known to decrease pain after anal surgery while patients undergo a postoperative anal examination.[28] Monitoring the recurrent laryngeal nerve is known to decrease transient vocal cord palsy and increase identification of the superior laryngeal nerve.[29,30] The neuromonitoring technique is gaining increasingly more acceptance among surgeons.[31] Our protocol may benefit this population of patients undergoing RoT with neuromonitoring.

In our investigation, low-dose ketamine infusion reduced the analgesic requirement and pain scores for 24 h. In a previous investigation by Abd El-Rahman et al.,[32] local ketamine instillation decreased pain scores in the immediate postoperative period in patients who underwent open thyroidectomy. Ketamine instillation was performed at the end of the procedure, and the preventative effect on postoperative pain did not last after the first postoperative hour. In the present study, ketamine was infused before the surgical injuries occurred. Considering that the elimination half-life of ketamine is 130 to 155 min,[33] the effect of the low-dose ketamine infusion lasted markedly longer than the pharmacologic actions of ketamine in our investigation. The preventative effect of ketamine on the development of central sensitisation in patients with surgical injuries may increase the duration of ketamine's effectiveness.[34] Prevention of acute postoperative pain by ketamine may decrease the sensitisation caused by the pain itself. These factors may explain the long-lasting effect of ketamine seen in our investigation.

Postoperative rescue analgesics may expose patients to a risk of side effects. Opioids such as morphine for the management of severe postoperative pain after remifentanil-based anaesthesia increases the risk of respiratory depression.[12,35] Opioids may exaggerate respiratory depression because thyroid surgery can injure the recurrent laryngeal nerve and cause airway oedema. Ketorolac may increase the risk of postoperative bleeding[36] and renal failure.[37] Bleeding after thyroid surgery is a life-threatening complication that may require tracheostomy.[38] In the present study, the low-dose ketamine infusion decreased the need for postoperative rescue analgesics. In this regard, a low-dose ketamine infusion may decrease the risk of opioid-related side effects by reducing analgesic requirements. Low-dose ketamine infusion did not delay the time to extubation or increase the ketamine-related side effects such as increased intracranial pressure, hypertension, pulmonary hypertension, pulmonary oedema, respiratory depression, dysphoria, hallucination, diplopia, and nightmares.[39–41] In our study, low-dose ketamine infusion during surgery showed satisfactory analgesia for patients undergoing RoT without ketamine-related side effects. However, our study was not designed to detect side effects related to opioids and ketamine. Further investigation regarding the side effects of opioids and ketamine in patients receiving a low-dose ketamine infusion during surgery is necessary.

A ketamine bolus of 0.15 mg/kg and maintenance at 2 μg/kg/min were administered in the present study; in contrast, a bolus of 1 mg/kg and maintenance at 1 μg/kg/min were administered in a study by Kim et al.[17] Their 1-mg/kg ketamine bolus is relatively high compared with that in other investigations.[12,42] Additionally, their maintenance rate of 1 μg/kg/min was lower than that in our investigation. We determined that our ketamine dosage achieves a target theoretical plasma concentration of 60 ng/ml,[43] which is within the range of concentrations that prevent hyperalgesia without serious side effects.[12,44] Our ketamine dosage is also in line with that in previous investigations regarding low-dose

ketamine infusion during surgery for postoperative pain.[12,42] Our ketamine infusion protocol decreased the patients' acute postoperative pain scores in the anterior chest area, while the infusion protocol in the study by Kim et al.[17] did not. The more stable plasma concentration of ketamine during surgery may have been associated with the prevention of acute postoperative pain in the chest area in this study. Further investigation regarding the plasma ketamine concentration and postoperative analgesia is necessary.

Our study had some limitations. First, the low-dose ketamine infusion did not reduce the intraoperative remifentanil requirements. The relatively short procedure time and reduced surgical stimulation after the initial exploration may have decreased the remifentanil requirements. High-dose remifentanil can increase postoperative hyperalgesia.[45] Second, we did not perform a test to differentiate pain from hyperalgesia. Further investigations that employ a quantitative sensory test of the mechanical pain threshold using von Frey filaments may be needed. Third, we did not evaluate the size of the removed thyroid tissues. The size of the thyroid tissue is related to the degree of tissue injury, which may affect postoperative pain and analgesic requirements. The size of the thyroid cancer should be limited or equally distributed to decrease the bias caused by the extent of the surgery itself.

Conclusions

The low-dose ketamine infusion in the present study provided more satisfactory analgesia for the first 24 h postoperatively and decreased analgesic requirements without serious complications in patients undergoing RoT. The low-dose ketamine infusion did not improve the chronic pain caused by RoT. These findings suggest that a low-dose ketamine infusion should be considered for the treatment of acute postoperative pain in patients undergoing RoT.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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