Original Article

Effects of perioperative intravenous lidocaine and esketamine on the quality of recovery and emotional state of patients after thyroidectomy: A randomised, double-blind, controlled trial

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ABSTRACT

Background and Aims: Perioperative intravenous (IV) infusions of lidocaine and esketamine reduce postoperative pain, but there are few studies on the quality of recovery and patients' emotional states postoperatively. We aimed to explore the effects of perioperative IV lidocaine and esketamine on the quality of recovery and emotional state after thyroidectomy. **Methods:** In this randomised trial, 137 patients undergoing thyroidectomy were randomly assigned to three groups: a lidocaine group (Group L), an esketamine group (Group E) and a normal saline placebo group (Group C). The primary outcome was the Quality of Recovery 40 (QoR-40) on postoperative days (PODs) 1 and 2. The secondary outcomes included Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scores on days 1 and 2 after surgery, pain scores, opioid consumption and incidence of postoperative nausea and vomiting (PONV). Statistical analysis was performed using the one-way analysis of variance (ANOVA), the Kruskal-Wallis and Chi-square tests. **Results:** The global QoR-40 scores in groups L and E on POD 1 and POD 2 were significantly higher than in group C ($P < 0.001$). The SAS and SDS scores on POD 1 and POD 2 in groups L and E were significantly lower than in group C ($P < 0.05$). There were statistically significant differences in Numerical Rating Scale (NRS) scores among the three groups at 1 h, 2 h, 6 h and 12 h ($P < 0.05$). **Conclusion:** Perioperative IV lidocaine and esketamine improve the quality of postoperative recovery and the emotional state of patients undergoing thyroidectomy.

Keywords: Emotions, esketamine, lidocaine, quality of recovery, Self-Rating Anxiety Scale, Self-Rating Depression Scale, thyroidectomy

INTRODUCTION

Thyroidectomy, as a treatment for thyroid diseases such as giant goitre, thyroid tumours and thyroid cancer, can be used as an outpatient procedure in some countries with particular safety.[1,2] However, it is not popular in China, possibly due to complications after thyroid surgery. The complications cause patients to feel uncomfortable due to postoperative pain, leading to subsequent physiological and psychological alterations that impede postoperative recovery and prolonged hospitalisation. Therefore, many measures have been proposed to improve postoperative negative emotions and promote enhanced recovery after surgery (ERAS) programmes. Lidocaine and esketamine have been included in ERAS programmes as part of general anaesthesia adjuncts and multimodal analgesia.[3]

Lidocaine, a widely used local anaesthetic and antiarrhythmic medication, has been extensively

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investigated in numerous studies. These investigations have consistently demonstrated that the intravenous (IV) administration of lidocaine yields notable benefits, including the reduction in postoperative pain and enhanced postoperative recovery. Furthermore, research has indicated that IV lidocaine can effectively ameliorate the emotional well-being of patients experiencing neuralgia following herpes zoster surgery.[4] Esketamine, the mirror image of ketamine, blocks the N-methyl D-aspartate (NMDA) receptor. It is more effective at relieving pain than ketamine while having fewer adverse effects, such as hallucinations. Moreover, it has been demonstrated to induce a prompt antidepressant response.[5] Esketamine, as an adjunct to general anaesthesia, is effective in adjunctive analgesia and reduces pain intensity and opioid requirements in the short-term postoperative period.[6]

Theoretically, both lidocaine and esketamine have the effect of promoting postoperative recovery and improving negative emotions in patients. This study aimed to assess the impact of IV lidocaine and esketamine on postoperative recovery quality and emotional state in patients who underwent thyroidectomy. The primary objective was to measure the postoperative quality of recovery in patients who underwent thyroidectomy. Secondary objectives were to assess anxiety, depression, pain, perioperative use of opioids and propofol, and occurrence of postoperative nausea and vomiting (PONV).

METHODS

This study has been conducted in accordance with the regulations and guidelines set by the medical ethics committee of the Second Hospital of Huai'an City (vide approval number HEYLL202006, dated 06/05/2020). The study was registered at www.chictr.org.cn (registration number: ChiCTR2100043935, dated 5 March 2021). All procedures performed in research involving human participants were in accordance with the ethical standards of the institutional and national research committee, as well as the 1975 Helsinki Declaration and its later 2013 amendments. Before participating in the study, all patients had to provide informed consent by signing the appropriate documentation.

One hundred thirty-seven patients undergoing thyroidectomy at our hospital between April 2021 and May 2022 were assessed for eligibility to be included in this randomised, double-blind study. To be included, subjects must have been between 18 and 65 years of age and have American Society of Anesthesiologists (ASA) physical status I–II. Patients with a body mass index (BMI) exceeding 30 kg/m^2; those suffering from severe cardiopulmonary, liver or kidney disorders; diabetes mellitus and neuropsychiatric disorders; patients with allergies to lidocaine, esketamine and other experimental drugs; patients with uncontrolled hypertension and hyperthyroidism; pregnant and lactating women; patients with long-term sedative and analgesic use and long-term alcohol consumption; patients who were unable to understand the content of the study; and patients with an intraoperative change in the scope of surgery were excluded from the study. The study also set exclusion criteria: a change in surgical approach, the duration of the surgery more than three hours, and the patient non-return for a postoperative visit.

Computer-generated random numbers were used to assign patients to three groups: the lidocaine group (Group L), the esketamine group (Group E) and the normal saline placebo group (Group C). The random numbers were handed over in sealed, opaque, sequentially numbered envelopes. One researcher not involved in the study prepared the experimental drugs in envelopes according to the grouping and then gave them to the anaesthesiologist. The anaesthesiologist and patient were blinded entirely to the treatment assignment.

There were no preoperative medications. After admission, the patients were monitored for vital signs such as blood pressure, pulse oximetry, electrocardiogram and entropy index. Before administering anaesthesia, all patients were preoxygenated with 100% oxygen through a facemask for 3 to 5 minutes. Anaesthesia induction was performed with IV midazolam (0.05 mg/kg), propofol (1.5 mg/kg), sufentanil (0.5 mg/kg) and rocuronium (0.6 mg/kg). Following the induction, endotracheal intubation was performed. Mechanical ventilation was maintained during the surgery to ensure an appropriate carbon dioxide concentration. An IV infusion of propofol (4–10 mg/kg/h) with remifentanil (0.05–2 μg/kg/min) was used to maintain the level of anaesthesia. Additional doses of IV rocuronium were given as required. After the surgery, patients were transferred to the postanaesthetic care unit (PACU). Extubation was

performed once patients met the necessary criteria. Finally, patients were discharged from the recovery room based on the steward scoring criteria. If the patient's Numerical Rating Scale (NRS) score was >5, we would administer IV tramadol (25 mg) for postoperative pain.

In Group L, patients received a 1.5 mg/kg bolus of IV lidocaine 10 minutes before anaesthesia induction. They were then administered a continuous IV infusion of lidocaine at a rate of 1.5 mg/kg/h until the end of the closure of the skin incision. In Group E, patients received a 0.25 mg/kg bolus of IV esketamine 10 minutes before anaesthesia induction. They were also given a continuous IV infusion of esketamine at 0.25 mg/kg/h until the end of the closure of the skin incision. In Group C, patients were injected with equivalent volumes and rates of 0.9% saline using the same application scheme as the lidocaine and esketamine groups. The researcher individually dispensed drugs in 20-ml clear syringes according to body weight. They were dispensed separately for pre-induction and maintenance medication, thus setting the pumping rate at 120 ml/h before induction and 10 ml/h for intraoperative maintenance.

The primary outcome measures were the Quality of Recovery 40 (QoR-40) on postoperative day (POD) 2. Secondary outcomes included the following variables: Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scores on POD 2; the NRS score at time points (1 hour, 2 hours, 6 hours, 12 hours, 24 hours and 48 hours after surgery); perioperative use of opioids and propofol; and PONV.

The QoR-40 questionnaire[7] comprises 40 inquiries across five domains. Each question gauges the extent of a patient's recuperation by employing a five-point Likert scale (ranging from 1, indicating no occurrence, to 5, signifying constant presence). The five areas of the QoR-40 questionnaire include physical comfort, pain, physical independence, psychological support and emotional state. The overall QoR-40 scores encompass a range spanning from 40 to 200.

The SAS[8] and SDS[9] are standardised instruments consisting of 20 items each, designed to assess the severity of anxiety and depressive symptoms experienced by patients. Each item on the scale represents a symptom and is categorised into four levels. The total score for each item is determined by summing the scores assigned to each level. This total score is then multiplied by a factor of 1.25 and rounded to the nearest whole number, resulting in the final standard score. A higher standard score indicates elevated levels of anxiety and depression in the patient.

The sample size was determined using the Power Analysis and Sample Size (PASS) 15.0 software. We implemented a pretest and calculated a standard deviation of 9.8. According to the study,[10] a QoR-40 difference of 6.3 is clinically significant, so we set a difference of 6.3. While assuming a similar standard deviation for patients in the experimental group, we calculated that at least 35 patients or groups were needed, with a two-tailed α of 0.05 and a power of 80%. Based on an anticipated follow-up loss rate of 20%, a sample size of 135 patients was determined to be necessary for inclusion in this study.

The statistical analysis was conducted utilising the Statistical Package for the Social Sciences (SPSS) version 26.0 (International Business Machines Corporation, Armonk, NY, USA). Data are expressed as numbers, percentages, means, standard deviations or medians (interquartiles Q1, Q3). The normality of the measurement data was assessed using the Kolmogorov-Smirnov method, while the homogeneity of variance was examined using the Levine method. The analysis of the quantitative variables was conducted using either a one-way analysis of variance (ANOVA) (parametric, such as the QoR-40 score and the consumption of opioids) or the Kruskal-Wallis test (nonparametric, such as the NRS scores). Enumerated data are expressed as constituent ratios or ratios (%) and analysed using the Chi-square or Fisher's exact test for comparison. If notable distinctions were observed among the three groups, *post hoc* multiple comparisons were conducted. The comparison of different time points within the group was analysed by repeated measures of variance. The test levels were $\alpha = 0.05$, and $P < 0.05$ was deemed statistically significant.

RESULTS

The study consisted of a cohort of 137 patients, and the allocation of patients across the three groups is visually represented in Figure 1. The demographic and surgical characteristics of the groups were comparable [Table 1]. No statistically significant differences deemed clinically relevant were observed in the baseline data.

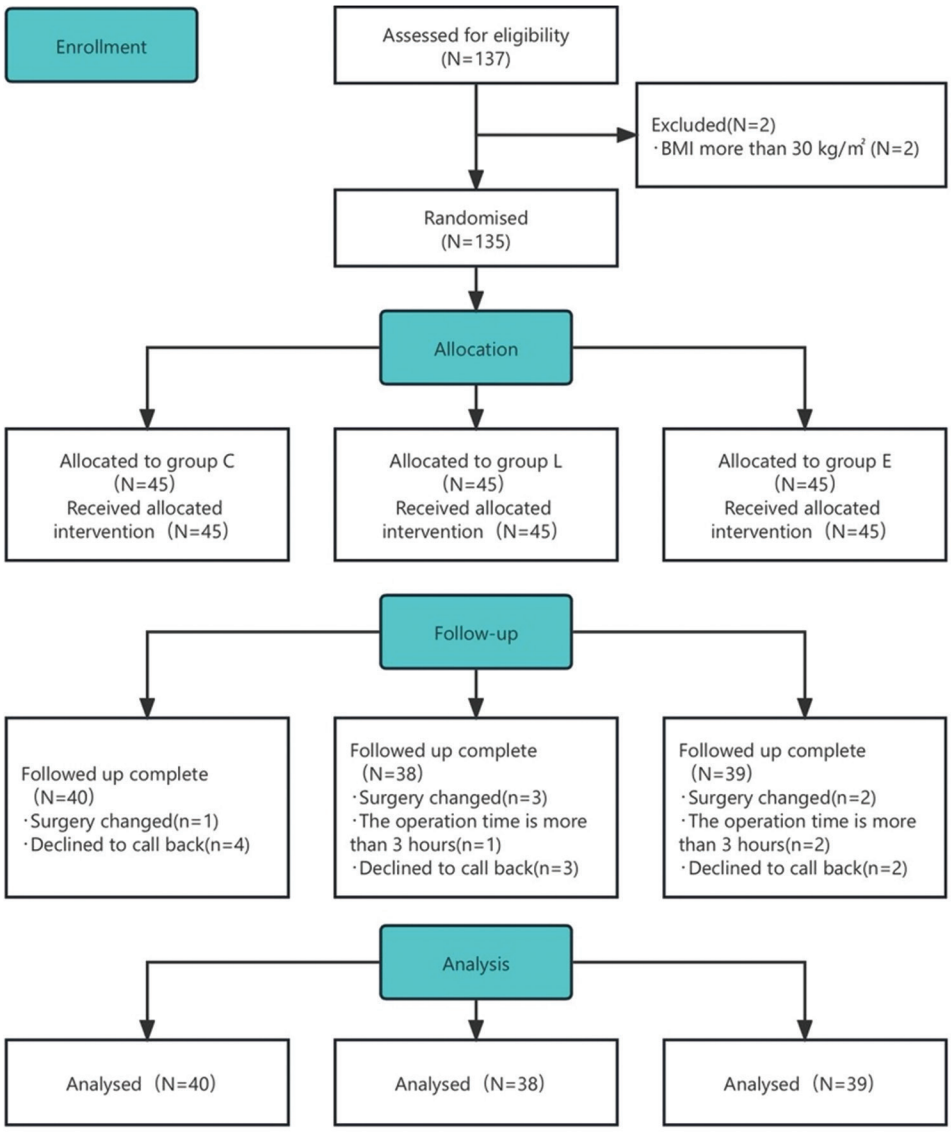

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram. N= Number of cases; Group C= Group Placebo; Group L= Group Lidocaine; Group E= Group Esketamine

The patients in groups L and E exhibited significantly higher scores in total QoR-40 and in the physical comfort, emotional state and pain subscales compared with Group C ($P < 0.001$) [Figure 2]. No statistically significant differences were observed between groups L and E ($P > 0.05$).

The postoperative anxiety and depression scores of patients in groups L and E were significantly lower compared with those of Group C ($P < 0.05$) [Figure 3]. No statistically significant differences were observed between groups L and E ($P > 0.05$).

The NRS scores of Group L and Group E exhibited a statistically significant decrease following the operation compared with those of Group C ($P < 0.05$) [Table 2]. Nevertheless, no statistically significant disparities were observed in the scores recorded at the 24-hour and 48-hour marks after the surgical procedure ($P > 0.05$). No statistically significant differences were observed between groups L and E ($P > 0.05$).

The total remifentanil consumption in Group C was significantly higher than in Group L and Group E ($P < 0.05$) [Table 3]. However, there was no significant difference in propofol consumption among the three groups ($P > 0.05$). The incidence of PONV was significantly lower in Group L compared with Group C ($P < 0.05$). There were no indications of lidocaine toxicity or esketamine side effects among any participants.

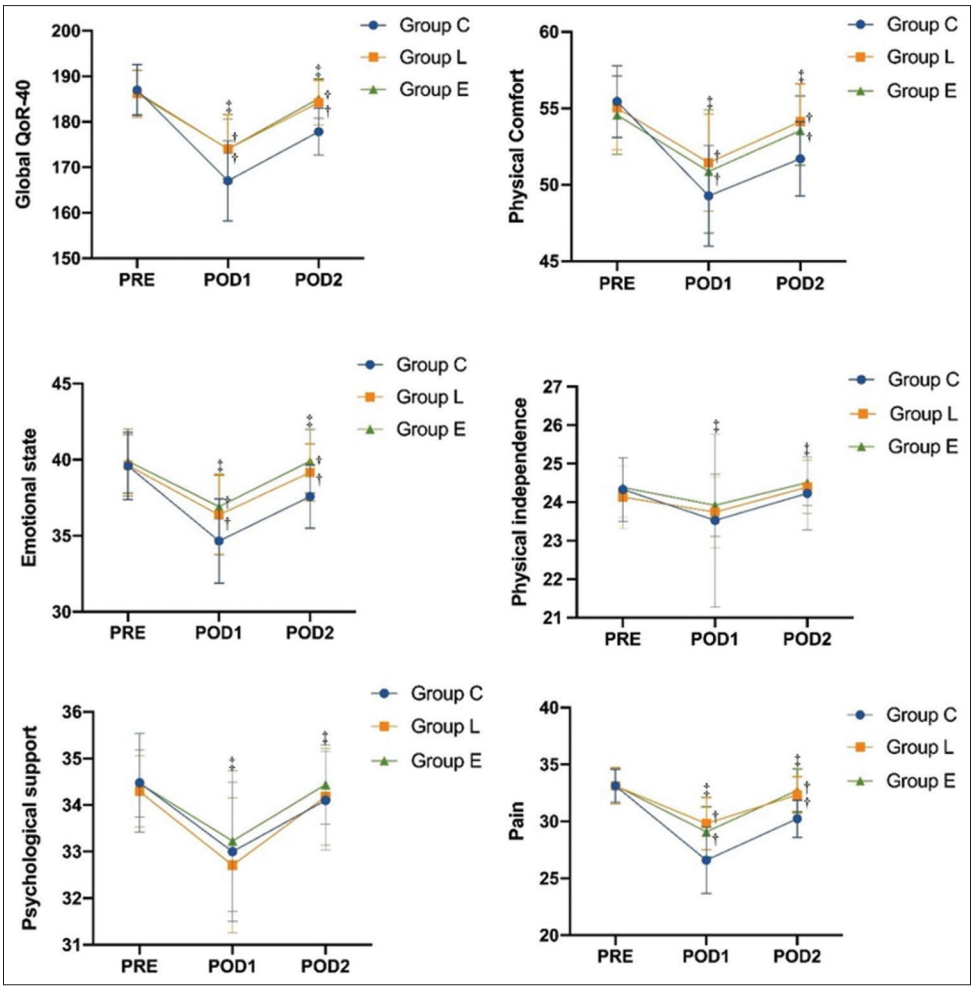

Figure 2: Global QoR-40 scores and the subscores of the five dimensions. †: *P* comparing group C versus group L and group E. ‡: *P* comparing PRE versus POD1 and POD2. QoR-40 = Quality of Recovery 40; PRE = preoperative day; POD1 = postoperative day 1; POD2 = postoperative day 2. Group C= Group Placebo;Group L= Group Lidocaine; Group E=Group Esketamine

Table 1: Patient characteristics and surgical data

	Group C (*n*=40)	Group L (*n*=38)	Group E (*n*=39)	*P*
Age (years)	54.30 (6.99)	51.95 (8.00)	52.00 (8.51)	0.318
Gender (male/female)	8/32	11/27	11/28	0.601
Height (cm)	161.83 (6.54)	163.29 (5.79)	163.21 (5.94)	0.491
Weight (kg)	67.79 (8.12)	68.22 (7.97)	66.18 (8.25)	0.507
ASA physical status I/II	33/7	30/8	32/7	0.910
Smoking history (yes/no)	5/35	7/31	6/33	0.769
Hypertension (yes/no)	8/32	5/33	7/32	0.714
Surgery type				0.793
Subtotal thyroidectomy	4	4	6	
Total thyroidectomy	10	11	13	
Thyroid carcinoma resection	26	23	20	

Data are presented as the mean (standard deviation) or numbers. ASA=American Society of Anesthesiologists, *n*=number of patients, Group C= Group Placebo, Group L= Group Lidocaine, Group E=Group Esketamine

DISCUSSION

Based on our results, perioperative IV lidocaine and esketamine improve the quality of postoperative recovery and the emotional state of patients after thyroidectomy. These drugs also alleviate postoperative pain and do not increase the incidence of postoperative complications.

Although thyroid surgery is not particularly traumatic, the stress response it causes can result in a variety of perioperative complications, such as

pain, unfavourable emotions and PONV. Studies have shown that pain can cause negative emotions, and negative emotions can also increase pain.[11] If there is no improvement, it will reduce the patient's postoperative recovery quality. Simultaneously, ERAS programmes prioritise optimal postoperative recovery and efficient pain management.[12] At present, the indicator of the quality of postoperative recovery has developed into a multidimensional assessment of physical comfort, pain, emotions, function and cognitive performance.[13] Therefore, the QoR-40 scale was employed in this study to assess the level of patient recovery following surgical procedures.[14] Recent research by Myles *et al*.[10] indicates that a change of 6.3 in the overall QoR-40 score may show clinically considerable improvement or deterioration.

Our results indicate that esketamine and lidocaine infusions during surgery have a significant positive effect on improving the quality of recovery for patients. Similarly, in experiments on supratentorial tumour resection,[15] upper airway surgery[16] and video-assisted thoracic surgery,[17] the administration of lidocaine or esketamine through IV infusion during the perioperative period demonstrated a notable enhancement in the postoperative recovery outcomes. However, some reports have come to different conclusions. Maheshwari *et al*.[18] employed a comprehensive strategy encompassing preoperative acetaminophen and gabapentin, along with intraoperative infusions of lidocaine and ketamine. There was no observed disparity in the quality of postoperative recovery at the 72-hour mark between the treatment above and the placebo. They used other analgesic regimens during the perioperative period, which may have masked the effects of lidocaine or ketamine and are therefore inconsistent with our conclusions.

The IV infusions of lidocaine and esketamine can significantly improve patients' anxiety and depression, thereby helping them recover after surgery. At present, the mechanism by which lidocaine improves mood is not precise. In studies of the effect of lidocaine on improving mood, improved mood has been attributed to lidocaine analgesia.[4] As an antidepressant drug, esketamine's mechanism of improving mood mainly relates to the following factors: Glutamate neurotransmission through NMDA receptors and α-amino-3-hydroxy-5-

Table 2: NRS scores at each time after the surgery

Time	NRS scores			*P*
	Group C (*n*=40)	Group L (*n*=38)	Group E (*n*=39)	
1 h	3 (2,5)	3 (1,3)	2 (1,3)	0.002
2 h	4 (3,5)	3 (2.75,3)	3 (2,3)	0.003
6 h	4 (3,5)	3 (2,4)	3 (2,4)	<0.001
12 h	3 (2,4)	2.5 (2,3)	2 (1,3)	0.002
24 h	2 (1,3)	1.5 (1,3)	2 (1,3)	0.093
48 h	1.5 (1,2)	1 (1,2)	2 (1,3)	0.777

Data are presented as the median (interquartiles Q1, Q3). NRS=Numerical Rating Scale, *n*=Number of patients, Group C= Group Placebo, Group L= Group Lidocaine, Group E=Group Esketamine

Table 3: Perioperative parameters

	Group C (*n*=40)	Group L (*n*=38)	Group E (*n*=39)	*P*
Propofol (mg)	709.75 (274.58) (621.94,797.56)	640.26 (186.89) (578.83,701.69)	652.05 (264.70) (566.25,737.86)	0.409
Remifentanil (μg)	518.00 (217.20) (448.54,587.46)	380.00 (149.95) (330.71,429.29)	374.36 (165.88) (320.59,428.13)	0.002
PONV (*n*)	12	2	4	0.006

Data are presented as the mean (standard deviation) (95% confidence interval) or number. PONV=postoperative nausea and vomiting, *n*=Number of patients, Group C= Group Placebo, Group L= Group Lidocaine, Group E=Group Esketamine

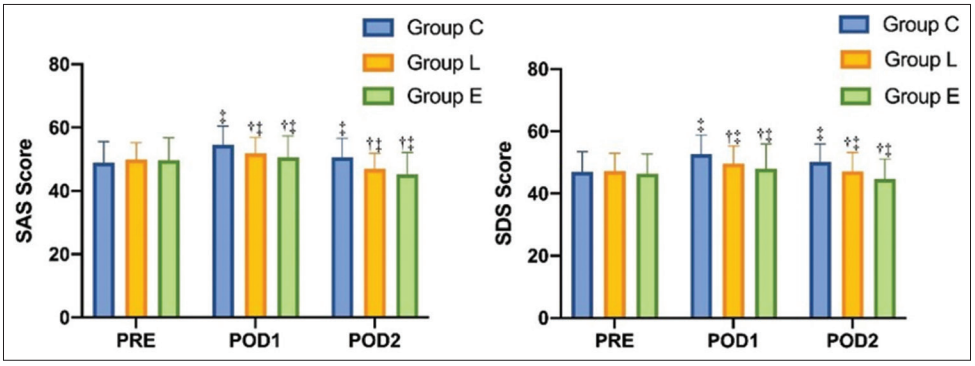

Figure 3: SAS and SDS scores. †: *P* comparing group C versus group L and group E. ‡: *P* comparing PRE versus POD1 and POD2. SAS = Self-Rating Anxiety Scale; SDS = Self-Rating Depression Scale; PRE = preoperative day; POD1 = postoperative day 1; POD2 = postoperative day, Group C= Group Placebo; Group L= Group Lidocaine; Group E=Group Esketamine

methyl-4-isoxazolepropionic acid receptors, synaptic structural modifications mediated by brain-derived neurotrophic factor signalling, interactions with opioid receptors and the augmentation of serotonin, norepinephrine and dopamine signalling pathways.[19]

In our study, in the pain subscale of the QoR-40, both Group L and Group E scored significantly higher than Group C. Moreover, IV infusions of lidocaine and esketamine enabled patients' NRS scores to be significantly lowered within 12 hours postoperatively, which indicates that both drugs have a good analgesic effect. Similarly, we also found that patients with IV infusions of lidocaine and esketamine consumed significantly less remifentanil intraoperatively than the control group. Overall, the findings of this study indicate that lidocaine and esketamine reduce postoperative pain scores and opioid consumption. Numerous studies have demonstrated the efficacy of lidocaine and esketamine in mitigating postoperative pain scores and diminishing opioid usage, which is consistent with the conclusions of this study.[6,20] The analgesic effects of lidocaine are attributed to multiple mechanisms, including sodium channel blockades, the inhibition of G protein coupling and NMDA receptors.[21] The primary site of action of esketamine is also the NMDA receptor, but other mechanisms, such as opioid receptors, have also been found.[22]

Additionally, this study showed that the incidence of PONV with lidocaine and esketamine was lower than that in the control group and significantly lower in the lidocaine group. Patients who undergo thyroid surgery have a higher occurrence of PONV.[23] PONV can not only make patients dissatisfied but may also lead to more severe consequences, such as poor surgical outcomes.[24] A systematic retrospective study found that esketamine did not result in a higher occurrence of PONV.[25] Lidocaine has also been found to enhance the management of PONV in patients undergoing thyroid surgery.[26] In the present investigation, the lower incidence of PONV in both the lidocaine and esketamine groups may be related to reduced intraoperative opioid use or reduced pain stimulation and gastrointestinal recovery.

According to the literature,[27,28] our study doses were within the safe range, and we did not find severe haemodynamic fluctuations or adverse effects.

However, we still have some shortcomings. First, our evaluation of postoperative pain was only based on NRS scores, and we should further measure NRS scores at rest and while moving. Additionally, we did not test the experimental drug's serum concentration, so we could not accurately determine the patients' toxicity. The establishment of an appropriate protocol for the perioperative administration of IV lidocaine and esketamine as an analgesic adjuvant remains uncertain.

CONCLUSION

Perioperative IV lidocaine and esketamine improved the quality of postoperative recovery and the emotional state of patients who underwent thyroidectomy, and both drugs also reduced postoperative pain.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest

There are no conflicts of interest.

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