

The effect of esketamine on postoperative anxiety and depression in patients with thyroid cancer

A randomized, double-blind, placebo-controlled, parallel-group trial

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Abstract

Background: This study aimed to investigate the effects of a single intravenous injection of esketamine during general anesthesia on postoperative anxiety and depression in patients with thyroid cancer.

Methods: In this randomized, double-blind, placebo-controlled, parallel-group trial, eighty female patients with thyroid cancer were scheduled to undergo surgery under general anesthesia. The patients were randomly divided into an esketamine group (group E) and a control group (group C), with 40 patients in each group. During the induction period of general anesthesia, group E received an intravenous injection of esketamine (0.5 mg/kg), while group C received an intravenous injection of 0.9% sodium chloride. The Zung Self-Rating Anxiety Scale and Zung Self-Rating Depression Scale scores for all patients were evaluated on the day before surgery and the second day after surgery. At the same time point, venous blood was collected twice from all patients, and the levels of serum factors, such as mature brain-derived neurotrophic factor (mBDNF), 5-hydroxytryptamine (5-HT), insulin-like growth factor-1 (IGF-1), and irisin, were measured. Intraoperative vital signs and general situation were recorded for all patients.

Results: Compared with group C, group E showed a significant decrease in postoperative anxiety and depression scores ($P < .05$). Compared with group C, group E showed a significant increase in postoperative mBDNF and 5-HT levels ($P < .05$), and the postoperative IGF-1 level in group E was significantly lower ($P < .05$). Compared with group C, the proportion of patients in group E who received pump infusion of vasopressors during surgery was significantly reduced ($P < .05$).

Conclusion: Intravenous injection of 0.5 mg/kg esketamine during the induction period of general anesthesia can prevent and alleviate postoperative anxiety and depression in patients with thyroid cancer, and its mechanism may be related to increased mBDNF and 5-HT levels and reduced IGF-1 levels. At the same time, hemodynamics during anesthesia surgery are more stable.

Abbreviations: 5-HT = 5-hydroxytryptamine, IGF-1 = insulin-like growth factor-1, mBDNF = mature brain-derived neurotrophic factor, SAS = Zung Self Rating Anxiety Scale, SDS = Zung Self Rating Depression Scale.

Keywords: affective symptoms, esketamine, postoperative complication, thyroid cancer

1. Introduction

As one of the most common tumors in humans, thyroid cancer ranks first in the incidence of endocrine system malignancies.^[1,2] Surgical resection of the tumor is currently the primary treatment for patients with thyroid cancer. However, due to disease-related fear, surgical trauma, and inherent introverted personality traits, the majority of thyroid cancer patients frequently experience perioperative psychological issues such as insomnia, fatigue, anorexia, anxiety, and palpitations, which may progress to depression.^[3] If patients develop depression, it can suppress immune function, accelerate tumor angiogenesis

and metastasis, promote tumor progression, and ultimately increase mortality rates.^[4] These complications not only impair postoperative recovery but also reduce patients' quality of life.^[5] Therefore, preventing and mitigating the development of depression in cancer patients has become critically important. Current clinical interventions for depression primarily rely on pharmacotherapy and psychotherapy. However, pharmacotherapy is characterized by slow onset, low remission rates, and significant side effects such as dependency development. Psychotherapy is often limited by multiple confounding factors that complicate its implementation.^[6] Most notably, preventive

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The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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measures for depression remain scarce beyond psychotherapy-based interventions.^[7] Research works have shown that esketamine, a sedative and analgesic drug widely used in clinical anesthesia,^[8] has achieved significant therapeutic effects in the treatment of depression.^[9,10] However, further research is needed to determine whether esketamine could prevent postoperative anxiety in patients with thyroid cancer, thereby avoiding the further development of depression.

Therefore, in this study, patients undergoing thyroidectomy were treated with a single intravenous injection of esketamine during general anesthesia induction. The effects of esketamine on the postoperative short-term psychological state in thyroid cancer patients were observed to determine whether a single intravenous administration of esketamine during general anesthesia induction could prevent and alleviate postoperative anxiety and depression in thyroid cancer patients.

2. Materials and methods

2.1. Ethics and trial registration

This randomized controlled clinical trial was prospectively registered at the China Clinical Trial Center (registration number: ChiCTR2200063302) and approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (approval number: KY2022235). Informed consent forms were signed by patients and their families. The patients selected for this study underwent thyroid cancer surgery at the Affiliated Hospital of Southwest Medical University between February 2023 and June 2023.

2.2. Sample size

This study has a completely randomized design; therefore, when comparing the means of two samples, the sample size estimation formula is as follows: $n1 = n2 = 2 * [(t\alpha + t\beta) \sigma / \delta]^2$, where σ is the required discrimination degree, δ is the overall standard deviation, and t_α and t_β can be queried from the t-bound table (α is set to 0.05, β is set to 0.10, and the degree of freedom u is infinite).

For the Zung Self-Rating Depression Scale (SDS), the depression level was changed every 8 points ($\sigma=8$). According to relevant literature, the standard deviation of the SDS score for patients with thyroid cancer is 5.3 ($\delta = 5.3$).^[11] To prevent the patients from withdrawing from the study, the sample size for each group was 40.

2.3. Participants

The inclusion criteria were as follows: preoperative pathological examination of thyroid mass diagnosed with thyroid cancer, American Society of Anesthesiologists classification of I-II, with no severe abnormalities in preoperative cardiopulmonary function and no serious complications in other systems, female, aged 18 to 70 years old.

The exclusion criteria were as follows: pregnant and lactating women, those with distant metastasis of thyroid cancer, other malignant tumors, immune deficiencies, poor control of hypertension and diabetes, mental disorders, long-term psychological stress, and antidepressant and antipsychotic medication users.

Patients were assessed using the inclusion and exclusion criteria. Patients could withdraw from this study at any time without reason. Enrolled patients were randomly assigned to the esketamine (group E) and saline (group C) groups using a random number table method, with 40 patients in each group.

2.4. General anesthesia and interventions

After rapid induction with sufentanil, cisatracurium, and propofol, the airway was controlled by using a tracheal tube.

During the operation, volume mode was used to control ventilation, and anesthesia was maintained through inhalation of sevoflurane, intravenous infusion of remifentanyl, and intermittent intravenous infusion of cisatracurium until the end of the surgery.

Group E: In addition to conventional induction, an intravenous injection of 0.5 mg/kg of esketamine (prepared with 0.9% sodium chloride at a concentration of 5 mg/mL) was administered during the induction period of general anesthesia. The dosage of esketamine used was recommended by the drug manufacturer (Nhwa, Xu Zhou, Jiang Su, China) for anesthesia induction. Group C: In addition to conventional induction, 0.9% sodium chloride 0.1 mL/kg was administered intravenously during the induction period of general anesthesia.

The above procedures (including outcome evaluation) were performed by the same anesthesiologist, who was blinded to the use of ketamine or saline. The person who enrolled patients generated the random allocation sequence, prepared the medication, and did not participate in anesthesia.

2.5. Research indicators

The main indicators of this study were as follows: patients were assessed using the Zung Self-Rating Anxiety Scale (SAS) and SDS on the days before and after surgery, respectively. On the day before surgery and the second day after surgery, 3 mL of venous blood was collected from both groups of surgical patients, and the serum was separated by centrifugation. Enzyme-linked immunosorbent assay kits (Andy Gene Co., Ltd., Richardson, TX) were used to measure the serum levels of mature brain-derived neurotrophic factor (mBDNF), 5-hydroxytryptamine (5-HT), insulin-like growth factor-1 (IGF-1), and irisin levels in the serum.

The secondary indicators were mean arterial pressure (MAP) and heart rate (HR) before and after anesthesia, operation time, postoperative recovery time, visual analog scale score after recovery, and anesthesia-related complications.

2.6. Statistics

Data analysis was performed using IBM SPSS Statistics version 26.0. Quantitative data were presented as the mean \pm standard deviation, and t -tests were performed to compare the 2 sets of data. Multiple sets of data were compared using one-way analysis of variance, with $P < .05$ indicating statistically significant differences. If the data in the study were count data, they were presented as a number of cases (%). The chi-square test was used for data comparison, and statistical significance was set at $P < .05$.

3. Results

3.1. General situation

In total, 101 patients were assessed. Eighty enrolled patients were randomly assigned to groups E and C by using a random number table method, with 40 patients in each group. Finally, only 1 patient in group C withdrew from the study because of a refusal to continue, as shown in Figure 1.

There were no statistically significant differences in age, BMI, American Society of Anesthesiologists grade, surgery time, recovery time, or visual analog scale score between the 2 groups ($P > .05$), as shown in Table 1.

3.2. Self-Rating Anxiety Scale and Self-Rating Depression Scale

There were no statistically significant differences in the preoperative SAS and SDS scores between the 2 groups ($P > .05$), as

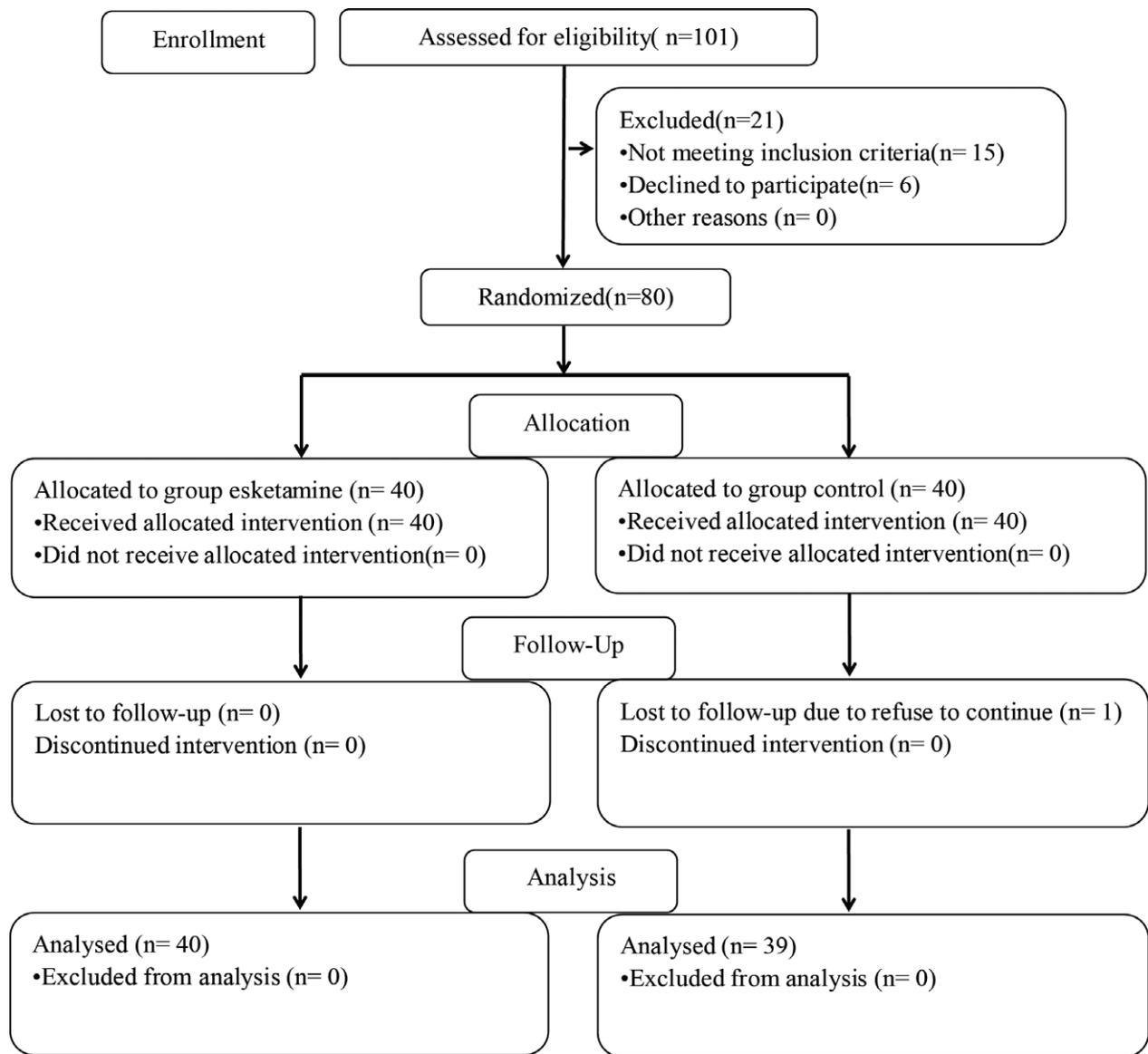


Figure 1. Flow diagram. A total of 101 patients with thyroid cancer were evaluated in this study, of which 15 were excluded because they did not meet the inclusion criteria, and 6 refused to participate in the study. Eighty patients were randomly divided into 2 groups, with 40 patients in each group. Finally, in the control group, 1 patient refused to continue the study for personal reasons.

Table 1
The general conditions of patients in the esketamine and control group.

Variables	Group E (n = 40)	Group C (n = 39)	t/χ ² value	P
Age (years)	40.2 ± 10.5	39.1 ± 10.7	0.449	.66
BMI (kg/m ²)	23.0 ± 1.8	22.9 ± 2.4	0.101	.92
ASA I/II	23/17	21/18	0.107	.74
Operation time (min)	170.8 ± 32.3	169.7 ± 35.7	0.132	.90
Recovery time (min)	14.4 ± 2.9	14.5 ± 2.8	-0.137	.89
VAS score after recovery	0.98 ± 0.73	0.97 ± 0.87	0.04	.99

Values are presented as mean ± SD or the number of cases.
ASA = American Society of Anesthesiologists, BMI = body mass index, VAS = visual analogue scale.

shown in Figures 2 and 3. Compared with group C, the postoperative SAS and SDS scores of group E patients were significantly reduced ($P < .05$), as shown in Figures 2 and 3.

3.3. Anxiety- and depression-related protein factors

There were no statistically significant differences in the levels of mBDNF, 5-HT, IGF-1, or irisin between the 2 groups before surgery ($P > .05$) (Figs. 4–7). Compared with group C, the postoperative mBDNF and 5-HT levels in group E increased significantly ($P < .05$), and the postoperative IGF-1 level in group E was significantly lower ($P < .05$), as shown in Figures 4–6. There was no statistically significant difference in the postoperative irisin levels between the 2 groups of patients ($P > .05$), as shown in Figure 7.

3.4. Vital signs

There was no statistically significant difference in MAP between the 2 groups before anesthesia and after intubation ($P > .05$). However, before intubation and after entering the postanesthesia care unit (PACU), the MAP in group E was higher than that in group C ($P < .05$), as shown in Table 2. There was no statistically significant difference in HR between the 2 groups before anesthesia, after intubation, or after admission to the PACU

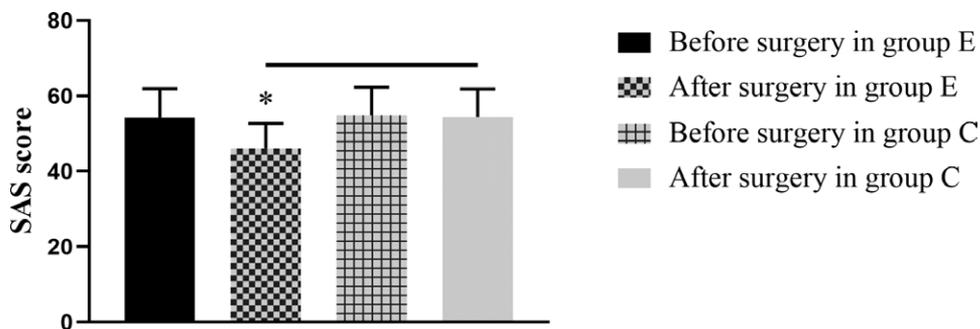


Figure 2. SAS score. Values are presented as mean \pm standard deviation. * $P < .05$ versus after surgery in group C. SAS = Zung Self Rating Anxiety Scale.

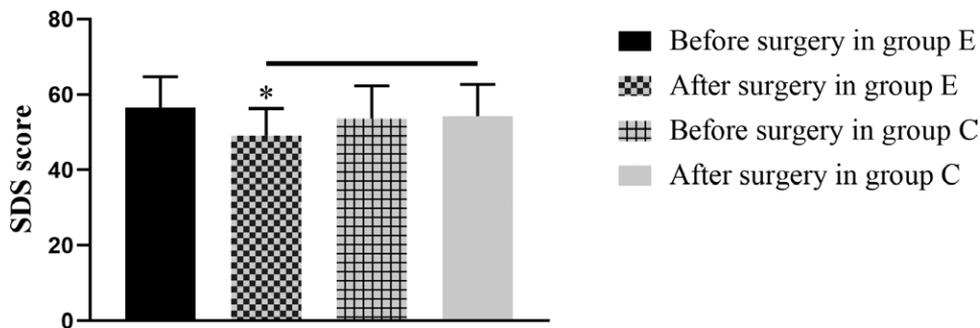


Figure 3. SDS score. Values are presented as mean \pm standard deviation. * $P < .05$ versus after surgery in group C. SDS = Zung Self Rating Depression Scale.

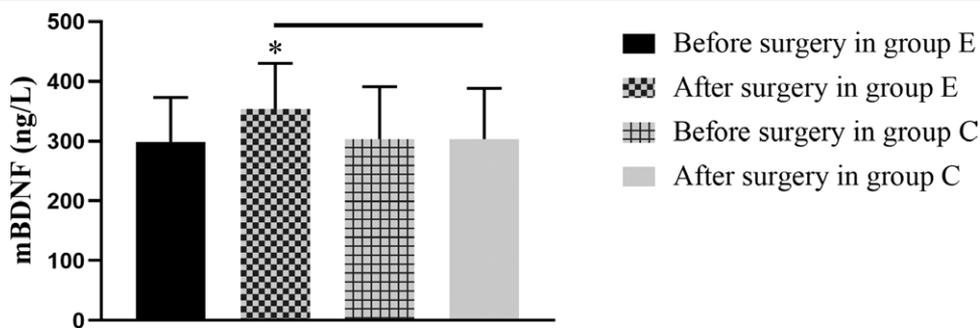


Figure 4. The level of mBDNF in serum. Values are presented as mean \pm standard deviation. * $P < .05$ versus after surgery in group C. mBDNF = mature brain-derived neurotrophic factor.

($P > .05$). However, before intubation, the HR in group E was higher than that in group C ($P < .05$) (Table 2). Compared with group C, the proportion in group E who received an intraoperative infusion of vasopressors was significantly reduced ($P < .05$), as shown in Table 2.

3.5. Postoperative adverse reactions

There were no statistically significant differences in postoperative adverse reactions between the 2 groups, including restlessness, nausea and vomiting, bradycardia, tachycardia, and vertigo ($P > .05$), as shown in Table 3.

4. Discussion

Thyroid cancer, the most common malignant tumor of the endocrine system, often leads to psychological problems such as anxiety and depression due to fear of the disease, surgical trauma, and adverse reactions to medication. The main symptoms include insomnia, decreased appetite, anxiety, and palpitations,

which can lead to a decline in the quality of life and affect the treatment effectiveness and recovery of patients.^[12,13]

Currently, psychological therapy is the main treatment for anxiety and depression. However, owing to many interfering factors, psychological therapy is limited to a certain extent. However, drug therapy is often used to treat patients diagnosed with depression, and further research is needed to prevent the occurrence of anxiety and depression.^[7,14]

4.1. Esketamine alleviates postoperative anxiety and depression

Currently, surgical resection is the main treatment for thyroid cancer; therefore, patients inevitably require general anesthesia. Numerous studies have shown that esketamine, an anesthetic, has a good therapeutic effect on patients with depression.^[9,10] So, does esketamine have a preventive effect on anxiety and depression that may occur in patients with thyroid cancer after surgery? In this study, a single intravenous injection of 0.5 mg/kg esketamine was administered during the anesthesia induction period to observe its effect on

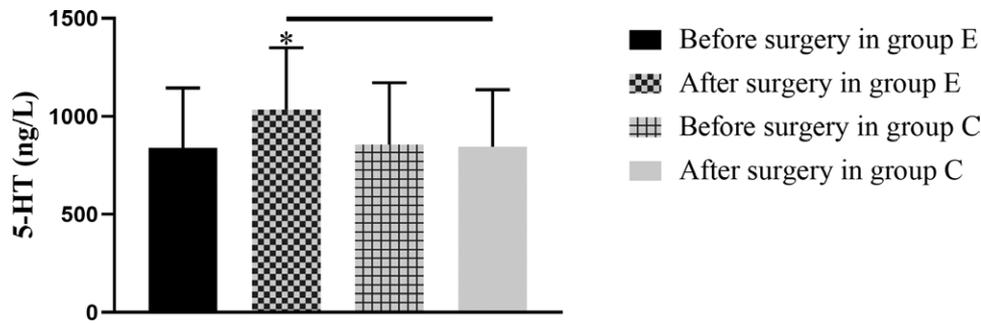


Figure 5. The level of 5-HT in serum. Values are presented as mean ± standard deviation. *P < .05 versus after surgery in group C. 5-HT = 5-hydroxytryptamine.

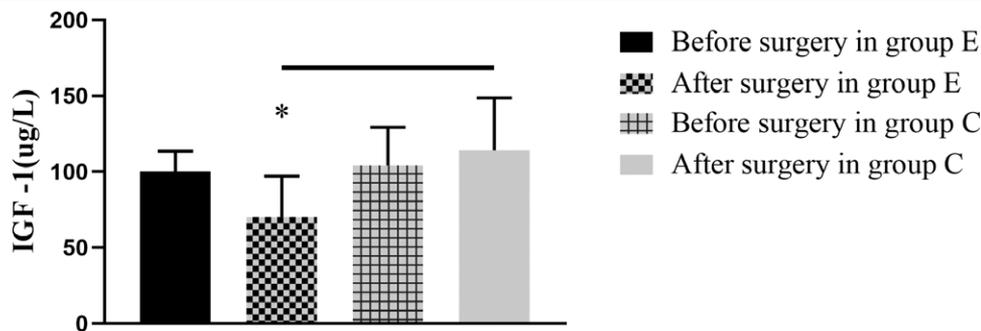


Figure 6. The level of IGF-1 in serum. Values are presented as mean ± standard deviation. *P < .05 versus after surgery in group C. IGF-1 = insulin-like growth factor-1.

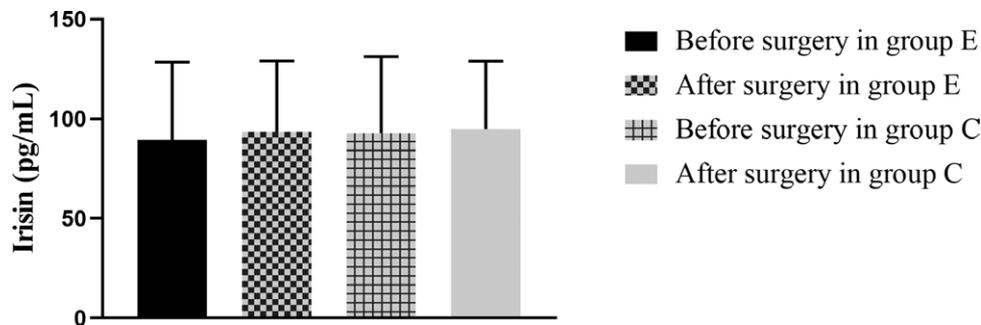


Figure 7. The level of irisin in serum. Values are presented as mean ± standard deviation.

Table 2
The vital signs of patients in the esketamine and control group.

Variables		Group E (n = 40)	Group C (n = 39)	t/χ ² value	P
MAP (mm Hg)	Before surgery	92.1 ± 9.6	88.8 ± 9.1	1.604	.11
	Before intubation	79.4 ± 9.5*	74.4 ± 8.5	2.492	.02
	After intubation	81 ± 9.6	77.6 ± 10.2	1.529	.13
HR (time/min)	Entering PACU	91.7 ± 10*	86.7 ± 8.7	2.391	.02
	Before surgery	79 ± 9.4	76.7 ± 12.3	0.921	.36
	Before intubation	70.7 ± 10.8*	64.8 ± 10.1	2.458	.02
Continuous pumping of vasopressors during surgery [cases (%)]	After intubation	73.2 ± 12.3	68.7 ± 11.6	1.642	.11
	Entering PACU	77.9 ± 12.2	74.1 ± 10.5	1.479	.14
		3(7.5)*	11(28.2)	5.806	.02

Values are presented as mean ± SD or the number of cases (%).
HR = heart rate, MAP = mean arterial pressure, PACU = postanesthesia care unit.
*Compared with Group C, P < .05.

the short-term psychological status of thyroid cancer patients after surgery.

The research results indicate that intravenous administration of 0.5 mg/kg esketamine during the induction period of general anesthesia significantly reduces postoperative anxiety and depression scores in thyroid cancer patients. A single intravenous injection of esketamine during the induction period of general anesthesia can reduce the occurrence of postoperative anxiety and depression, which provides the possibility for esketamine to prevent postoperative depression in thyroid cancer patients during the induction period of general anesthesia. The research results also indicate that intravenous administration of 0.5 mg/kg esketamine during the induction period of general anesthesia can significantly reduce the fluctuation of MAP and HR before intubation, significantly reduce the proportion of intraoperative vasopressors used, and reduce the occurrence of intraoperative hypotension. At the same time, it does not increase postoperative adverse reactions such as restlessness, nausea and vomiting, tachycardia, and dizziness. This indicates that the use of esketamine during the induction

Table 3**The postoperative adverse reactions in the esketamine and control group.**

Variables	Group E (n = 40)	Group C (n = 39)	χ^2 value	P
Restlessness	1 (2.5)	1 (2.6)	0.000	.99
Nausea and vomiting	4 (10)	3 (7.7)	0.000	1
Bradycardia	3 (7.5)	6 (15.4)	0.560	.45
Tachycardia	1 (2.5)	1 (2.6)	0.000	.99
Vertigo	1 (2.5)	1 (2.6)	0.000	.99

Values are presented as the number of cases (%).

period of general anesthesia can alleviate the decrease in blood pressure and HR in patients, maintain peripheral vascular tone, reduce the use of vasopressors, and stabilize intraoperative hemodynamics.

Therefore, a single intravenous administration of esketamine during the induction period of general anesthesia can achieve stable hemodynamic effects and prevent anxiety and depression without increasing postoperative adverse reactions.

4.2. The prevention of postoperative anxiety and depression by esketamine is closely related to multiple protein factors

BDNF, an important neurotrophic factor in the brain, can protect neurons through various pathways, such as promoting the occurrence of hippocampal neurons and clearing excitatory amino acids, thereby exerting its antidepressant effect. mBDNF is a mature form of BDNF.^[15-17] In this study, patients with thyroid cancer showed an increase in serum mBDNF levels after using esketamine, indicating that the use of esketamine during general anesthesia induction may have a preventive effect on reducing postoperative anxiety and depression in patients with thyroid cancer by increasing mBDNF.

5-HT, as an inhibitory neurotransmitter, has a significant impact on emotional control in the human body, and its 5-HT content is significantly reduced in patients with depression.^[18] A large number of antidepressant drugs can also exert antidepressant effects by increasing 5-HT levels in the body.^[19,20] In this study, thyroid cancer patients showed a significant increase in serum 5-HT levels after using esketamine, indicating that the use of esketamine during the induction period of general anesthesia may also have a preventive effect on anxiety and depression by increasing 5-HT levels in the body.

IGF-1 is a growth-promoting peptide-like substance, and studies have found that its levels increase in patients with depression. The level of IGF-1 is positively correlated with the severity of depression in patients.^[21,22] Meanwhile, IGF-1 is also closely associated with the prognosis of thyroid cancer. Higher levels of IGF-1 are correlated with poorer patient prognosis and can serve as auxiliary indicators for evaluating prognosis.^[23] In this study, thyroid cancer patients showed a significant decrease in serum IGF-1 levels after using esketamine, indicating that its preventive effect on anxiety and depression may be related to reducing IGF-1 levels in the body. Furthermore, esketamine may improve the prognosis of thyroid cancer patients by reducing IGF-1 levels.

Irisin has often been studied as a treatment for fat metabolism and obesity^[24] and current research has shown that irisin is closely related to depression.^[25,26] In this study, thyroid cancer patients showed no significant changes in serum irisin levels after using esketamine. The mechanism of action of esketamine in preventing and reducing anxiety and depression in patients with thyroid cancer may not significantly correlate with irisin levels.

4.3. Limitations

This study has some limitations, such as the single postoperative detection time of depression-related protein factors. To obtain more accurate protein factor fluctuations, longer monitoring periods may be required, which require further research.

5. Conclusions

The anesthesia induction dose of 0.5 mg/kg esketamine can alleviate postoperative anxiety and depression in thyroid cancer patients, and its mechanism may be related to increasing mBDNF and 5-HT levels and reducing IGF-1 levels. Simultaneously, esketamine stabilizes the anesthesia surgery process in terms of hemodynamics without causing significant adverse reactions. Therefore, esketamine can exert sedative and analgesic effects during general anesthesia as well as prevent postoperative anxiety and depression in patients with thyroid cancer. Meanwhile, reduced IGF-1 levels may also indicate a better prognosis in thyroid cancer patients.^[23] This investigation thereby provides clinical evidence supporting esketamine's prophylactic efficacy against postoperative anxiety and depressive symptoms, offering a novel pharmacological intervention strategy for preventing depression in oncological populations.

Author contributions

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Writing – original draft: Xiaobo Bi.

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Funding acquisition: Junchao Dai, Jin Li.

Supervision: Junchao Dai, Jin Li.

Conceptualization: Jin Li.

References

- [1] Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic review of trends in the incidence rates of thyroid cancer. *Thyroid*. 2016;26:1541–52.
- [2] Pizzato M, Li M, Vignat J, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. *Lancet Diabetes Endocrinol*. 2022;10:264–72.
- [3] Haymart P, Levin NJ, Haymart MR. The psychosocial impact of thyroid cancer. *Curr Opin Endocrinol Diabetes Obes*. 2023;30:252–8.
- [4] Dionisi-Vici M, Fantoni M, Botto R, et al. Distress, anxiety, depression and unmet needs in thyroid cancer survivors: a longitudinal study. *Endocrine*. 2021;74:603–10.
- [5] Miccoli P, Minuto MN, Paggini R, et al. The impact of thyroidectomy on psychiatric symptoms and quality of life. *J Endocrinol Invest*. 2007;30:853–9.
- [6] Schramm E, Elsaesser M, Müller J, et al. Efficacy of psychotherapy versus pharmacotherapy, or their combination, in chronic depression: study protocol for a systematic review and network meta-analysis using aggregated and individual patient data. *BMJ Open*. 2025;15:e089356.
- [7] Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. *BMJ*. 2018;361:k1415.
- [8] Liu J, Wang T, Song J, Cao L. Effect of esketamine on postoperative analgesia and postoperative delirium in elderly patients undergoing gastrointestinal surgery. *BMC Anesthesiol*. 2024;24:46.
- [9] Swainson J, Thomas RK, Archer S, et al. Esketamine for treatment resistant depression. *Expert Rev Neurother*. 2019;19:899–911.
- [10] McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression:

- an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;178:383–99.
- [11] Mingxu HU, Wei X, Xuelian Z. Study on method of dispersing stagnation of liver-qi on depression and related cytokines of postoperative patients with thyroid cancer. *Chin J Tradit Med Sci Technol*. 2022;29:178–81.
- [12] Helvacı BC, Yalçın MM, Yalcin SNG, Arslan E, Altinova AE, Törüner FB. Differentiated thyroid cancer: effect on quality of life, depression, and anxiety. *Hormones (Athens)*. 2023;22:367–74.
- [13] Chen L, Ren N, Yang Q, Tian X. Short-Term postoperative depression and anxiety in patients with differentiated thyroid carcinoma: assessment of potential oncologic-psycho relevance. *Int J Endocrinol*. 2024;2024:1717119.
- [14] Ribeiro A, Ribeiro JP, von Doellinger O. Depression and psychodynamic psychotherapy. *Braz J Psychiatry*. 2018;40:105–9.
- [15] Cavaleri D, Moretti F, Bartocetti A, et al. The role of BDNF in major depressive disorder, related clinical features, and antidepressant treatment: insight from meta-analyses. *Neurosci Biobehav Rev*. 2023;149:105159.
- [16] Gong G, Ganesan K, Wang Y, et al. Ononin ameliorates depression-like behaviors by regulating BDNF-TrkB-CREB signaling in vitro and in vivo. *J Ethnopharmacol*. 2024;320:117375.
- [17] Tekşen Y, Gündüz MK, Berikten D, Özatik FY, Aydın HE. Peganum harmala L. seed extract attenuates anxiety and depression in rats by reducing neuroinflammation and restoring the BDNF/TrkB signaling pathway and monoamines after exposure to chronic unpredictable mild stress. *Metab Brain Dis*. 2024;39:1523–41.
- [18] Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in depression. *Mol Brain*. 2017;10:28.
- [19] Huang D, Jiang Y, Wu M, et al. Association Between FABP7-5-HT pattern and anxiety or depression in patients with psoriasis: a cross-sectional study. *Stress Health*. 2024;40:e3498.
- [20] Li B, Ran K, Jing Z, Han W, Peng X. Glioma induces atypical depression-like behaviors in mice through the 5-HT and glutamatergic synapse pathways. *Biochem Biophys Res Commun*. 2024;704:149706.
- [21] Mosiołek A, Mosiołek J, Jakima S, Pięta A, Szulc A. Effects of antidepressant treatment on neurotrophic factors (BDNF and IGF-1) in patients with major depressive disorder (MDD). *J Clin Med*. 2021;10:3377.
- [22] Yang C, Sui G, Li D, et al. Exogenous IGF-1 alleviates depression-like behavior and hippocampal mitochondrial dysfunction in high-fat diet mice. *Physiol Behav*. 2021;229:113236.
- [23] Lawnicka H, Motylewska E, Borkowska M, et al. Elevated serum concentrations of IGF-1 and IGF-1R in patients with thyroid cancers. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2020;164:77–83.
- [24] Pinho-Jr J, Camacho FA, Cavararo C, et al. Irisin and cardiometabolic disorders in obesity: a systematic review. *Int J Inflamm*. 2023;2023:5810157.
- [25] Liu X, Hu Q, Xu T, et al. Fndc5/irisin deficiency leads to dysbiosis of gut microbiota contributing to the depressive-like behaviors in mice. *Brain Res*. 2023;1819:148537.
- [26] Pignataro P, Dicarlo M, Suriano C, et al. Once-daily subcutaneous irisin administration mitigates depression- and anxiety-like behavior in young mice. *Int J Mol Sci*. 2023;24:6715.