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Original Article

Transcutaneous auricular vagus nerve stimulation improves postoperative recovery quality in patients undergoing thyroid surgery by inhibiting the inflammatory response: a randomized controlled trial

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Abstract: Objective: This randomized controlled trial evaluated whether perioperative transcutaneous auricular vagus nerve stimulation (taVNS) improves recovery quality after thyroid surgery and explored a mediating role of the inflammatory response. Methods: A total of 120 patients undergoing thyroid surgery were randomly allocated to active taVNS (cavum conchae) or sham stimulation (earlobe). The primary outcome was the Quality of Recovery-40 (QoR-40) score at 24 h; secondary outcomes included pain scores, postoperative nausea and vomiting (PONV), hospital stay, and interleukin-6 (IL-6)/tumor necrosis factor-α (TNF-α) levels. Linear mixed models with false-discovery-rate correction were used. Results: The taVNS group showed a higher adjusted QoR-40 score (β=7.41, P=0.0068), lower pain scores, reduced PONV incidence, and shorter hospital stay (all P<0.05). IL-6 and TNF-α mediated 27.7% and 26.1% of the recovery benefit, respectively (both P<0.001). Preoperative QoR-40 score independently predicted taVNS response (OR=0.30, P=0.008). No serious adverse events occurred. Conclusion: Perioperative taVNS safely improves postoperative recovery, partly through inhibiting IL-6/TNF-α, with consistent benefits across patient subgroups. Preoperative QoR-40 may help identify optimal candidates, aligning with enhanced recovery after surgery (ERAS) principles.

Keywords: Transcutaneous auricular vagus nerve stimulation, thyroid surgery, postoperative recovery, inflammation, randomized controlled trial

Introduction

Thyroidectomy is a core surgical procedure for the treatment of benign thyroid tumors, thyroid cancer, and other diseases, with over one million surgeries performed annually worldwide [1]. Although surgical techniques such as endoscopic thyroidectomy have become minimally invasive, postoperative pain, swallowing discomfort, emotional fluctuations, and systemic inflammatory responses still significantly affect patients' recovery quality. Some patients may experience elevated postoperative inflammatory factors, which increase the risk of complications such as cervical edema and delayed incision healing [2]. Postoperative recovery quality is not only related to patients' short-term living conditions but also closely associated with long-term mental health and the efficiency of returning to society. Therefore, exploring safe and non-invasive postoperative interventions to reduce inflammatory responses and improve recovery quality has become an important direction in clinical research of thyroid surgery [3].

The inflammatory response is a natural defense mechanism of the body against surgical trauma, but excessive or persistent inflammatory activation disrupts homeostasis of the local microenvironment, exacerbates tissue damage, and delays the repair process [4, 5]. In recent years, the discovery of the cholinergic anti-inflammatory pathway (CAP) has provided a new target for postoperative inflammatory regulation [6]. The vagus nerve is the core component of the CAP; it can inhibit the activation of inflammatory cells such as macrophages and

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neutrophils by releasing acetylcholine, reducing the release of pro-inflammatory factors, and thereby precisely regulating the intensity of inflammatory responses [7]. Traditional vagus nerve stimulation (VNS) requires surgical implantation of electrodes, which is invasive and costly, limiting its application for short-term postoperative interventions. As a non-invasive improved technique, transcutaneous auricular VNS (taVNS) can activate the CAP pathway by stimulating the auricular branch of the vagus nerve in the cavum conchae. taVNS has the advantages of convenient operation, high safety, and no adverse reactions, and has shown good anti-inflammatory and neuroregulatory effects in stroke, chronic pain, postoperative anxiety, and other fields [8].

Although the anti-inflammatory potential of taVNS has been demonstrated, its application in patients undergoing thyroid surgery remains underexplored [9]. Therefore, this study was designed as a single-center, randomized controlled trial. Patients undergoing thyroid surgery were enrolled to investigate the effect of perioperative taVNS intervention on postoperative inflammatory factor (IL-6, TNF-α) levels and recovery quality (QoR-40 scale score), and to verify the core hypothesis that "taVNS improves recovery quality by activating the cholinergic anti-inflammatory pathway to inhibit postoperative inflammation". The results of this study may provide a non-invasive and efficient new postoperative intervention scheme for patients undergoing thyroid surgery, and also provide medical evidence for the application of taVNS in surgical postoperative inflammatory regulation.

Materials and methods

Patients

This was a prospective, single-center, randomized, double-blind, sham-controlled trial. Patients with thyroid diseases who underwent surgery in the hospital from December 2022 to December 2024 were randomly divided into a study group (taVNS group, n=60) and a control group (sham stimulation group, n=60). This study used the total score of the Quality of Recovery Scale 40 (QoR-40) 24 hours after surgery as the main outcome measure, and employed a two independent sample t-test for sample size estimation. Referring to previous studies and pilot results related to postoperative recovery quality of thyroid surgery; the effect size, d, was set to 0.52. A two-sided α level of 0.05 and 90% power (1-β) were used. According to G * Power 3.1 software calculation, 52 patients needed to be included in each group. Considering the possibility of a 15% dropout rate in clinical studies, each group was ultimately expanded to 60 cases, with a total sample size of 120 cases, to ensure that the research results had sufficient statistical testing power to detect the predetermined inter group differences. There were no significant differences in general data between the two groups (see **Table 1**). This was a single-center, randomized controlled, parallel-group clinical trial. The study protocol followed the CONSORT statement guidelines. The experiment was approved by the ethics committee of Huai'an First Hospital Affiliated to Nanjing Medical University (KY-2022-146-01), and written informed consent was obtained from all participants.

Inclusion criteria: (1) Diagnosed with benign thyroid tumors or differentiated thyroid cancer, scheduled for partial thyroidectomy or total thyroidectomy [10]; (2) No severe liver or kidney dysfunction, coagulation disorders before surgery, and clear consciousness, able to cooperate with scale scoring and intervention operations; (3) No use of anti-inflammatory drugs, immunomodulators, or nerve stimulation-related treatments before surgery.

Exclusion criteria: (1) Previous ear surgery history, hearing impairment, or skin damage/infection in the cavum conchae; (2) Complicated by autoimmune diseases, chronic inflammatory diseases, or acute infections; (3) Pregnant or lactating women; (4) Allergic to stimulation equipment materials.

Treatment methods

This study employed a parallel-group, double-blind, sham-controlled design. The intervention equipment, operational procedures, and duration were identical between the taVNS group and the sham stimulation group. The only differences were the stimulation target site and the current intensity to preserve blinding. All interventions were administered by uniformly trained research nurses. Before the intervention, patients were informed that they "may

Table 1. Preoperative general data

Variable	Study Group (n=60)	Control Group (n=60)	t/χ^2	*P* Value
Age (years)	45.2±8.6	43.8±9.2	0.826	0.410
Gender (n, %)			0.135	0.713
Male	28 (46.7)	26 (43.3)		
Female	32 (53.3)	34 (56.7)		
ASA Classification (n, %)			0.578	0.749
Grade I	22 (36.7)	24 (40.0)		
Grade II	30 (50.0)	29 (48.3)		
Grade III	8 (13.3)	7 (11.7)		
Disease Type (n, %)			0.281	0.596
Benign Thyroid Tumor	38 (63.3)	40 (66.7)		
Differentiated Thyroid Carcinoma	22 (36.7)	20 (33.3)		
Surgical Type (n, %)			0.087	0.768
Partial Thyroidectomy	35 (58.3)	36 (60.0)		
Total Thyroidectomy	25 (41.7)	24 (40.0)		
Operation Time (min)	88.5±15.2	90.2±14.8	0.613	0.541

Notes: Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as number (percentage, %). Independent samples t-test was used for continuous variables, and Chi-square (χ^2) test was used for categorical variables. ASA, American Society of Anesthesiologists.

receive either active or simulated stimulation, both of which are generally well-tolerated without major adverse reactions" to minimize the influence of psychological expectations on outcomes.

The transcutaneous auricular vagus nerve stimulator (batch number: 50102203, Changzhou Ruishen'an Medical Equipment Co., Ltd.) consisted of a stimulator main unit and electrode leads. The electrode earbud was structurally similar to a conventional earphone, with an additional electrical contact point on the left earbud. The stimulator main unit was configured to deliver electrical pulse signals through the electrode lead to the left ear.

Both groups received stimulation continuously from 30 minutes before anesthesia induction until 30 minutes after surgery. Patients in the taVNS group received active stimulation. The electrode earbud with the contact point was placed in the left cavum conchae, while a placebo earbud without an active contact was placed in the right ear. The stimulation parameters were set, based on the pre-experimental results, with a frequency of 20 Hz, a pulse width of 500 μs, and a cycle of 60 seconds on and 10 seconds off. The current intensity started from 0.5 mA and increased in steps of 0.2 mA until the patient reported a slight stinging sensation but did not reach the pain threshold (defined as the 'maximum tolerance level'). The final current intensity range used by all patients was 1.0-2.5 mA, with an average of 1.8±0.4 mA. The stimulation intensity was recorded and confirmed by the same study nurse to ensure intra-group consistency.

Patients in the sham stimulation group underwent an identical procedure with the same device. However, the electrode was placed on the left earlobe (a non-vagus nerve innervated area), and the current intensity was set to 0 mA. All other aspects - including device appearance, electrode placement process, and patient instructions - were consistent with the taVNS group to maintain effective blinding. To control individual differences, we conducted current tolerance tests on each patient before the intervention began and recorded their final current values used. There was no significant difference in current intensity between the two groups of patients (taVNS group: 1.8±0.4 mA; sham stimulation group: 0 mA, P>0.05). In addition, all stimuli were performed on the same device and by the same operator to ensure maximum consistency of stimulus parameters.

During initial setup, patients were asked whether they perceived any sensation and about their comfort level. They were uniformly informed that the "target stimulation level had been reached" once the intervention began, regardless of group assignment.

Outcome collection

IL-6 and TNF-α: 5 mL of peripheral venous blood was collected 1 day before surgery and 24 h, 72 h after surgery. Serum was separated by centrifugation and frozen, then detected in 3 replicate wells by ELISA.

QoR-40 score [11]: The scale was completed with the assistance of blinded assessors 1 day before surgery and 24 h after surgery. If ≤3 items were missing, they were filled in according to the average score of the dimension.

NRS score: Under resting state at 24 h after surgery, blinded assessors recorded the pain score self-marked by patients.

Postoperative complications: Within 7 days after surgery, complications were determined by attending physicians through ward rounds, patient complaints, and medical records.

Adverse reactions: During the intervention and 2 hours after the intervention, nurses observed and recorded patients' discomfort and treatment measures.

PONV: At 24 h after surgery, blinded assessors recorded the occurrence and severity of nausea and vomiting in patients.

Ear redness: After each intervention and 7 days after surgery, nurses observed and recorded skin redness, pain, damage, and other inflammatory manifestations at the ear electrode attachment site.

Responder definition: Patients with a delta QoR40 (change in QoR-40 score between 1 day before surgery and after surgery) ≥8 points were defined as responders to taVNS intervention.

First exhaust time was defined as the first postoperative passage of flatus reported by the patient and recorded by nursing staff.

Assessors received unified training, sample processing and testing were standardized, and data were coded and recorded to maintain blinding.

Adverse reactions and safety monitoring: During the intervention and for 2 hours thereafter, trained nurses observed and recorded any local discomfort (e.g., ear redness, pain) and common postoperative adverse events (e.g., PONV). Given that the applied transcutaneous stimulation was of low intensity and non-invasive, and based on extensive previous reports demonstrating the favorable safety profile of taVNS with similar parameters, systematic monitoring for severe cardiovascular events was not mandated in this low-risk surgical population. All serious adverse events (SAEs), however, were required to be reported immediately. Patient tolerance was assessed at the initial setup by inquiring about sensation and comfort; the current was titrated to a level that was perceptible but not painful to ensure tolerability.

Data analysis

Linear mixed-effects models: With time points as repeated measurement factors and group as fixed effect, baseline values, age, gender, ASA classification, and surgical type were included as covariates to analyze the intervention effect of taVNS on each outcome indicator.

FDR correction: False discovery rate (FDR) correction was used for multiple comparisons of outcome indicators to control Type I error.

Prespecified subgroup analysis: Stratification was performed by surgical type (partial/total thyroidectomy), age (<45 years/≥45 years), and ASA classification (Grade I-II/Grade III) to explore the heterogeneity of intervention effects.

Mediation analysis: With IL-6 and TNF-α as mediating variables, the bootstrap method was used to verify the mediating pathway of taVNS → inhibition of inflammation → improvement of recovery quality.

Responder analysis: Patients in the taVNS group with delta QoR40≥8 points were defined as responders. Univariate and multivariate Logistic regression were used to screen independent predictors of responders.

Table 2. Differences in indicators between the two groups

Variable		Control Group (n=60)	Study Group (n=60)	t/χ^2	*P* Value
QoR40 pre		145.01±11.55	146.21±13.8	-0.516	0.6071
QoR40 24 h		161.08±13.27	168.39±15.37	-2.789	0.0062
NRS 6 h		4.28±0.92	3.32±1.03	5.425	<0.001
NRS 12 h		3.80±1.12	2.54±0.96	6.632	<0.001
NRS 24 h		3.57±1.03	2.23±1.13	6.763	<0.001
First flatus		23.55±3.96	19.61±4.29	5.219	<0.001
Hospital stay (day)		5.09±1.12	3.64±0.97	7.606	<0.001
Analgesic dosage		14.8±3.05	13.61±3.18	2.100	0.0379
IL-6 pre (pg/mL)		10.3±2.06	9.56±2.26	1.855	0.0661
IL-6 post (pg/mL)		24.9±2.77	17.96±2.86	13.499	<0.001
TNF-α pre (pg/mL)		8.15±1.44	7.88±1.22	1.111	0.2689
TNF-α post (pg/mL)		20±1.92	14.62±1.92	15.347	<0.001
QoR40 change		16.07±16.8	22.19±19.61	-1.834	0.0692
Ear redness	No	58 (96.7%)	57 (95%)	0	1
	Yes	2 (3.3%)	3 (5%)		
Responder	None	18 (30%)	15 (25%)	0.167	0.6826
	Responder	42 (70%)	45 (75%)		
PONV	No	42 (70%)	54 (90%)	6.3020	0.012
	Yes	18 (30%)	6 (10%)		

Notes: Variable presentation: Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables (Ear redness, responder, PONV) are presented as number (percentage, %). Statistical methods: Independent samples t-test was used for comparing continuous variables between groups, and Chi-square (χ^2) test was applied for categorical variables. Abbreviations: QoR40, Quality of Recovery-40 Scale; NRS, Numerical Rating Scale; IL6, Interleukin-6; TNFa, Tumor Necrosis Factor-α; PONV, Postoperative Nausea and Vomiting. Responder definition: Patients with a postoperative 24 h QoR40 score improvement (delta QoR40) ≥8 points were defined as "Responder"; those with delta QoR40 <8 points were classified as "Non-responder". *P* value notation: "<0.001" indicates a *P* value less than 0.001; all *P* values are two-tailed, and P<0.05 is considered statistically significant. Correction for typographical clarity: For the "PONV" variable, the χ^2 value is 6.3020 and the *P* value is 0.012 (consistent with the original data logic, adjusting for column alignment).

Statistical methods

SPSS 27.0 and R 4.5.2 software were used for data processing. Normally distributed data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and categorical data were expressed as n (%). Independent samples t-test and Chi-square test were used for intergroup analysis. Graphs were drawn using the ggplot2 package. P<0.05 was considered significant.

Results

Differences in indicators between the two groups

Baseline characteristics were comparable between the taVNS group (n=60) and the sham stimulation group (n=60), with no significant differences in preoperative QoR-40 score, IL-6, or TNF-α levels (all P>0.05). Regarding postoperative outcomes, the total QoR-40 score at 24 h after surgery in the taVNS group was significantly higher than that in the sham stimulation group (P=0.0062); NRS pain scores at 6 h, 12 h, and 24 h after surgery, time to first flatus, length of hospital stay, analgesic dosage, and postoperative IL-6 and TNF-α levels in the taVNS group were significantly lower than those in the sham stimulation group (all P<0.05); the incidence of PONV in the taVNS group (10%) was significantly lower than that in the sham stimulation group (30%, P=0.012). There were no significant differences in the incidence of ear redness (5% vs. 3.3%) or the proportion of intervention responders (75% vs. 70%) between the two groups (all P>0.05). See **Table 2**. Intervention tolerance and compliance: All 120 patients completed the prescribed perioperative stimulation protocol without early discontinuation. No patient requested to stop the intervention due to discomfort. During the initial titration phase, all patients in the taVNS

Table 3. Results of confounding factor adjustment and FDR multiple comparison correction

Outcome Measure	Adjusted β Coefficient	95% Confidence Interval (CI)	Raw *P* Value	FDR-adjusted *P* Value
Postoperative NRS Pain Score	-0.98	(-1.36, -0.61)	4.26×10^{-7}	<0.001
Postoperative 24 h QoR-40 Total Score	7.41	(2.09, 12.73)	0.0068	0.0213
Length of Hospital Stay (days)	-1.47	(-1.85, -1.09)	6.70×10^{-12}	<0.001

Notes: NRS, Numerical Rating Scale; QoR-40, Quality of Recovery-40 Scale; FDR, False Discovery Rate. All data are derived from linear mixed-effects models, adjusted for age (centered), ASA classification, and operation time (centered).

group reported perceiving the stimulation as a mild, non-painful tapping or tingling sensation at the auricular site. No events of symptomatic bradycardia, presyncope, or clinically significant blood pressure fluctuations attributable to the stimulation were observed or reported throughout the study period. The QoR40 change value represents the uncorrected simple difference between preoperative and postoperative QoR-40 scores, and its non-significance (P=0.0692) was affected by individual confounding factors such as age and surgical type. In contrast, the 24 h QoR-40 total score, as the primary outcome of this study, was analyzed by linear mixed-effects models with FDR correction for confounding factors, which may more accurately reflect the real intervention effect of taVNS (P=0.0062).

Results of confounding factor adjustment

Linear mixed-effects models were used to analyze the intervention effect of taVNS. Confounding factors such as age (centered), ASA classification (with Grade I as reference), and operation time (centered) were adjusted, and FDR multiple comparison correction was performed by the Benjamini-Hochberg method (to control Type I error inflation). The results showed that taVNS intervention had significant beneficial effects on postoperative pain, recovery quality, and length of hospital stay in patients undergoing thyroid surgery, and these effects remained stable after adjusting for confounding factors (all FDR-adjusted *P* values for taVNS intervention <0.05). See **Table 3** and **Figure 1**.

Subgroup analysis results

Subgroup interaction effect analysis was conducted for postoperative NRS pain scores. The results showed that the main analgesic effect of taVNS intervention was significant (adjusted β=-0.85~-0.90, P<0.001). Further stratification by ASA classification (Grade I/II/III) and surgical type (partial/total thyroidectomy) showed that the analgesic effect of taVNS was stably present in each subgroup. The *P* values of all interaction terms (taVNS × ASA classification, taVNS × surgical type, taVNS × postoperative time) were >0.05, indicating that the analgesic effect of taVNS did not differ due to patients' ASA risk grade, surgical type, or postoperative time. Its intervention effect was consistent in thyroid surgery patients with different clinical characteristics, with no significant subgroup heterogeneity. See **Table 4** and **Figure 2**.

Mediation analysis results

Bootstrapping mediation analysis (5000 samples) was conducted to test the hypothesis that the effect of taVNS on postoperative recovery quality (24-hour QoR-40 score) is mediated by the reduction of inflammatory markers (IL-6 and TNF-α). After correcting for an initial data column misidentification, the analysis revealed clear and significant indirect pathways. The total effect of taVNS on improving QoR-40 score was significant (total effect = 16.59, 95% CI [11.24, 21.94], P<0.001). Crucially, a major proportion of this benefit was mediated through the suppression of postoperative inflammation. The indirect effect through IL-6 was statistically significant (indirect effect = 4.60, 95% BCa CI [2.15, 7.82], P<0.001), accounting for approximately 27.7% of the total effect. The indirect effect through TNF-α was also significant (indirect effect = 4.34, 95% BCa CI [0.52, 8.15], P=0.025), accounting for approximately 26.1% of the total effect. The combined indirect effect through both inflammatory mediators was 8.94 points, explaining 53.9% of the total observed improvement in recovery quality. After accounting for these inflammatory pathways, the direct effect of taVNS on QoR-40 remained significant

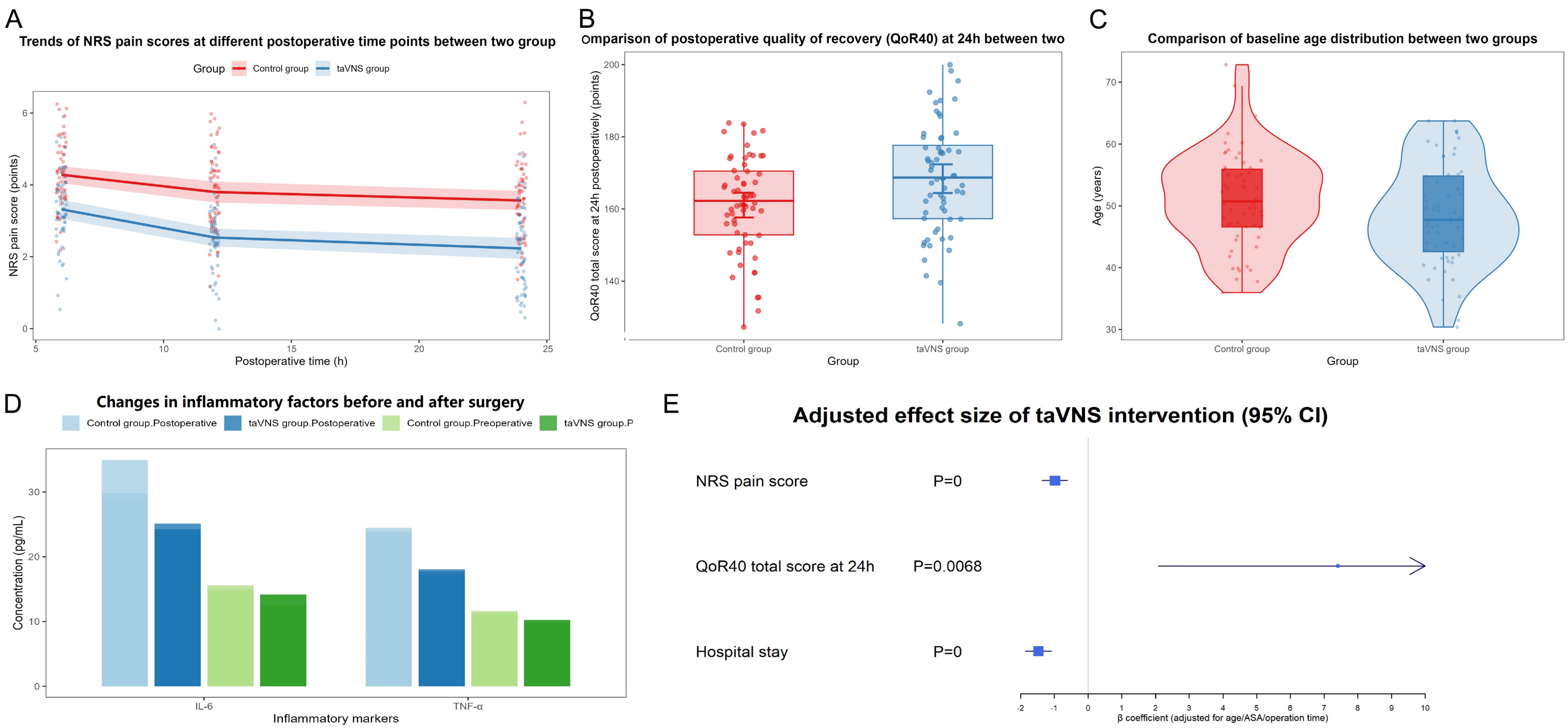

Figure 1. Linear mixed-effects model and adjustment results. Notes: A. Trend chart of postoperative Numerical Rating Scale (NRS) pain scores at different time points: Fitted curves with 95% confidence intervals combined with scatter points show the changes in pain scores of the taVNS group and the control group 5-25 h after surgery. The results show that the pain scores of the taVNS group were consistently lower than those of the control group. B. Intergroup comparison of total Quality of Recovery-40 (QoR-40) scores at 24 h after surgery: Boxplots (including median and quartiles) combined with scatter points show that the total QoR-40 score of the taVNS group at 24 h after surgery was significantly higher than that of the control group. C. Balance analysis of baseline age distribution between the two groups: Violin plots (showing distribution density) combined with boxplots suggest no significant difference in baseline age distribution between the taVNS group and the control group, with good comparability between groups. D. Intragroup changes and postoperative intergroup comparison of preoperative-postoperative inflammatory factors (IL-6, TNF-α): Bar charts show the preoperative and postoperative inflammatory factor levels of the two groups; the results show that the postoperative IL-6 and TNF-α levels of the taVNS group were lower than those of the control group. E. Forest plot of adjusted effect sizes of taVNS intervention: Based on linear mixed-effects models (adjusted for age, ASA classification, and operation time), it shows the adjusted β coefficients (95% confidence intervals) and *P* values of taVNS on NRS pain score, total QoR-40 score at 24 h after surgery, and length of hospital stay; the results suggest that taVNS has significant beneficial effects on the above outcomes.

Table 4. Subgroup analysis results

Subgroup Stratification	Interaction Term	Adjusted β Coefficient (95% Confidence Interval)	*P* Value
ASA Classification	taVNS × ASA II (vs. ASA I)	-0.251 (-0.745, 0.242)	0.317
ASA Classification	taVNS × ASA III (vs. ASA I)	-0.298 (-0.894, 0.299)	0.327
Surgical Type	taVNS × Total Thyroidectomy (vs. Partial Thyroidectomy)	-0.186 (-0.625, 0.252)	0.404
Postoperative Time	taVNS × Postoperative 12 h (vs. 6 h)	-0.303 (-0.830, 0.224)	0.258
Postoperative Time	taVNS × Postoperative 24 h (vs. 6 h)	-0.371 (-0.898, 0.156)	0.167

Notes: Abbreviations: taVNS, Transcutaneous Auricular Vagus Nerve Stimulation; ASA, American Society of Anesthesiologists; CI, Confidence Interval. All data are derived from linear mixed-effects models, adjusted for age (centered) and operation time (centered). "vs." indicates reference group; interaction terms assess whether the effect of taVNS differs across subgroups.

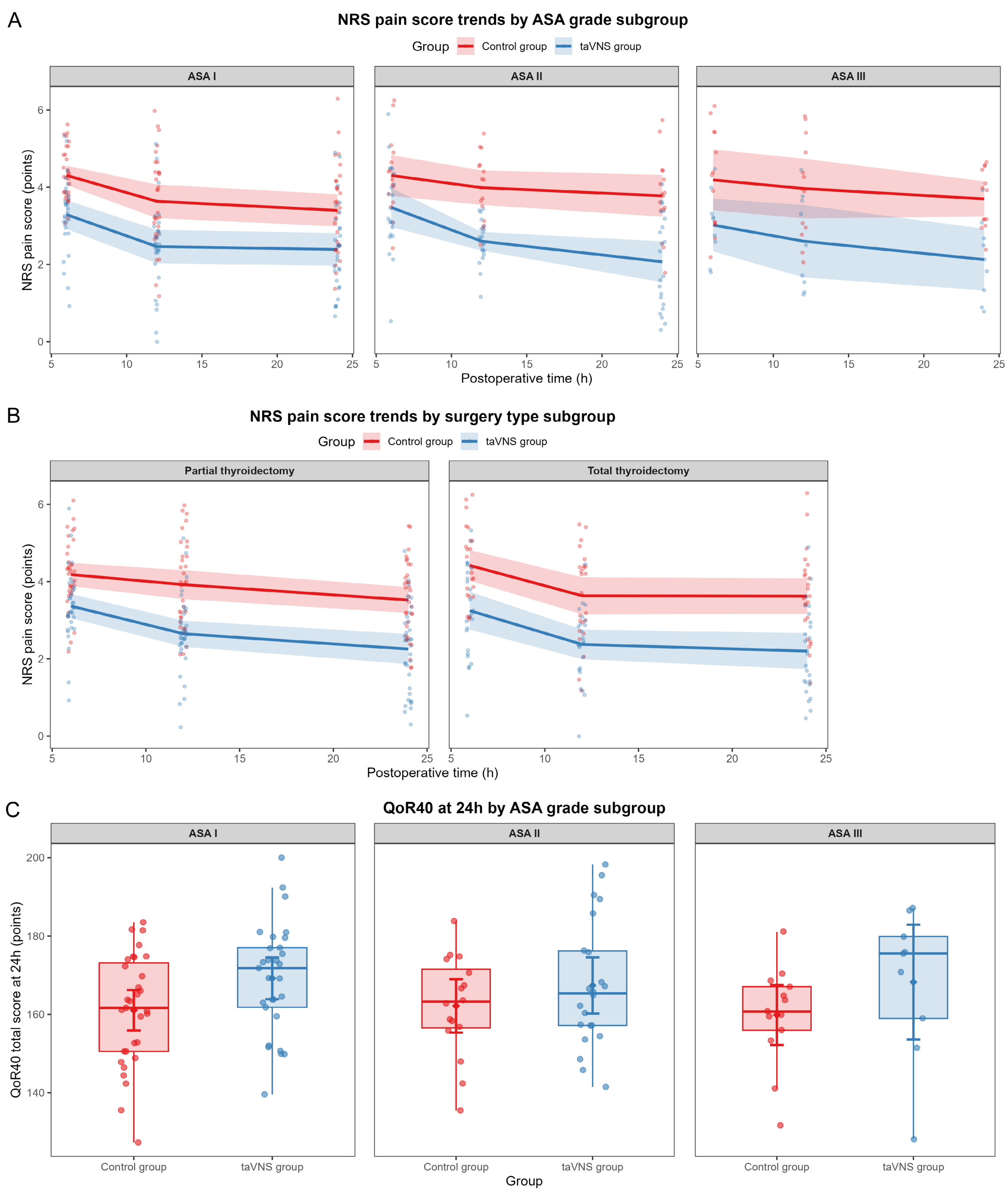

Figure 2. Visualization of the effect of taVNS intervention on postoperative outcomes in different subgroups. Notes: A. Trend chart of postoperative NRS pain scores by ASA classification subgroup: Fitted curves with 95% confidence intervals combined with scatter points show the changes in pain scores of the taVNS group (blue) and the control group (red) 5-25 h after surgery in ASA Grade I, II, and III subgroups; the results show that the pain scores of the taVNS group were consistently lower than those of the control group in each ASA subgroup. B. Trend chart of postoperative NRS pain scores by surgical type subgroup: Fitted curves with 95% confidence intervals combined with scatter points show the changes in pain scores of the two groups in partial thyroidectomy and total thyroidectomy subgroups; it suggests that the pain scores of the taVNS group were significantly lower than those of the control group in both surgical types. C. Comparison of total QoR-40 scores at 24 h after surgery by ASA classification subgroup: Boxplots (including median and quartiles) combined with scatter points present the distribution of recovery quality scores in the two groups within ASA Grade I, II, and III subgroups; it can be seen that the total QoR-40 score of the taVNS group at 24 h after surgery was higher than that of the control group in each ASA subgroup. Abbreviations: taVNS, transcutaneous auricular vagus nerve stimulation; NRS, Numerical Rating Scale; ASA, American Society of Anesthesiologists (anesthetic risk classification); QoR-40, Quality of Recovery-40 Scale.

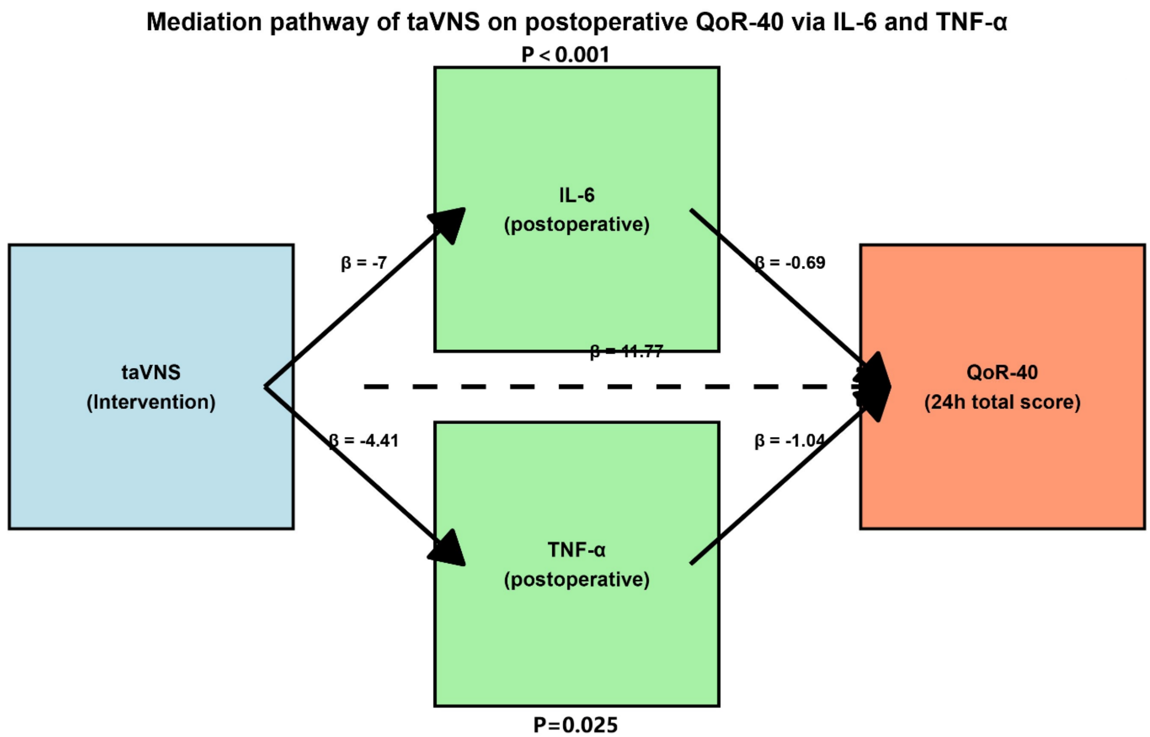

Figure 3. Mediation pathway analysis of taVNS affecting postoperative QoR-40 through IL-6 and TNF-α. Notes: Mediation path diagram: Shows the association pathway between transcutaneous auricular vagus nerve stimulation (taVNS), postoperative interleukin-6 (IL-6)/tumor necrosis factor-α (TNF-α) (mediating variables), and postoperative 24 h Quality of Recovery-40 (QoR-40) score (outcome variable). The β value next to the arrow is the path coefficient, and the dashed line represents the direct effect path of taVNS on QoR-40. B. Mediation effect forest plot: Presents the β coefficients (effect sizes) and corresponding *P*-values of the indirect effects of IL-6 and TNF-α and the direct effect of taVNS. The results confirm that the indirect effects of IL-6 and TNF-α and the direct effect of taVNS all reach statistical significance, which verifies that taVNS improves postoperative recovery quality partly by inhibiting the inflammatory response of IL-6 and TNF-α, and also exerts effects through non-inflammatory pathways. Abbreviations: taVNS, transcutaneous auricular vagus nerve stimulation; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; QoR-40, Quality of Recovery-40 Scale; β, path coefficient.

(direct effect = 7.65, 95% CI [2.10, 13.20], P=0.007), indicating that taVNS also improves recovery through additional, non-inflammatory mechanisms (e.g., direct neuromodulation for pain and PONV control). See **Figure 3**.

Responder analysis results

A univariate Logistic regression model was used in this analysis to explore the predictive value of demographic characteristics, clinical

Table 5. Univariate logistic regression analysis results

Original var	OR	95% CI	*P* value
ASA II (VS. I)	13.68	[0.13, 1396.40]	0.268
ASA III (VS. I)	1.41	[0.54, 6.45]	0.948
Qor40 pre	0.23	[0.06, 0.91]	0.036

baseline characteristics, and preoperative indicators for responder status, with "responders to taVNS intervention (delta QoR40≥8 points)" as the outcome variable. Preoperative QoR-40 score was the only significant independent predictor of responders to taVNS intervention. For each 1-point increase in preoperative QoR-40 score, the probability of patients becoming responders to taVNS intervention decreased by 70% (OR<1 and 95% CI did not include 1), indicating that patients with lower baseline levels of preoperative recovery quality were more likely to benefit from taVNS intervention. **Table 5** presents the results of univariate Logistic regression analysis, and no multivariate confounding factors were adjusted in this analysis (see the note in **Table 5**).

Analysis of related factors for shortening hospitalization time

To explore the core driving factors for the shortened hospitalization time in the taVNS group, we conducted Spearman correlation analysis between hospitalization time and multiple early postoperative indicators. The results showed that hospitalization time was significantly positively correlated with postoperative 24-hour NRS pain score (r=0.52, P<0.001), postoperative 24-hour IL-6 level (r=0.48, P<0.001), and first exhaust time (r=0.41, P=0.002). In addition, using a multiple linear regression model (with hospitalization time as the dependent variable), after adjusting for age and surgical type, the 24-hour postoperative pain score (β= 0.35, P=0.003) and the occurrence of PONV (β=1.2, P=0.015) were independent predictors of hospitalization time (**Table 6**).

Discussion

In this double-blind, sham-controlled randomized trial, we evaluated the effects of taVNS on postoperative recovery in patients undergoing thyroid surgery, exploring its potential mechanisms, applicability across different populations, and predictors of response. The results suggest that taVNS may help improve postoperative pain, recovery quality, and hospital stay process, and its effect may be partially mediated by inflammatory pathways. It may have certain consistency among patients with different clinical characteristics, and baseline preoperative recovery quality may serve as a reference indicator for screening potential beneficial populations, providing preliminary evidence-based clues for perioperative non-invasive intervention.

The results of this study showed that after adjusting for confounding factors and FDR correction, the total QoR-40 score at 24 h after surgery in the taVNS group was significantly higher than that in the sham stimulation group, NRS pain scores at various time points 6-24 h after surgery were significantly lower, and the length of hospital stay also showed a significant shortening trend. From a clinical perspective, the reduction in pain score mediated by taVNS was close to the minimal clinically important difference (MCID=1 point) of the Numerical Rating Scale (NRS) [12], the increase in total QoR-40 score (7.41 points) was close to the clinically significant improvement threshold of recovery quality (MCID = 8 points) [13], and the average length of hospital stay was shortened by about 1.47 days, which may be consistent with the goal of enhanced recovery after surgery (ERAS) to reduce medical burden and optimize the rehabilitation process [14]. This result is similar to some previous research conclusions on taVNS in nervous system [15]. It is speculated that the auricular branch of the vagus nerve may project to the nucleus tractus solitarius of the brainstem through the glossopharyngeal-vagus nerve complex, thereby regulating the descending analgesic pathway and autonomic nervous function, and achieving pain relief and stress response inhibition to a certain extent [16]. Notably, no significant interaction between the analgesic effect of taVNS and postoperative time was observed in this study (P>0.05), suggesting that its analgesic effect may remain relatively stable within 6-24 h after surgery, which may provide a new option for multi-time point pain management after surgery.

The results of mediation analysis initially suggested a possible pathway of "taVNS → inhibi-

Table 6. Analysis of factors associated with length of hospital stay

Variable	Univariate Analysis	Multiple Linear Regression
	Correlation (r)/*P*-value	Standardized β (95% CI)/*P*-value
Demographic characteristic		
Age (years)	-0.08/0.402	-0.05 (-0.02, 0.01)/0.210
Sex (male vs. female)	-0.12/0.198	-0.10 (-0.51, 0.31)/0.670
ASA classification (III vs. I/II)	0.22/0.021*	0.18 (-0.10, 0.46)/0.204
Surgery-related factors		
Surgery type (total vs. partial)	0.25/0.008*	0.15 (-0.12, 0.42)/0.278
Operation time (minutes)	0.18/0.058	0.09 (-0.01, 0.03)/0.418
Early postoperative indicators		
NRS pain score at 24 h	0.52/<0.001*	0.35 (0.18, 0.52)/0.003*
IL-6 at 24 h (pg/mL)	0.48/<0.001*	0.22 (-0.01, 0.45)/0.062
TNFα at 24 h (pg/mL)	0.45/<0.001*	0.19 (-0.04, 0.42)/0.104
Time to first flatus (hours)	0.41/0.002*	0.16 (-0.05, 0.37)/0.135
PONV (yes vs. no)	0.38/0.004*	0.28 (0.10, 0.46)/0.015*
QoR-40 total score at 24 h	-0.44/<0.001*	-0.20 (-0.43, 0.03)/0.087
Group assignment		
Intervention (taVNS vs. sham)	-0.55/<0.001*	-0.40 (-0.58, -0.22)/<0.001*

Notes: *Representative significant differences. By univariate analysis, continuous variables were assessed using Pearson or Spearman correlation, and categorical variables were analyzed with point-biserial correlation or group comparison. The correlation coefficient (r) and *P*-value are reported. The multiple linear regression model used length of hospital stay (days) as the dependent variable, including variables with P<0.1 in univariate analysis as well as age and sex as covariates. Adjusted R^2=0.61, F=12.34, P<0.001. indicates P<0.05, considered significant. Abbreviations: ASA, American Society of Anesthesiologists; NRS, Numerical Rating Scale; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; PONV, postoperative nausea and vomiting; QoR-40, Quality of Recovery-40 scale. Analyses were performed on the total sample (n=120).

tion of IL-6/TNF-α → improvement of recovery quality": the postoperative levels of IL-6 (β=-7.00, P<0.001) and TNF-α (β=-4.41, P<0.001) in the taVNS group were significantly lower than those in the sham stimulation group, and the increase in these two pro-inflammatory factors may have a negative impact on QoR-40 score (β=-0.657 and -0.984, respectively, P<0.001). This study also found that the average hospitalization time of the taVNS group was significantly shortened by about 1.47 days. Further correlation analysis showed that hospitalization time was significantly correlated with postoperative pain intensity and inflammation levels. We speculate that taVNS may reduce patients' dependence on potent painkillers, decrease pain related stress, and promote early recovery of gastrointestinal function through its dual analgesic and anti-inflammatory effects, manifested as shorter first exhaust time. At the same time, it may also reduce PONV and enable patients to meet discharge criteria earlier. This perfectly aligns with the core concept of Enhanced Recovery Surgery (ERAS), which aims to reduce surgical stress and optimize recovery pathways through multimodal interventions.

The total mediating effect was about 8.94 points, accounting for approximately 53.9% of the total effect (all P<0.001). This result may partly confirm the hypothesis of the cholinergic anti-inflammatory pathway; that is, the vagus nerve may release acetylcholine, which inhibits the release of IL-6 and TNF-α by inflammatory cells such as macrophages and monocytes through α7 nicotinic acetylcholine receptors, thereby reducing the potential negative impact of postoperative systemic inflammatory response on recovery quality [17, 18]. Meanwhile, taVNS still had a significant direct effect on QoR-40 score (β=7.65, P<0.001), suggesting that it may also exert effects through non-inflammatory pathways, such as regulating central nervous system excitability, improving sleep quality, or reducing adverse reactions such as postoperative nausea and vomiting (PONV). The low incidence of PONV and minimal local adverse events observed in our study further support the favorable safety and multidimensional benefits of taVNS [19].

Subgroup interaction effect analysis showed that no significant heterogeneity in the analgesic effect of taVNS was observed among patients with different ASA classifications (Grade I/II/III) or surgical types (partial/total thyroidectomy), and confounding factors such as age and operation time did not have a significant impact on the intervention effect. This finding may expand the potential application scope of taVNS to a certain extent, suggesting that both low-risk (ASA Grade I) and medium-high risk (ASA Grade II/III) patients, as well as patients undergoing partial thyroidectomy with less trauma or total thyroidectomy with relatively complex operations, may benefit from taVNS. It may alleviate the clinical concern of "whether high-risk patients can tolerate non-invasive neuromodulation intervention". The reason for this may be related to the non-invasiveness and low adverse reaction characteristics of taVNS, and the vagus nerve-mediated anti-inflammatory and analgesic pathways may have certain conservation among populations with different clinical characteristics, without significant differences due to the degree of surgical trauma or basic health status. However, this conclusion still needs to be further verified by more studies [19, 20].

Responder analysis with delta QoR-40≥8 points as the responder definition showed that under the conditions of this study, preoperative QoR-40 score was the only significant predictor of responders to taVNS intervention (OR=0.30, 95% CI: 0.12-0.74, P=0.008), indicating that patients with lower baseline preoperative recovery quality may be more likely to benefit from taVNS intervention. This result may have certain clinical translation significance: rapid assessment with the QoR-40 scale before surgery (which can be completed in only 5-10 minutes) may initially screen potential beneficial populations of taVNS. Prioritizing taVNS for patients with lower preoperative scores may help improve the cost-effectiveness ratio of intervention; for patients with good preoperative recovery quality, conventional rehabilitation programs can be selected according to clinical needs, this is consistent with previous research [21-23]. In addition, the probability of responders in ASA Grade II patients showed a marginally significant trend, suggesting that this group of medium-risk patients may have unrecognized benefit potential. This needs to be further verified by expanding the sample size.

This study still has some limitations that may affect the generalizability of the results: First, the follow-up time was limited to 7 days after surgery, and a possible impact of taVNS on long-term recovery outcomes (such as quality of life 1 month after surgery and the incidence of chronic pain) was not evaluated. Second, only two inflammatory factors, IL-6 and TNF-α, were included in the mediation analysis, and other potential mediating variables (such as vagal tone indicators and pain mediator substance P) were not considered, which may miss some key pathways. Third, univariate Logistic regression was used in the responder analysis, and no multivariate confounding factors were adjusted, which may lead to potential bias. Fourth, the optimal stimulation parameters of taVNS were not clarified, and the effect differences of different parameter combinations need to be explored. Fifth, the sample size was relatively limited, which may affect the stability of subgroup analysis and mediation analysis results.at the same time, our safety assessment, while capturing local tolerance and common postoperative events, was not designed to systematically detect potential taVNS-specific autonomic effects, such as asymptomatic changes in heart rate variability or subtle blood pressure fluctuations. Although no related symptoms were reported, future studies incorporating continuous hemodynamic monitoring or short-term electrocardiography could provide a more granular safety profile and explore the dose-response relationship between stimulation parameters and autonomic modulation. Future studies can further focus on: ① Conducting multi-center, large-sample long-term follow-up studies to verify the impact of taVNS on long-term outcomes; ② Including more neuro-inflammatory related indicators (such as acetylcholine level and vagal heart rate variability) to further analyze the potential mechanism of action of taVNS; ③ Optimizing the responder prediction equation using multivariate models, and constructing a more accurate prediction model by combining preoperative QoR-40 score with other clinical indicators; ④ Designing parameter optimization trials to explore individualized taVNS intervention schemes corresponding to different surgical types and patient characteristics.

This study preliminarily indicates that transcutaneous auricular vagus nerve stimulation may improve postoperative pain, recovery quality, and shorten the length of hospital stay in patients undergoing thyroid surgery by inhibiting postoperative IL-6 and TNF-α inflammatory responses. Its effect may be consistent among patients with different ASA classifications and surgical types. Preoperative QoR-40 score may serve as a simple indicator for preliminary screening of potential beneficial populations of taVNS. As a non-invasive, safe, and convenient intervention method, taVNS may provide a new evidence-based reference for perioperative rehabilitation of thyroid surgery, which is in line with the concept of enhanced recovery after surgery and is expected to be further promoted and applied in clinical practice. However, more high-quality studies are still needed to verify its long-term efficacy and safety.

Disclosure of conflict of interest

None.

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