

The Effect of Percutaneous Auricular Vagus Nerve Stimulation on Postoperative Delirium in Elderly Patients Undergoing Colorectal Cancer Surgery

Ying Zhu

657969412@qq.com

The First Affiliated Hospital of Hebei North University

Juan Fan

The First Affiliated Hospital of Hebei North University

Xiaowen Yan

The First Affiliated Hospital of Hebei North University

Tingxue Wang

The First Affiliated Hospital of Hebei North University

Hongru Liu

The First Affiliated Hospital of Hebei North University

Jie Yao

The First Affiliated Hospital of Hebei North University

Article

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Abstract

Objective

To observe the effect of transcutaneous auricular vagus nerve stimulation (TAVNS) on postoperative delirium (POD) in elderly patients undergoing colorectal cancer surgery, and to explore its possible anti-inflammatory and neuroprotective mechanisms.

Methods

A total of 180 elderly patients (age ≥ 65 years, ASA grade I–II) scheduled for elective laparoscopic radical resection of colorectal cancer were enrolled and randomly divided into a TAVNS group, a sham stimulation group, and a blank control group, with 60 cases in each group. The TAVNS group received daily electrical stimulation of the auricular concha region (30 min, 1 mA, 20–30 Hz) from 1 day before surgery to 3 days after surgery. The sham group received stimulation with the same parameters but at non-vagus areas of the auricle, while the blank control group received no intervention. The incidence of POD was assessed using the 3-Minute Diagnostic Interview for CAM-Defined Delirium (3D-CAM) at 1 day before surgery and at 1, 3, and 7 days after surgery. Serum levels of neuron-specific enolase (NSE), S100 β protein, tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) were measured before surgery, at the end of surgery, and at 1 and 3 days postoperatively.

Results

A total of 174 patients (58 per group) completed the study. The incidence of POD in the TAVNS group at 1, 3, and 7 days postoperatively was significantly lower than that in the sham and blank control groups ($P < 0.05$), with no significant difference between the latter two groups ($P > 0.05$). Serum levels of NSE, S100 β , TNF- α , and IL-6 in the TAVNS group at 1 and 3 days postoperatively were also significantly lower than those in the other two groups ($P < 0.05$), while no statistically significant differences were found between the sham and blank control groups for any of these markers ($P > 0.05$).

Conclusion

Transcutaneous auricular vagus nerve stimulation can effectively reduce the incidence of postoperative delirium in elderly patients undergoing colorectal cancer surgery. Its effect may be related to the inhibition of central nervous system injury markers (NSE and S100 β) and inflammatory cytokines (TNF- α and IL-6).

Introduction

The incidence and mortality rates of colorectal cancer in China are continuously rising. Currently, it ranks second in incidence and fourth in mortality in our country ^[1]. Postoperative delirium (POD) is a common complication in elderly patients after surgery, which can lead to a series of adverse clinical outcomes,

affecting prognosis and even causing death ^[2]. Studies have shown that the use of drugs to reduce central nervous system inflammation and nourish central nervous system cells can improve POD, but all drugs have certain side effects. Some studies have found that physical therapy methods, with negligible side effects, can achieve similar effects, among which auricular vagus nerve stimulation is one commonly used method ^[3]. However, there are few reports on whether vagus nerve stimulation can improve POD. Therefore, this study intends to use transcutaneous auricular vagus nerve stimulation to observe its effect on postoperative delirium in elderly patients undergoing colorectal cancer surgery.

Methods

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital of Hebei North University (Ethics Approval Number: K2025338). A total of 180 elderly patients scheduled for elective surgery under general anesthesia were randomly divided into the transcutaneous auricular vagus nerve stimulation (TAVNS) group, the sham stimulation group, and the blank control group, with 60 cases in each group. This study was a single-center, prospective observational investigation and was not registered in a clinical trial registry, as it was designed as an exploratory, non-randomized study conducted within routine clinical practice.

1. Clinical Data

1.1 General Information

Comparison of general information among the three groups showed no statistically significant differences ($P > 0.05$), Table 1.

1.2 Inclusion Criteria

☐ MoCA score ≥ 26 ; ☐ Age ≥ 65 years; ☐ Pathologically confirmed colorectal cancer, planned for laparoscopic radical colorectal surgery; ☐ Preoperative anesthesia assessment ASA I–II; ☐ Ability to understand and cooperate to complete the 3-Minute Diagnostic Interview for CAM-Defined Delirium (3D-CAM) assessment; ☐ Patient or authorized representative provides informed consent and signs the informed consent form.

1.3 Exclusion Criteria

☐ MoCA score < 26 ☐ Individuals who have previously participated in clinical trials involving electrical stimulation therapy; ☐ Presence of skin damage or dermatological conditions at the stimulation site; ☐ History of ear diseases, ear surgery, or structural abnormalities of the right auricle; ☐ Implantation of electronic devices such as cardiac pacemakers or deep brain stimulators; ☐ Severe dysfunction of the heart, lungs, liver, or kidneys; ☐ History of mental illness or long-term use of antipsychotic medications.

2. Treatment Methods

2.1 TAVNS Group

After routine ethanol disinfection, anatomically locate the auricular vagus nerve distribution area at the concha and cavum conchae. The posterior-inferior edge of the cavum conchae corresponds to auricular point 12 (Liver); the posterior-superior edge of the cavum conchae corresponds to auricular point 13 (Spleen); the cavum conchae at the point directly opposite the lower limb of the auricle corresponds to auricular point 10 (Kidney), and between the Liver and Kidney points is auricular point 11 (Pancreas and Gallbladder); the center of the cavum conchae is auricular point 15 (Heart); around the Heart point is auricular point 14 (Lung); from the Heart point to the external auditory canal is auricular point 16 (Trachea); the inner edge of the intertragic notch is auricular point 17 (Triple Energizer); the outer edge is auricular point 18 (Endocrine) Figure 1.

After placing the electrode patches, use a low-frequency pulse stimulator (G6805-2) for 30 minutes of stimulation with an intensity of 1 mA, frequency of 20–30 Hz, pulse duration of 1 ms, and stimulation interval of 10 seconds. This treatment is administered once daily, from 1 day before surgery to 3 days after surgery.

2.2 Sham Stimulation Group

Electrical stimulation was applied with the same parameters, but the electrode stimulation sites were located in areas of the auricle not innervated by the vagus nerve.

2.3 Blank Control Group

No treatment is applied.

3. Treatment Effects

3.1 Observational Indicators

3.1.1 Behavioral Indicators

One day before surgery, the Montreal Cognitive Assessment (MoCA) was used for screening, and individuals with MoCA scores below 26 were excluded. After enrollment, all patients were assessed by trained personnel, and 3D-CAM scores were recorded 1 day before surgery and 1, 3, and 7 days after surgery. The Chinese version of the 3D-CAM scale contains 22 questions, is simple to operate, and takes a relatively short time to complete. Its sensitivity has been validated at 84.6%–87.2%, and specificity at 96.7%–97.4%, making it reasonably accurate for diagnosing POD in Chinese surgical patients.

3.1.2 Serum Biochemical Indicators

The expression levels of neuron-specific enolase (NSE), S100 β , tumor necrosis factor (TNF)- α , and interleukin (IL)-6 were measured preoperatively, immediately postoperatively, and on postoperative days 1 and 3 using enzyme-linked immunosorbent assay (ELISA).

3.2 Statistical Methods

All data were analyzed using SPSS 21.0 statistical software. Measurement data that followed a normal distribution are expressed as mean ± standard deviation. Comparisons between groups at different time points were done using one-way ANOVA, and comparisons within the same group at different time points were done using paired t-tests. For data that did not follow a normal distribution, the Wilcoxon rank-sum test was used. The significance level was set at α = 0.05.

3.3 Treatment Outcomes

A total of 180 patients were initially enrolled in this study. Among them, in the TAVNS group, 1 patient had a surgery duration exceeding 5 hours, and 1 patient refused postoperative follow-up; in the blank control group, 2 patients had surgery durations exceeding 5 hours; and in the sham stimulation group, 2 patients were converted to open surgery during the procedure and were excluded. Ultimately, 174 patients were included, with 58 patients in each group. There were no statistically significant differences between the groups in terms of gender, age, BMI, ASA classification, education level, anesthesia time, surgery duration, awakening time, propofol dosage, remifentanil dosage, sufentanil dosage, total fluid input, and total fluid output (Table 1).

Table 1. Comparison of General Data Among Three Groups

Project	TAVNS Group	Sham Stimulation Group	Blank Control Group
Age (x±s, years)	72±6	71±6	72±7
Gender (Male/Female, example)	27/31	26/32	24/34
Height (x±s, cm)	160.2±6.3	160.6±6.7	161.3±6.0
Weight (x±s, kg)	62.5±8.3	59.1±6.9	57.6±8.1
ASA (Class I/II, example)	31/27	25/33	32/26
Education Level (Above/Below High School, example)	24/34	36/22	27/31
Anesthesia Time (min)	211.8±45.2	210.1±28.8	208.1±29.8
Surgery Time (min)	187.9±45.7	188.3±30.2	187.3±31.1
Recovery Time (min)	18.7±7.2	18.7±6.7	19.2±6.8
Propofol Dosage (mg)	481.2±138.4	452.1±133.9	442.1±133.9
Rocuronium Dosage (mg)	2.2±0.5	2.1±0.6	2.2±0.4
Sufentanil Dosage (μg)	45(40~45)	45(40~50)	45(40~50)
Total Infusion Volume (ml)	1700 (1500~2100)	1650 (1500~2000)	1700 (1500~2100)
Total Output Volume (ml)	400(300~550)	400(250~600)	450(300~550)

3.3.1 Comparison of Delirium Incidence Within 7 Days Postoperatively Among the Three Groups

The incidence of delirium on postoperative days 1, 3, and 7 in the sham stimulation group and the blank control group was higher than that in the TAVNS group, with statistically significant differences (P < 0.05).

There was no statistically significant difference between the sham stimulation group and the blank control group ($P > 0.05$). For details, see Table 2.

Table 2. Incidence of Postoperative Delirium in Three Groups (%)

Group (n=58)	Preoperative	Postoperative Day 1	Postoperative Day 3
TAVNS Group	8.33	5.17	1.72
Sham Stimulation Group	16.67	10.34	5.17
Blank Control Group	15.52	12.07	6.89

3.3.2 Comparison of Serum NSE and S100 β Levels at Different Time Points Among Three Groups

There was no statistically significant difference in serum NSE and S100 β levels before and after surgery among the three groups ($P > 0.05$). Compared with the blank control group and the sham stimulation group, the NSE and S100 β levels in the TAVNS group decreased on postoperative day 1 and day 3 ($P < 0.05$); there was no statistically significant difference between the sham stimulation group and the blank control group ($P > 0.05$). Table 3.

Table 3. Comparison of serum NSE and S100 β among three groups of patients ($\bar{x} \pm s$, ng/mL)

Indicator	Group (n=58)	Preoperative	Postoperative Day 1	Postoperative Day 3
NSE	TAVNS Group	9.22 $\pm$ 2.11	9.54 $\pm$ 1.32	9.02 $\pm$ 1.33
	Sham Stimulation Group	8.27 $\pm$ 2.27	18.05 $\pm$ 2.21 ^{ab}	17.56 $\pm$ 1.21 ^{ab}
	Blank Control Group	8.39 $\pm$ 2.16	18.67 $\pm$ 2.54 ^{ab}	17.37 $\pm$ 2.24 ^{ab}
S100 β	TAVNS Group	0.10 $\pm$ 0.05	0.14 $\pm$ 0.03	0.13 $\pm$ 0.02
	Sham Stimulation Group	0.09 $\pm$ 0.04	0.29 $\pm$ 0.11 ^{ab}	0.26 $\pm$ 0.12 ^{ab}
	Blank Control Group	0.09 $\pm$ 0.05	0.30 $\pm$ 0.12 ^{ab}	0.29 $\pm$ 0.11 ^{ab}

Note: Compared with preoperative values, ^a $P < 0.05$; compared with the TAVNS group, ^b $P < 0.05$

3.3.3 Comparison of Serum TNF- α and IL-6 Levels at Different Time Points in Three Groups

Comparison of preoperative and postoperative serum TNF- α and IL-6 levels among the three groups showed no statistically significant differences ($P > 0.05$). Compared with the blank control group and the sham stimulation group, serum TNF- α and IL-6 levels in the TAVNS group were reduced on postoperative days 1 and 3 ($P < 0.05$); there was no statistically significant difference between the sham stimulation group and the blank control group ($P > 0.05$). See Table 4 for details.

Table 4. Comparison of Inflammatory Factor Concentrations in Three Groups of Patients ($\bar{x} \pm s$, pg/ml)

Indicator	Group (n=58)	Preoperative	Postoperative Day 1	Postoperative Day 3
IL-6	TAVNS Group	75.2 $\pm$ 13.7	125.3 $\pm$ 13.5 ^a	112.3 $\pm$ 9.5 ^a
	Sham Stimulation Group	78.1 $\pm$ 16.6	155.3 $\pm$ 12.5 ^{ab}	145.2 $\pm$ 10.5 ^{ab}
	Blank Control Group	76.1 $\pm$ 15.6	156.4 $\pm$ 13.5 ^{ab}	146.3 $\pm$ 11.5 ^{ab}
TNF- α	TAVNS Group	58.2 $\pm$ 6.3	76.7 $\pm$ 5.4 ^a	70.6 $\pm$ 4.4 ^a
	Sham Stimulation Group	56.7 $\pm$ 5.7	87.7 $\pm$ 5.4 ^{ab}	81.6 $\pm$ 5.2 ^{ab}
	Blank Control Group	57.8 $\pm$ 6.7	85.3 $\pm$ 4.7 ^{ab}	79.6 $\pm$ 5.3 ^{ab}

Note: Compared with preoperative values, ^a $P < 0.05$; compared with the TAVNS group, ^b $P < 0.05$

Discussion

In recent years, with the increase in elderly patients with colorectal cancer and the continuous improvement in surgical treatment, some previously common complications have shown a declining trend, while mental and psychological complications such as delirium have gradually increased. Delirium refers to rich, vivid, and imaginative illusions and hallucinations that occur against a background of reduced consciousness, predominantly visual hallucinations, often accompanied by anxiety, fear, and other emotional responses, with poor orientation and an inability to correctly recognize the surrounding environment. We found that the incidence of delirium after surgery in elderly colorectal cancer patients was 12.5%, which is close to that reported in the literature [4].

Vagus nerve stimulation (VNS) is a physical therapy method that has emerged in recent years for the treatment of certain refractory diseases. The U.S. FDA approved cervical VNS as a feasible therapy for refractory epilepsy and depression in 1997 and 2005, respectively [5]. A small-sample clinical trial treated 10 patients with Alzheimer's disease (AD) using VNS, and the patients' cognitive function was significantly improved after treatment. Direct vagus nerve stimulation requires exposure of the vagus nerve and placement of a stimulator, which carries high surgical risks and numerous complications, limiting its widespread clinical application. In recent years, numerous studies have shown that transcutaneous auricular vagus nerve stimulation (TAVNS) does not require surgery, is less costly, has almost no adverse reactions, and can ensure effects comparable to traditional VNS [6]. Existing research has found that TAVNS plays an important role in treating various brain and related disorders, such as epilepsy [7], depression [8], and disorders of consciousness [9].

Auricular acupuncture is an important component of traditional Chinese medicine acupuncture. 'The ear is where the ancestral vessels converge.' The auricular concha region contains auricular points for the heart, liver, kidney, Shenmen, and others, referred to as the 'visceral representation area.' Neuroanatomical studies have shown that the concha is the only area on the body surface where the vagus nerve is distributed, and

stimulation of the concha region can activate the auricular branch of the vagus nerve, whose afferent fibers reach the central nervous system, and whose efferent fibers innervate peripheral organs such as the cardiovascular system, respiratory system, and gastrointestinal system. In theory, transcutaneous auricular vagus nerve stimulation can increase efferent vagal impulses by activating afferent vagal nerve fibers in the concha region, thereby activating the cholinergic anti-inflammatory pathway and ultimately inhibiting inflammatory responses.

Central nervous system inflammation is an important cause of POD, and the occurrence of POD is related to the concentration of postoperative peripheral blood inflammatory markers ^[10]. Therefore, theoretically, alleviating the inflammatory response can improve POD. TNF- α and IL-6 are commonly used indicators reflecting the body's inflammatory level; hence, in this study, their expression levels were selected to represent postoperative inflammation. The results showed that after surgery, due to trauma, stress, and anesthesia, TNF- α and IL-6 were significantly upregulated. After surgery, patients in the TAVNS group receiving auricular vagus nerve stimulation had significantly lower expression levels of TNF- α and IL-6 than the blank control group, and their MoCA scores were also significantly higher than those of the blank control group, suggesting that auricular vagus nerve stimulation participates in the improvement of POD by inhibiting the expression of postoperative inflammatory cytokines. However, the sham stimulation group showed no significant effect. Referring to the study by RONG P et al. ^[8], the sham stimulation in this trial involved moving the electrode to a non-auricular zone of the ear, and the results showed that, under the same stimulation parameters, the sham stimulation group's effect on inhibiting the upregulation of inflammatory cytokines TNF- α and IL-6 was significantly worse than that of the TAVNS group, indicating that stimulation of the auricular concha area has specific therapeutic effects. The study by Yang Huan et al ^[11] indicated that electroacupuncture stimulation can reduce the incidence of postoperative cognitive dysfunction in patients with diabetes and lower serum IL-6 levels.

Both NSE and S100 β expression are peripheral blood indicators reflecting brain injury. After brain injury, the expression of NSE and S100 β increases and can permeate into peripheral blood through the blood-brain barrier. Therefore, measuring the expression of NSE and S100 β in peripheral blood can reflect the extent of brain injury. The occurrence of POD is essentially brain injury caused by various factors during surgery, and thus the expression of peripheral blood NSE and S100 β is upregulated to varying degrees postoperatively. Research by RUSLINM et al ^[12] found that when neurons in brain injury patients are damaged, NSE is released into the intercellular space and cerebrospinal fluid, leading to elevated levels of NSE in cerebrospinal fluid and serum, and plasma NSE levels are significantly correlated with the severity of brain injury. Postoperative neuroinflammation leads to blood-brain barrier damage, synaptic injury, neuronal damage, and even apoptosis, with a large expression of various pro-inflammatory cytokines. The hippocampus is an important brain structure closely associated with cognitive activities. Microglial cells are immune cells in the central nervous system. Under normal physiological conditions, microglia play a crucial role in the development of the nervous system, stabilizing neuronal network systems, participating in signal transmission and synapse repair, and repairing damaged neurons ^[13]. During the inflammatory response period, peripheral inflammatory cells and factors enter the central nervous system through a compromised blood-brain barrier, activating microglia, increasing the production of pro-inflammatory cytokines such as TNF- α and IL-1 β , impairing hippocampal neuronal function, and ultimately inducing PND ^[14].

The possible mechanisms by which inflammatory cytokines lead to postoperative delirium are: ① Inflammation causes damage to the blood-brain barrier, making it easier for harmful substances from peripheral blood to enter the central nervous system [15-16]. ② Inflammation can promote neuronal apoptosis, leading to a reduction in the number of nerve cells. ③ Inflammation causes increased activation of glial cells, further amplifying the inflammatory response, leading to cellular edema and disruption of intercellular communication, manifesting as cognitive impairment. In recent years, numerous clinical and experimental studies [17-18] have confirmed that inflammatory factors such as TNF- α and IL-6 can participate in the physiological processes of learning and memory and play a certain role in the pathophysiology of cognitive dysfunction. Various pro-inflammatory cytokine levels are significantly elevated, further activating microglia and damaging the permeability of the blood-brain barrier, thereby causing brain injury and cognitive dysfunction.

Therefore, this study observed the expression levels of peripheral blood NSE and S100 β , as well as TNF- α and IL-6, in patients before and after percutaneous auricular vagus nerve stimulation (TAVNS) treatment. The study found that, compared with the blank control group and the sham stimulation group, the TAVNS group showed decreased levels of serum NSE, S100 β , TNF- α , and IL-6 on postoperative days 1 and 3, whereas there was no significant difference between the sham stimulation group and the blank control group. The incidence of delirium on postoperative days 1, 3, and 7 was higher in the sham stimulation group and the blank control group than in the TAVNS group, with no significant difference between the sham stimulation group and the blank control group.

In summary, percutaneous auricular vagus nerve stimulation can significantly improve the occurrence of postoperative delirium in elderly patients, while also suppressing the upregulation of NSE and S100 β levels and the inflammatory cytokines TNF- α and IL-6.

Declarations

Author Contribution

ZY is responsible for project design and article theme writing. FJ is responsible for project development. YXW is responsible for project implementation. WTX is responsible for chart and table statistics. LHR is responsible for data collection. YJ is responsible for article review.

Ethics approval and consent to participate: This study was conducted in accordance with the Declaration of Helsinki (revised 2013). The research protocol was approved by the Institutional Review Board (IRB) / Ethics Committee of Medical Ethics Committee of the First Affiliated Hospital of Hebei North University (Approval No.: K2025338, Date: 2025-10-17). The ethical approval document has been uploaded. Written informed consent was obtained from all individual participants (or their legal guardians) included in the study. Participants were informed about the purpose of the research, the procedures, potential risks, and their right to withdraw at any time without penalty.

Consent for publication: All participants provided written informed consent for the publication of any associated data, clinical details, and/or images contained within this manuscript. The authors affirm that the

participants have been fully anonymized to the extent possible, and that no identifiable personal information is disclosed without explicit consent. Copies of the signed consent forms are available for review by the Editorial Office upon request.

Funding Declaration

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DATA AVAILABILITY STATEMENT

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

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Figures

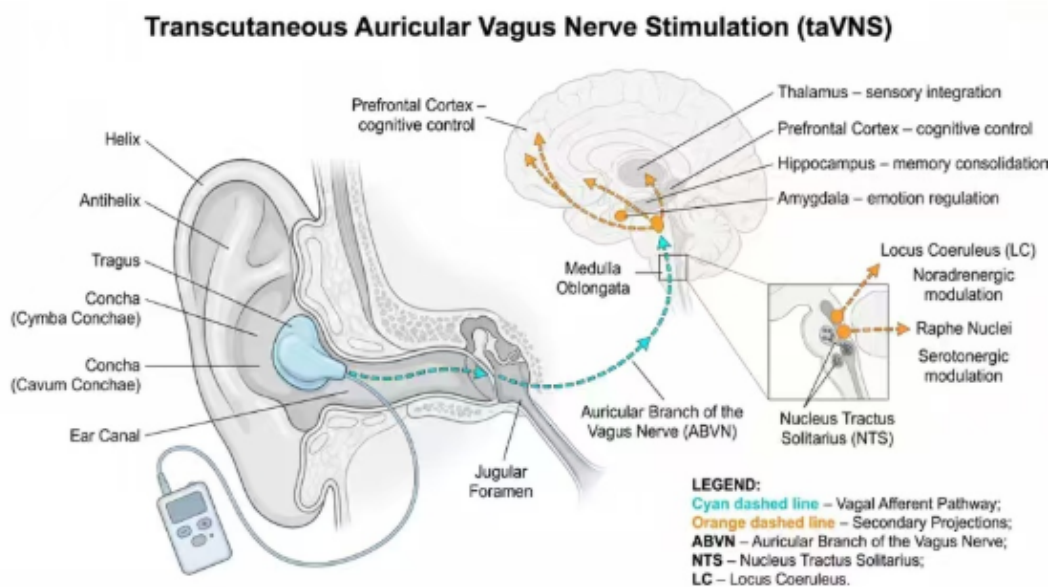


Figure 1

Mechanism Diagram of Transcutaneous Auricular Vagus Nerve Stimulation (taVNS)