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ORIGINAL ARTICLE

Effect of transcutaneous auricular vagus nerve stimulation on delayed neurocognitive recovery in elderly patients

Qi Zhou[1] · Lili Yu[2] · Chunping Yin[1] · Qi Zhang[3] · Xupeng Wang[1] · Kai Kang[4] · Decheng Shao[5] · Qiujun Wang[1]

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Abstract

Background The aim of this study was to investigate whether transauricular vagus nerve stimulation (taVNS) could decrease the incidence of delayed neurocognitive recovery (dNCR) in elderly adults after total joint arthroplasty (TJA).

Methods A prospective, randomized, double-blind, sham-controlled trial was designed. In total, 124 elderly patients undergoing TJA were enrolled and randomly assigned to taVNS group ($n=62$), who received taVNS at 1 h before anesthetic induction until the end of surgery, or sham stimulation (SS) group ($n=62$), who received SS in the same manner. Neuropsychological batteries were performed before and at 1 week after surgery to assess the incidence of dNCR. Blood samples were collected before surgery and at 1 day after surgery to detect the activity of cholinesterase (AChE and BChE), as well as the levels of inflammatory factors (TNF-α, IL-1β, IL-6, and HMGB1) and brain damage factor S100β.

Results Of 124 patients, 119 completed 1 week neuropsychological tests. The incidence of dNCR was significantly decreased in taVNS group [10% (6/60)] compared with the SS group [27.1% (16/59)] ($P<0.05$). Patients who received taVNS had lower blood levels of AChE, BChE, IL-6, HMGB1, and S100β after surgery ($P<0.05$), as compared with those in the SS group. There was no difference in TNF-α between the two groups.

Conclusion The taVNS can decrease the incidence of dNCR after TJA in elderly patients, which may be related to the inhibition of inflammatory cytokine production and the reduction of cholinesterase activity.

Keywords Transauricular vagus nerve stimulation · Postoperative cognitive decline · Cholinesterase · Inflammation

Introduction

Delayed neurocognitive recovery (dNCR), previously termed as postoperative cognitive dysfunction (POCD), is defined as a decline in cognitive function, including memory, information processing, and executive function, up to 30 days after surgery [1]. dNCR is associated with higher risk for impaired quality of life [2], longer term cognitive decline [3], and mortality within 1 year after surgery [4]. The incidence of dNCR varies by patient population, and it is even more frequent in elderly patients undergoing total joint arthroplasty (TJA) [5–8]. The pathophysiology of dNCR has not been fully understood, and no effective precautions and treatments are available currently.

Neuroinflammation is involved in the development of dNCR. Peripheral inflammatory responses to anesthesia and surgery disrupt the blood–brain barrier (BBB) and activate microglial function, leading to subsequent neuroinflammation [9]. Several animal studies have described that activation of cholinergic anti-inflammatory pathway (CAIP) may attenuate neuroinflammation and ameliorate POCD [10–12]. The CAIP refers to the binding of ACh to the α7nAChR of macrophages, which ultimately inhibits the release of inflammatory cytokines [13]. Cholinesterase hydrolyzes and inactivates ACh, thereby inhibiting the CAIP [14]. In animal studies, cholinesterase inhibitors reduced neuroinflammation and improved POCD [15, 16]. In human, a recent study also

✉ Qiujun Wang
wangqiujunsy@163.com

1 Department of Anesthesiology, The Third Hospital of Hebei Medical University, Shijiazhuang, China

2 Department of Anesthesiology, Cangzhou Central Hospital, Cangzhou, China

3 Department of Anesthesiology, Hebei Children's Hospital Affiliated to Hebei Medical University, Shijiazhuang, China

4 Department of Joint Surgery, The Third Hospital of Hebei Medical University, Shijiazhuang, China

5 Department of Sport Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang, China

showed that higher peripheral AChE activity in patients was likely associated with postoperative delirium (POD) [17]. Thus, restraining inflammatory response by activating CAIP may reduce the occurrence of dNCR in elderly patients.

Vagus nerve stimulation (VNS) is a novel neuromodulation therapy that has been successfully applied in refractory epilepsy [18], depression [19], and migraine headaches [20]. The transauricular VNS (taVNS) that stimulates the auricular branch of the VN in a completely non-invasive manner improves cholinergic activity and activates the CAIP [21]. Recent data also proved that taVNS decreased the activity of cholinesterase and surgery-induced acute inflammatory responses [22, 23]. In addition, an animal experiment also suggested that the taVNS inhibited neuroinflammation and alleviated postoperative memory impairment in aged rats [24]. However, taVNS has not been studied in the prevention of postoperative cognitive decline in elderly patients.

The aim of this study was to investigate the effect of taVNS on dNCR in elderly patients undergoing TJA and to explore the mechanism of this intervention. We hypothesize that taVNS could reduce the incidence of dNCR by activating CAIP.

Methods

This prospective, randomized, double-blind, sham-controlled trial was conducted at the Third Hospital of Hebei Medical University, approved by the Institutional Review Board of the Third Hospital of Hebei Medical University (No. 2021-004-1), and registered in Chinese Clinical Trial Registry (ChiCTR2100044905). Informed consent was signed by each participant after full explanation of the procedure.

Participants

This study consecutively recruited elderly patients who underwent TJA in the Third Hospital of Hebei Medical University from April 2021 to October 2021. The main inclusion criteria were 65 years of age or older, American Society of Anesthesiologists (ASA) physical status I–III, and Mini-Mental State Examination (MMSE) score 24 and above. The exclusion criteria were history of schizophrenia and Parkinson's disease; recent use of cholinergic and anticholinergic drugs, and hormones; suffering from inflammatory conditions, intake of anti-inflammatory drugs; communication issues such as serious hearing or visual impairment; an unwillingness to complete the experimental procedures.

Another 30 non-surgical matched control subjects who were primarily family members of surgical patients were enrolled to eliminate the practice effect [25] of repeated neuropsychological tests. The control group met the above inclusion and exclusion criteria except for surgery-related items. Non-surgical control subjects completed neuropsychological tests in the same manner as the surgery group.

Randomization and blinding

The consecutively recruited patients were divided into two groups according to a random number table: taVNS or sham stimulation (SS). The taVNS and SS were administered to the left ear by a commercial transcutaneous electrical nerve stimulation unit (Roscoe TENS 7000). For taVNS, a custom-developed stimulating electrode was placed on the cymba conchae and an available clip design behind the earlobe. For SS, the electrode clips were placed on the ear lobe and the tail of the helix (Fig. 1). The cymba conchae of the ear

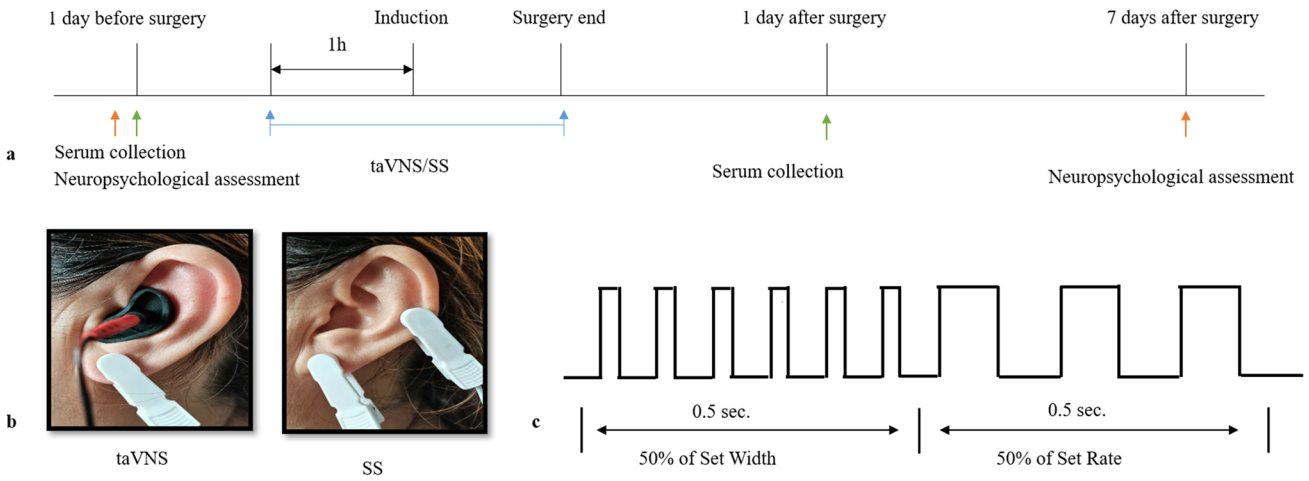

Fig. 1 Design of the study. **a** Experimental flow of the study. **b** Stimulation site of transauricular vagus nerve stimulation (taVNS) and Sham Stimulation (SS) on left ear. **c** Stimulation mode

contains the highest density of auricular vagus nerve projections (100%), while the earlobe and the tail of the helix of the ear are free of cutaneous vagal innervation [26]. Stimulation parameters were set at a modulation mode with a frequency of 10 Hz, a pulse width of 300 μs, and an amplitude of the maximum amount that the subject could tolerate without pain. The stimulation started at 1 h prior to the anesthetic induction to the end of surgery. The electrodes were placed by the nurse and covered with opaque earmuffs. Patients and investigators were blinded to research group assignment.

Anesthesia and perioperative management

Intraoperative monitoring included blood pressure, pulse oxygen saturation, electrocardiogram, bispectral index, and end-tidal CO_2 (ETCO2). Anesthesia was induced intravenously with midazolam, sufentanil, propofol, and cisatracurium, followed by placement of a laryngeal mask airway. Anesthesia was maintained with intravenous propofol infusion and remifentanil infusion. Depth of anesthesia was maintained by controlling BIS 40 to 60. Palonosetron hydrochloride of 0.25 mg was administrated before the end of surgery to prevent postoperative nausea and vomiting (PONV). The use of hormones, nonsteroidal anti-inflammatory drugs, and anticholinesterase drugs was not allowed during the perioperative period.

Blood sample collection

Venous blood specimens were collected before surgery and on the first day after surgery. Serum was centrifuged for 15 min at 3000 *g* and saved frozen at − 80 °C. The activity of serum acetylcholinesterase (AChE) (A024-1-1) and butyrylcholinesterase (BChE) (A025-1-1) was assayed by a commercial enzyme immunoassay kit (Nanjing Jiancheng Bioengineering Institute). The concentrations of tumor necrosis factor-α (TNF-α) (A18210642, MultiSciences, China), interleukin-1β (IL-1β) (101B10151, MultiSciences, China), interleukin-6 (IL-6) (A10610651, MultiSciences, China), high-mobility group protein 1 (HMGB1) (CSBE08223h, CUSABIO, USA), and S100β (CSBE08065h, CUSABIO, USA) were quantified with enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Neuropsychological assessment

All patients were assessed by the Mini-Mental State Examination before surgery. Each participant underwent neuropsychological testing (using parallel forms of each test to reduce practice effects) at two time points: up to 3 days before surgery and at 1 week after surgery. Neuropsychological tests were included based on the protocol in the International Study of Postoperative Cognitive Dysfunction 2 (ISPOCD2) [27]: (1) Rey Auditory Verbal Learning Test (RAVLT)-immediate recall: to assess memory; (2) Trail making test (TMT): as a test of executive function; (3) Digit symbol substitution test (DSST): to assess processing speed; (4) Stroop Color Word Test (SCWT), part 3: as a test of attention.

Statistical analysis

Sample size calculation

The incidence of dNCR in elderly patients was approximately 35% after non-cardiac surgery [4, 28]. We hypothesized that the incidence of dNCR would decrease from 35 to 10% after taVNS. With a significance of 0.05 and a strength of 0.9, the minimum sample size required was 57 subjects per group or a total of 114 subjects (PASS 15.0). Considering a 10% abscission rate, the sample size was 126.

Outcome analysis

The incidence of dNCR at 1 week after surgery was defined as a decline in performance on neuropsychological assessment beyond natural variation. We defined dNCR as: a combined *Z*-score>1.96. For each patient, the *Z*-score for each neuropsychological test was calculated by this equation: $Z = (\Delta X - \Delta X \text{ control}) / SD(\Delta X \text{ control})$. ΔX was the difference between postoperative and preoperative scores of surgical patients. The average practice effect ΔX control was the mean of the difference between before and after the test interval for non-surgical control subjects. SD(ΔX control) was the standard deviation of ΔX control. The sign should be adjusted to ensure that a positive *Z*-score corresponds to a deterioration in all tests. The combined *Z*-score in an individual patient was calculated as the sum of *Z*-scores of the four tests divided by the standard deviation for this sum of *Z*-scores in the non-surgical control subjects. For specific methods, please refer to the corresponding literature [29].

Categorical variables were analyzed using Chi-square test or Fisher's exact test. Continuous variables were tested with Student's *t* test or Mann–Whitney *U* test. Intraoperative data and safety data were analyzed in the intent-to-treat population. The primary endpoint was analyzed in patients who completed 1 week neuropsychological tests. We used R software version 4.0.3 for above analyses.

Results

Subject characteristics

In total, 140 patients were enrolled from April 1, 2021, to October 12, 2021. Of the 140 eligible patients, 124 were

randomized and finally analyzed (intention-to-treat analysis). Among 124 patients, 3 patients did not receive the assigned intervention (stimulation was terminated early in 2 patients, and 1 patient received combined intravenous-inhalation anesthesia). Of the 124 patients, 60 patients in the taVNS group and 59 patients in the SS group completed the neuropsychological tests (Fig. 2).

Demographic and intraoperative characteristics did not differ significantly between the taVNS and SS groups (Table 1). The controls and surgical patients were matched for age, sex, BMI, education level, and MMSE score (Supplementary Table S1).

Outcome analysis

Of all patients enrolled, 119 surgical patients (taVNS group, $n=60$; SS group, $n=59$) and 30 non-surgical control subjects completed 1 week neuropsychological tests. The mean scores for the neuropsychological tests and change scores (Z-score) corrected for learning effect are presented in Supplementary Table S2. The individual combined Z-score and the incidence of dNCR after surgery are shown in Fig. 3. The incidence of dNCR was significantly lower in the taVNS group (6 of 60 patients [10%]) than in the SS group (16 of 59 patients [27.1%]) ($P=0.016$) (Fig. 3).

There were no significant differences in cholinesterase activity and cytokines levels between the two groups at baseline. The postoperative AChE and BChE activity decreased significantly in the taVNS group compared to that preoperatively, but no significant change was found in the SS group (between-group comparison, $P=0.011$ in AChE and $P<0.001$ in BChE; Table 2). A marked inflammatory response occurred after TJA. All inflammatory factors in the two groups were significantly higher after surgery than those before surgery ($P<0.05$). Compared with the SS group, taVNS significantly inhibited the increase in IL-6 ($P=0.007$), HMGB1 ($P=0.012$), and S100β ($P=0.01$) induced by TJA. The magnitude of increase in TNF-α levels by TJA did not show any difference between the two groups (Table 2). IL-1β in a number of serum samples were below the limit of detection and no assessments could be made.

Safety analysis

taVNS was well tolerated and did not cause adverse reactions such as pain, itching, and headache. There was no significant difference in the occurrence of bradycardia, hypotension, tachycardia, hypertension, and POVN between the two groups (Table 3).

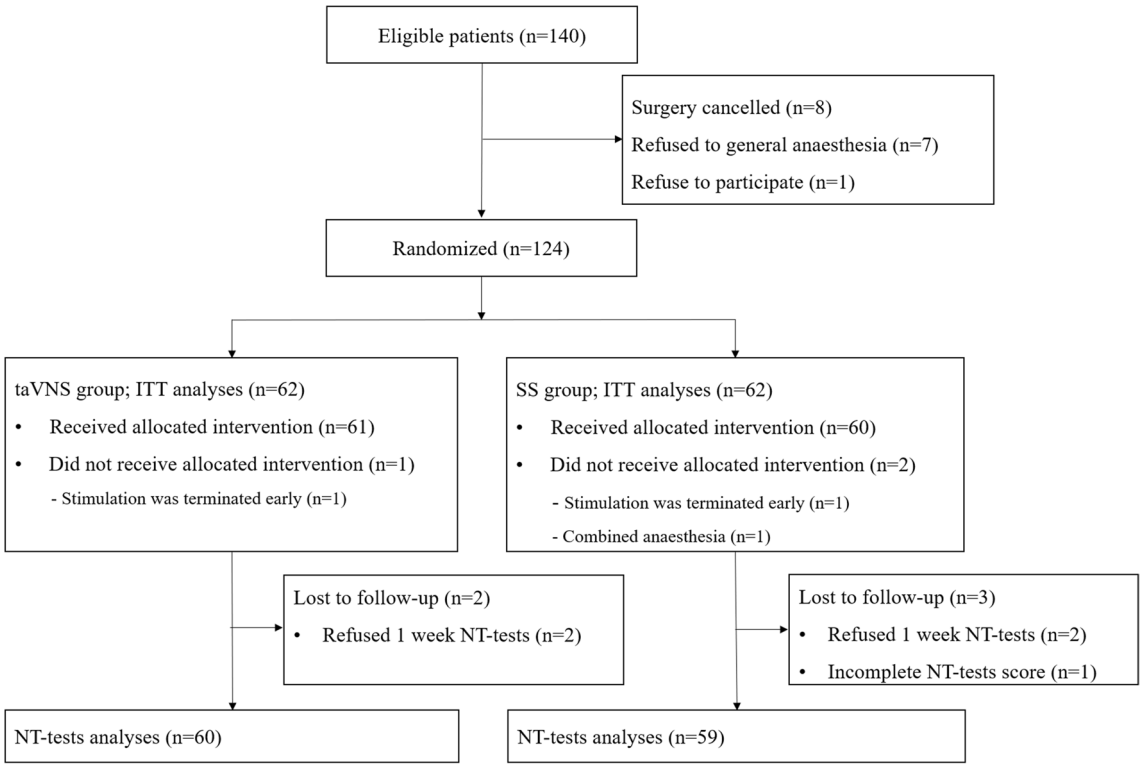

Fig. 2 Flowchart of the study. *ITT* intent-to-treat. *NT-tests* neuropsychological tests

Table 1 Baseline characteristics

	taVNS ($n=62$)	SS ($n=62$)	P value
Age, years	74.5 ± 5.6	74.2 ± 5.2	0.760
Sex, female	33 (53.2)	34 (54.8)	0.857
BMI, kg/m^2	23.9 ± 3.2	24.2 ± 2.8	0.614
Education, years	5 (3–8)	5 (3–6)	0.301
ASA			
I	11 (17.7)	12 (19.4)	0.844
II	41 (66.1)	38 (61.3)	
III	10 (16.1)	12 (19.4)	
Preoperative comorbidities			
Coronary artery disease	16 (25.8)	17 (27.4)	0.839
Hypertension	46 (74.2)	48 (77.4)	0.675
Diabetes	22 (35.5)	20 (32.3)	0.704
Cerebral infarction	20 (32.3)	16 (25.8)	0.429
Charlson comorbidity index	2 (1–2)	2 (2–2)	0.490
MMSE	28.1 ± 1.9	28 ± 1.6	0.590
Duration of anesthesia, min	122.3 ± 25.9	116.2 ± 21	0.111
Duration of tourniquet, min	104.1 ± 24.6	100.1 ± 18.1	0.347
Estimated blood loss, ml	117.5 ± 20.7	120 ± 33.9	0.489

Data are presented as mean (SD) or median (interquartile range) or number of patients (%)

BMI body mass index, *ASA* American Society of Anesthesiologists, *MMSE* Mini-Mental State Examination

Discussion

Our study found that taVNS during perioperative period could significantly reduce the incidence of dNCR at 1 week after TJA in elderly patients. The underlying mechanism may be related to the inhibition of inflammatory factors production and the reduction of AChE and BChE activity.

In this study, the incidence of dNCR in elderly adults undergoing TJA was 27.1%, which was consistent with the previous studies on postoperative cognitive decline in elderly patients undergoing orthopedic surgery (9.1–29%) [30, 31]. The taVNS significantly reduced the incidence of dNCR (10% vs. 27.1%). A recent animal experiment showed that the taVNS alleviated postoperative memory impairment in aged rats by inhibiting neuroinflammation [24]. Blood inflammatory factors that may cause neuroinflammation are closely related to POCD [32]. Therefore, we investigated serum levels of inflammatory markers.

The invasive nature of TJA activated an immune response and triggered the inflammatory cascade [33]. TNF-α, IL-6, and HMGB1 were significantly increased after TJA in this study. In addition, our results indicated that acute taVNS (approximately 3 h) significantly inhibited the surgery-induced increase of IL-6 and HMGB1 at 24 h after surgery, which was in accordance with the anti-inflammatory properties of the vagus nerve [34]. The activation of the anti-inflammatory response requires only a brief VNS stimulus and persists for more than 24 h [35]. The fMRI evidence in humans showed that the activation of all brain persisted throughout the 11 min after 7 min taVNS [36]. The taVNS may be followed by sustainable regeneration mechanisms which establish the sensory information flow to the brain

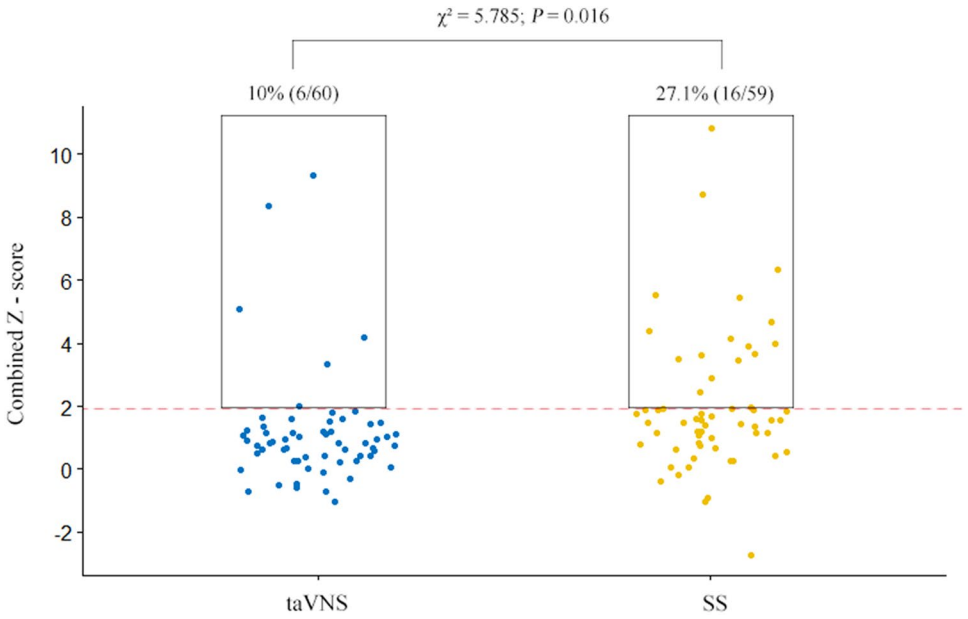

Fig. 3 Scatter plot of combined *Z*-score of the taVNS and the SS groups. The dashed line represents combined *Z*-score = 1.96. The scatter inside the box is combined *Z*-score > 1.96. The incidence of delayed neurocognitive recovery was significantly lower in the taVNS group than the SS group (6/60 patients [10%] vs. 16/59 patients [27.1%], $\chi^2 = 5.785$, $P = 0.016$), analyzed by Pearson's χ^2 test

Table 2 Cholinesterase activity and cytokine

	taVNS ($n=62$)		SS ($n=62$)		P value*
	Preoperative	Postoperative	Preoperative	Postoperative	
AChE, U/ml	13.78 ± 3.49	11.58 ± 3.96	13.37 ± 3.39	12.58 ± 2.83	0.011
BuChE, U/ml	24.45 ± 2.91	21.48 ± 3.93	23.69 ± 2.75	23.17 ± 3.27	< 0.001
TNF-α, pg/ml	6.56 ± 1.58	10.32 ± 3.07	6.7 ± 1.59	10.74 ± 2.89	0.349
IL-6, pg/ml	6.3 ± 4.03	31.08 ± 15.21	6.07 ± 3.3	39.56 ± 20.34	0.012
HMGB1, ng/ml	0.41 ± 0.09	0.65 ± 0.25	0.40 ± 0.12	0.85 ± 0.36	0.001
S100β, ng/ml	0.11 ± 0.02	0.29 ± 0.04	0.11 ± 0.02	0.33 ± 0.07	0.001

Data are mean ± SD

AChE acetylcholinesterase, *BuChE* butyrylcholinesterase, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *HMGB1* high-mobility group protein 1, *S100β* S100 calcium-binding protein B

*Comparison of the change in each parameter before and after surgery between the two groups

Table 3 Safety outcomes

	tsVNS ($n=62$)	SS ($n=62$)	P value
Bradycardia*	7 (11.3)	5 (8.1)	0.544
Hypotension‡	8 (12.9)	11 (17.7)	0.455
Tachycardia§	7 (11.3)	10 (16.1)	0.433
Hypertension†	17 (27.4)	20 (32.3)	0.556
POVN	18 (30)	16 (25.8)	0.687

Data are presented as number of patients (%)

POVN Postoperative nausea and vomiting

*Heart rate < 50 beats min^{-1} or a decrease of > 30% from baseline

‡Systolic blood pressure less than 90 mmHg or a decrease of systolic blood pressure more than 30% from the baseline

§Heart rate > 120 beats min^{-1}or an increase of > 30% from baseline

†Systolic blood pressure more than 180 mmHg or an increase of systolic blood pressure more than 30% from the baseline

[37]. Thus, the decrease of IL-6 and HMGB1 at 24 h after surgery may be attributed to the sustainable activation of VN and the initial inhibition of inflammatory cascade. IL-6 [38] and HMGB1 [39] disrupt BBB and contribute to subsequent neuroinflammation, resulting in elevated serum levels of S100β, a biomarker of cerebral or extra-cerebral neuron damage [40]. Thus, our study revealed that taVNS reduced the serum level of S100β, but did not decrease the level of TNF-α, which might be related to blood collection time and cytokine peak time [41].

Acetylcholine (ACh), as a main inflammation regulator in taVNS, can bind to α7 nicotinic acetylcholine receptor of macrophages and inhibit the production of pro-inflammatory cytokines (IL-6 and HMGB1) [42]. ACh is extremely unstable and difficult to use for clinical measurements, so the detection of hydrolyzing enzymes can be used as an indirect measure of Ach [43]. AChE and BChE hydrolyze and inactivate ACh [44]. The increase in the activity of enzymes AChE and BChE leads to reduced levels of ACh and systemic inflammatory response [45]. Byung et al. reported that VNS inhibited the production of pro-inflammatory cytokines by suppressing AChE in rats [46]. Our study showed that taVNS significantly reduced the postoperative activity of AChE and BChE as compared with the SS group. Our results support the hypothesis that AChE and BChE in serum antagonize CAIP at macrophage level and promote the systemic inflammatory response [47]. In addition, cholinesterase inhibitors also enhance vagus nerve activity to alleviate inflammation [48]. Therefore, the anti-inflammatory effect of taVNS may be related to the inhibition of cholinesterase activity.

Recently, several clinical studies reported the relationship between peripheral cholinesterase activity and POD. Muller et al. [17] reported higher peripheral AChE activity in patients with POD than in those without POD, possibly because higher AChE activity led to rapid degradation of ACh to impair cognition. However, Lin et al. [49] and Guenther et al. [50] showed low peripheral cholinesterase activity as a risk factor for POD. In their studies, in the absence of external intervention or cholinergic drugs' treatment, low cholinesterase activity represented cholinergic hypofunction. This may be because low cholinesterase activity is associated with negative feedback of cholinergic deficiency [51]. Our results suggested that reducing peripheral cholinesterase activity might be beneficial for dNCR. VNS has been proved to reduce the expression of AChE and increase the levels of ACh in animal studies [46, 52, 53]. In this study, the decreased cholinesterase activity by taVNS represented increased levels of ACh and enhanced function of cholinergic system. Therefore, the above studies all showed that peripheral cholinesterase activity is linked to postoperative cognition, and cholinergic hypofunction impairs postoperative cognition. The preventive effect of taVNS on dNCR may be due to both peripheral cholinergic and central cholinergic mechanisms. For peripheral cholinergic mechanism, based on the current data in this study, we assume that decreased cholinesterase activity alleviates its inhibitory effect on CAIP in peripheral immune cells (macrophages), thereby

reducing levels of peripheral inflammatory factors that penetrate the BBB and alter neuronal function. The central cholinergic nervous system is known to be critical for the development of POCD [54] and Alzheimer's disease [55]. In addition, peripheral BChE activity is considered a reasonable indicator of brain BChE [56]. taVNS could increase ACh levels in brain [53]. Therefore, taVNS may be enhancing the central cholinergic neurotransmission in neuronal cells to prevent dNCR. Notably, we did not examine the change of central cholinergic system, and further research is required to test the prediction of this view.

This study had several limitations. First, there is no widely accepted standard for optimal stimulation parameters for taVNS. In this study, we set parameters based on previous animal experiments [57]. Further studies are necessary to evaluate the shortest time period and the lowest stimulation strength of taVNS that would have a beneficial effect. Second, the cytokines were measured from peripherally obtained blood, which may not necessarily correspond to values in the brain. Third, cytokines were only measured once after surgery. A long observation period may be of importance in determining the relationship of the dNCR with the level of inflammatory factors and the activity of cholinesterase. Finally, the small sample size is a further potential limitation.

Conclusions

The taVNS exerted beneficial effects on dNCR in elderly patients at 1 week after TJA, which may be related to the inhibition of inflammatory cytokine production and the reduction of cholinesterase activity. The novel non-pharmacological neuromodulation approach for preventing dNCR would be welcome.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-022-02177-x.

Author contributions QZ designed the study, conducted the study, analyzed the data, and wrote the manuscript. LLY and CPY designed and conducted the study. QZ and XPW conducted the study. KK and DCS conducted the study and collected the data. QJW designed and supervised the study. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This trial was approved by the Institutional Review Board of the Third Hospital of Hebei Medical University (No.2021-004-1), and registered in Chinese Clinical Trial Registry (ChiCTR2100044905).

Informed consent The manuscript has been read and approved by all co-authors.

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