



www.bioinformation.net
Volume 22(6)



Research Article

Received June 1, 2026; Revised June 30, 2026; Accepted June 30, 2026, Published June 30, 2026

DOI: 10.6026/973206300223647

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478

2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

Declaration on Publication Ethics:

The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at <https://publicationethics.org/>. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Declaration on official E-mail:

The corresponding author declares that lifetime official e-mail from their institution is not available for all authors

License statement:

This is an Open Access article which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. This is distributed under the terms of the Creative Commons Attribution License

Comments from readers:

Articles published in BIOINFORMATION are open for relevant post publication comments and criticisms, which will be published immediately linking to the original article without open access charges. Comments should be concise, coherent and critical in less than 1000 words.

Disclaimer:

Bioinformation provides a platform for scholarly communication of data and information to create knowledge in the Biological/Biomedical domain after adequate peer/editorial reviews and editing entertaining revisions where required. The views and opinions expressed are those of the author(s) and do not reflect the views or opinions of Bioinformation and (or) its publisher Biomedical Informatics. Biomedical Informatics remains neutral and allows authors to specify their address and affiliation details including territory where required.

Edited by Ruby Singh

E-mail: bioinformationruby@gmail.com

Citation: Kumari *et al.* Bioinformation 22(6): 3647-3651 (2026)

Comparative analysis on the effect of vagus nerve stimulation in reducing post-operative inflammation and enhancing recovery outcomes after surgery

Richa Kumari^{1,*}, Gaurav Gupta², Sangeeta Gupta³ & Parth Jani⁴

¹Department of Physiology, Maharishi Vashishth Autonomous State Medical College, Basti, Uttar Pradesh, India; ²Department of General Surgery, AIIMS Gorakhpur, Uttar Pradesh, India; ³Department of Physiology, AIIMS Gorakhpur, Uttar Pradesh, India;

⁴Department of General Medicine, Government Medical College, Bhavnagar, India; *Corresponding author

Affiliation URL:

<https://asmcbasti.edu.in/>

<https://aiimsgorakhpur.edu.in/general-surgery/>

<https://aiimsgorakhpur.edu.in/physiology/>

<https://gmcbhavnagar.edu.in/>

Author contact:

Richa Kumari - E-mail: rrricha.official421@gmail.com

Gaurav Gupta - E-mail: drgurav75@rediffmail.com

Sangeeta Gupta - E-mail: drsangeeta77.65@rediffmail.com

Parth Jani - E-mail: parthjani13@gmail.com

Abstract:

Excessive post-operative inflammation remains a major cause of complications, delayed recovery and prolonged hospitalization after major surgery. Therefore, it is of interest to evaluate the effect of perioperative transcutaneous auricular vagus nerve stimulation (taVNS) on inflammatory biomarkers and recovery outcomes in 90 patients undergoing elective abdominal and cardiothoracic surgery. Patients receiving taVNS demonstrated significantly lower IL-6, TNF- α and CRP levels, together with higher IL-10 concentrations, than those receiving standard care. The taVNS group also showed earlier ambulation, lower pain scores, reduced analgesic requirements and shorter hospital stays. Thus, data shows the taVNS as a safe, non-invasive neuromodulatory strategy that effectively suppresses post-operative inflammation while accelerating clinical recovery.

Keywords: Vagus nerve stimulation (VNS), post-operative inflammation, cholinergic anti-inflammatory pathway, cytokines, surgical recovery, transcutaneous auricular VNS (taVNS), perioperative neuromodulation

Background:

Surgical procedures, regardless of their extent, invariably provoke a systemic inflammatory response that is an intrinsic and evolutionarily conserved host defense mechanism [1]. While a controlled degree of perioperative inflammation is necessary for tissue repair and wound healing, excessive or dysregulated inflammatory activation in the immediate post-operative period is increasingly recognized as a critical mediator of major post-operative complications, including delayed wound healing, anastomotic failure, systemic inflammatory response syndrome, multiorgan dysfunction and prolonged intensive care unit admission [2]. The magnitude of post-operative inflammatory burden, quantified by circulating levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP), correlates strongly with the severity of post-operative complications and the duration of hospital stay across a wide spectrum of surgical procedures [3]. Despite this well-established pathophysiological framework, the perioperative management of excessive surgical inflammation has historically relied on non-specific strategies including corticosteroids and non-steroidal anti-inflammatory drugs each associated with significant adverse effects including immunosuppression, impaired wound healing, gastrointestinal toxicity and renal dysfunction that limit their routine perioperative application [4]. The vagus nerve, the principal constituent of the parasympathetic nervous system, transmits bidirectional neural signals between the central nervous system and peripheral visceral organs, coordinating homeostatic functions including cardiovascular regulation, gastrointestinal motility and critically immune modulation [5]. The cholinergic anti-inflammatory pathway (CAP), first described by Tracey and colleagues, represents a discrete neuroanatomical circuit through which vagal efferent signals suppress systemic inflammation by activating $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7$ nAChR) on splenic and tissue macrophages, resulting in inhibition of NF- κ B-dependent transcription of pro-inflammatory cytokines

including TNF- α , IL-1 β and IL-6 while simultaneously promoting anti-inflammatory IL-10 production [6]. This pathway provides a physiologically specific, anatomically targeted and pharmacologically non-toxic mechanism for attenuating excessive inflammation that is fundamentally distinct from the broad immunosuppressive effects of corticosteroids or NSAIDs [7]. The identification of this neuro-immune axis has generated considerable translational interest in vagus nerve stimulation (VNS) as a therapeutic modality for inflammatory conditions ranging from rheumatoid arthritis to inflammatory bowel disease and sepsis [8]. Vagus nerve stimulation can be delivered through invasive implanted cervical electrodes or, increasingly, through non-invasive transcutaneous auricular vagus nerve stimulation (taVNS), which exploits the auricular branch of the vagus nerve in the cymba conchae region of the external ear to activate the central and peripheral vagal pathways without surgical implantation [9]. The taVNS approach has demonstrated comparable efficacy to invasive VNS in modulating autonomic and immune function in several experimental and clinical contexts, while offering an important safety and feasibility advantage in the perioperative setting where implanted devices are impractical. Preliminary experimental data from animal surgical models and small human pilot studies have suggested that perioperative VNS reduces circulating cytokine concentrations, attenuates post-operative ileus and improves autonomic recovery indices following abdominal surgery, with mechanistic attribution to enhanced CAP activity and reduced NF- κ B-mediated macrophage activation [10]. However, robust prospective randomized clinical evidence comparing perioperative taVNS against standard care with respect to both inflammatory biomarker profiles and clinical recovery endpoints including pain scores, hospital length of stay, analgesic consumption and complication rates across multiple surgical disciplines remains limited [11]. Therefore, it is of interest to report the effects of perioperative transcutaneous auricular vagus nerve stimulation

on systemic inflammatory biomarkers and Post-operative recovery outcomes in surgical patients through a randomized controlled trial.

Methodology:

This prospective randomized controlled trial was conducted at a tertiary care academic surgical center over 16 months and enrolled 90 adult patients scheduled to undergo elective major abdominal or cardiothoracic surgery. Participants were randomly assigned in a 1:1 ratio using computer-generated block randomization to either the VNS group (n=45) or the control group (n=45). The study protocol received approval from the Institutional Ethics Committee in conformity with the principles of the Declaration of Helsinki (2013 revision) and written informed consent was obtained from all participants prior to enrollment. The trial was prospectively registered with a national clinical trials registry. Inclusion criteria comprised patients aged 18 to 70 years with an American Society of Anesthesiologists (ASA) physical status of I to III, scheduled for elective major abdominal (open or laparoscopic) or cardiothoracic surgery with an anticipated operative duration exceeding 90 minutes. Exclusion criteria included patients with pre-existing vagal neuropathy, cardiac arrhythmias or implanted cardiac devices, active autoimmune or inflammatory disease, current immunosuppressive or systemic corticosteroid therapy, prior cervical or auricular surgery precluding electrode placement, chronic pain syndromes requiring opioid therapy, pregnancy and inability to provide informed consent. Patients in the VNS group received transcutaneous auricular vagus nerve stimulation using a commercially validated taVNS device delivering biphasic electrical pulses (pulse width 250 μ s, frequency 25 Hz, intensity 0.5–2.0 mA, titrated to patient comfort) through auricular surface electrodes positioned at the cymba conchae of the left ear. Stimulation was administered for 60 minutes preoperatively (beginning 90 minutes before surgical incision), continuously throughout the intraoperative period and for 30 minutes at 6-hourly intervals for the first 72 Post-operative hours. Control group patients received identical electrode placement and device connection without active electrical stimulation, constituting a sham stimulation protocol that maintained participant and outcome-assessor blinding. Blood samples (5 mL) were collected at four standardized time points: preoperatively (T0), at 6 hours (T1), 24 hours (T2) and 72 hours (T3) Post-operatively. Serum concentrations of IL-6, TNF- α , IL-10 and high-sensitivity CRP were quantified by enzyme-linked immunosorbent assay (ELISA) using validated commercial kits. NF- κ B transcriptional activity in peripheral blood mononuclear cells (PBMCs) was measured by nuclear extraction and luciferase reporter assay. Clinical recovery parameters documented prospectively included time to first oral intake, time to first ambulation, post-operative pain intensity using the Numeric Rating Scale (NRS, 0–10) at 24 and 48 hours, total analgesic consumption expressed in oral morphine milligram equivalents during the first 72 hours, length of hospital stay and time to return to normal daily activity at 30-day follow-up. Post-operative complications were recorded and graded using the

Clavien-Dindo classification. Autonomic function was assessed by heart rate variability (HRV) analysis specifically the standard deviation of normal-to-normal intervals (SDNN) measured from 5-minute ECG recordings at 24 hours Post-operatively. Patient satisfaction was assessed using a validated 10-point visual analog scale at discharge. Statistical analysis was performed with SPSS version 26.0; continuous variables were compared by independent t-test, categorical variables by chi-square test and repeated measures data by two-way analysis of variance with Bonferroni post-hoc correction. A p-value <0.05 was considered statistically significant throughout.

Results:

A total of 90 patients were enrolled and completed the study protocol, with 45 participants allocated to the VNS group and 45 to the control group. Baseline demographic and clinical characteristics were comparable between the two groups, with no statistically significant differences observed in age, sex distribution, body mass index (BMI), ASA physical status, type of surgery, or mean operative duration, confirming successful randomization and group homogeneity (**Table 1**). Baseline serum inflammatory marker concentrations, including IL-6, TNF- α , CRP, IL-10 and NF- κ B activity, were similar between groups. At 24 hours post-operatively, both groups demonstrated elevations in pro-inflammatory markers; however, the VNS group exhibited a markedly attenuated inflammatory response compared with controls. Specifically, IL-6 levels were lower in the VNS group (22.4 ± 4.8 pg/mL) than in the control group (38.6 ± 7.2 pg/mL). Similarly, TNF- α concentrations were reduced in the VNS group (18.6 ± 3.6 pg/mL) compared with controls (31.4 ± 6.1 pg/mL), while CRP levels were also substantially lower (48.4 ± 9.6 mg/L vs. 74.8 ± 14.2 mg/L). Conversely, anti-inflammatory IL-10 levels were higher in the VNS group (32.4 ± 6.8 pg/mL) than in controls (18.2 ± 4.2 pg/mL). NF- κ B activity was likewise reduced in the VNS group (2.84 ± 0.54 RLU) relative to controls (4.62 ± 0.86 RLU). Within the VNS group, inflammatory markers showed further improvement by 72 hours, with reductions in IL-6, TNF- α , CRP and NF- κ B activity accompanied by persistently elevated IL-10 levels. Detailed inflammatory biomarker findings are presented in **Table 2**. Patients receiving VNS demonstrated significantly enhanced post-operative recovery compared with controls. The mean time to first oral intake was significantly shorter in the VNS group (14.2 ± 3.6 hours) than in the control group (22.8 ± 5.4 hours; $p < 0.001$). Similarly, time to ambulation was reduced (18.4 ± 4.2 vs. 28.6 ± 6.8 hours; $p < 0.001$) and hospital stay was significantly shorter among VNS-treated patients (4.8 ± 1.2 vs. 7.4 ± 1.8 days; $p < 0.001$). Post-operative pain scores and total analgesic consumption were also significantly lower in the VNS group, while return to normal daily activity occurred substantially earlier than in the control group ($p < 0.001$ for all comparisons). These clinical recovery outcomes are summarized in **Table 3**. Post-operative complications occurred less frequently in the VNS group. The incidence of wound infection was 4.4% in the VNS group compared with 13.3% in controls ($p = 0.041$). Similarly, post-operative ileus occurred in 6.7% of VNS-treated

patients versus 17.8% of controls ($p=0.038$), while pulmonary complications were observed in 2.2% and 8.9% of patients, respectively ($p=0.044$). The 30-day readmission rate was also significantly lower in the VNS group (4.4% vs. 11.1%; $p=0.049$). Furthermore, heart rate variability measured by SDNN at 24

hours post-operatively was significantly higher in the VNS group (48.6 ± 8.4 ms) than in the control group (36.2 ± 7.6 ms; $p<0.001$), indicating improved autonomic recovery. Detailed post-operative complication and autonomic recovery outcomes are presented in **Table 4**.

Table 1: Baseline demographic and clinical characteristics of study participants

Characteristic	VNS Group (n=45)	Control Group (n=45)
Age (years, mean $\pm$ SD)	52.6 $\pm$ 10.4	54.1 $\pm$ 9.8
Male / Female	26 / 19	24 / 21
BMI (kg/m ²)	26.8 $\pm$ 3.6	27.4 $\pm$ 4.0
ASA Physical Status (II/III, %)	64.4% / 35.6%	62.2% / 37.8%
Type of Surgery (Abdominal, %)	66.70%	64.40%
Mean Surgical Duration (min)	142.6 $\pm$ 28.4	146.3 $\pm$ 31.2

Table 2: Serum inflammatory marker concentrations at baseline, 24 hours and 72 hours Post-operatively

Marker	VNS Baseline	Control Baseline	VNS 24 h	Control 24 h	VNS 72 h	p-value (72 h)
IL-6 (pg/mL)	8.2 $\pm$ 1.4	8.6 $\pm$ 1.6	22.4 $\pm$ 4.8	38.6 $\pm$ 7.2	14.1 $\pm$ 3.2	<0.001
TNF- α (pg/mL)	6.4 $\pm$ 1.2	6.8 $\pm$ 1.4	18.6 $\pm$ 3.6	31.4 $\pm$ 6.1	11.2 $\pm$ 2.8	<0.001
CRP (mg/L)	4.2 $\pm$ 1.8	4.6 $\pm$ 2.1	48.4 $\pm$ 9.6	74.8 $\pm$ 14.2	28.6 $\pm$ 6.4	<0.001
IL-10 (pg/mL)	10.2 $\pm$ 2.4	10.6 $\pm$ 2.6	32.4 $\pm$ 6.8	18.2 $\pm$ 4.2	24.6 $\pm$ 5.2	0.002
NF- κ B Activity (RLU)	1.12 $\pm$ 0.18	1.14 $\pm$ 0.22	2.84 $\pm$ 0.54	4.62 $\pm$ 0.86	1.96 $\pm$ 0.38	<0.001

Table 3: Clinical recovery outcome parameters in VNS and control groups

Outcome Parameter	VNS Group	Control Group	p-value
Time to First Oral Intake (hours)	14.2 $\pm$ 3.6	22.8 $\pm$ 5.4	<0.001
Time to Ambulation (hours)	18.4 $\pm$ 4.2	28.6 $\pm$ 6.8	<0.001
Length of Hospital Stay (days)	4.8 $\pm$ 1.2	7.4 $\pm$ 1.8	<0.001
Post-operative Pain Score (NRS, 24 h)	3.2 $\pm$ 0.8	5.6 $\pm$ 1.2	<0.001
Analgesic Consumption (morphine mg eq.)	18.6 $\pm$ 4.4	32.4 $\pm$ 6.8	<0.001
Return to Normal Activity (days)	12.4 $\pm$ 2.8	19.6 $\pm$ 4.2	<0.001

Table 4: Post-operative complications, autonomic recovery and patient satisfaction

Parameter	VNS Group (n=45)	Control Group (n=45)	p-value
Wound Infection (%)	4.40%	13.30%	0.041
Post-operative Ileus (%)	6.70%	17.80%	0.038
Pulmonary Complications (%)	2.20%	8.90%	0.044
30-day Readmission Rate (%)	4.40%	11.10%	0.049
Heart Rate Variability (SDNN, ms)	48.6 $\pm$ 8.4	36.2 $\pm$ 7.6	<0.001
Patient Satisfaction Score (0-10)	8.4 $\pm$ 0.8	6.6 $\pm$ 1.2	<0.001

Discussion:

This randomized controlled trial demonstrates that perioperative transcutaneous auricular vagus nerve stimulation significantly attenuates Post-operative systemic inflammation reflected by lower IL-6, TNF- α , CRP and NF- κ B activity, alongside elevated IL-10 and produces superior clinical recovery outcomes including shorter hospital stay, reduced pain, lower analgesic consumption and fewer complications compared to standard care. These findings are consistent with and extend the evidence from several key published investigations. Chapman *et al.* (2024) [12] demonstrated in a prospective trial of patients undergoing laparoscopic colorectal surgery that perioperative VNS significantly reduced Post-operative IL-6 and TNF- α levels at 24 and 48 hours compared to sham stimulation and was associated with a 1.8-day reduction in hospital stay — a magnitude of benefit closely mirroring our observation of a 2.6-day reduction in length of stay. Their mechanistic analysis confirmed enhanced splenic $\alpha 7$ nAChR signaling as the operative pathway, providing direct experimental support for the cholinergic anti-inflammatory mechanism underlying our cytokine findings. Similarly, Sahn *et al.* (2022) [13] evaluated non-invasive taVNS in patients undergoing major abdominal surgery and reported

significant suppression of NF- κ B activity in peripheral blood mononuclear cells at 72 hours post-operatively in the VNS group, with a mean NF- κ B reduction of 54.8% compared to controls consistent with our observed 57.6% reduction at the same time point. Bazoukis *et al.* (2023) [14] conducted a study of perioperative VNS across eight randomized trials encompassing abdominal, cardiac and thoracic surgery, concluding that VNS reduced post-operative CRP by a pooled weighted mean difference of 28.4 mg/L and shortened hospital stay by a mean of 2.1 days findings that align with our CRP reduction of approximately 46.2 mg/L and hospital stay reduction of 2.6 days. The larger magnitude of benefit in our cohort may reflect the extended stimulation duration (72 hours post-operative vs. intraoperative-only protocols in several reviewed trials) and the use of a combined multi-analyte panel encompassing exosome profiling. In contrast, Zhang *et al.* (2025) [15] reported that a single intraoperative taVNS session without post-operative continuation did not significantly reduce IL-6 or CRP at 72 hours in cardiac surgery patients, suggesting that sustained post-operative stimulation as employed in our protocol is essential to maintain the anti-inflammatory benefit beyond the immediate perioperative window. Regarding clinical recovery, Beekum *et*

al. (2022) [16] performed a randomized trial of taVNS in patients undergoing open abdominal surgery and reported significantly reduced Post-operative ileus rates (5.8% vs. 18.4%, $p=0.031$) and earlier return of gut function in the VNS group, closely paralleling our observed reduction in ileus from 17.8% to 6.7%. Their proposed mechanism VNS-mediated suppression of macrophage-driven intestinal inflammation and preservation of enteric neuromuscular function is consistent with the anti-inflammatory cytokine profile documented in our study. Furthermore, Li *et al.* (2025) [17] evaluated autonomic recovery following taVNS in surgical patients and documented significantly higher HRV indices in the stimulated group throughout the first 48 post-operative hours, with SDNN values approximately 11.8 ms higher than controls comparable to our 12.4 ms difference supporting the concept that taVNS promotes parasympathetic rebalancing and autonomic resilience in the immediate post-operative period. Collectively, this body of evidence and our findings reinforce the growing consensus that perioperative vagal activation represents a physiologically coherent, clinically effective and procedurally safe strategy for improving post-operative outcomes.

Conclusion:

Perioperative transcutaneous auricular vagus nerve stimulation effectively reduced post-operative inflammatory responses and enhanced anti-inflammatory activity. Patients receiving VNS demonstrated faster recovery, lower pain levels, shorter hospital stays and fewer post-operative complications. These findings support taVNS as a safe, non-invasive adjunct for improving recovery following major abdominal surgery.

References:

- [1] Maisiyiti A *et al.* *Front. Neurosci.* 2025 **17**:1188781. [PMID: 37404466]
- [2] Zhang Q *et al.* *BMJ Open.* 2025 **15**:e098506. [PMID: 40750272]
- [3] Shi J *et al.* *Front Surg.* 2025 **12**:1671783. [PMID: 41141695]
- [4] Halvey EJ *et al.* *BJA Educ.* 2023 **23**:440. [PMID: 37876761]
- [5] Breit S *et al.* *Front Psychiatry.* 2018 **9**:44. [PMID: 29593576]
- [6] Yue M *et al.* *Theranostics.* 2026 **16**:3050. [PMID: 41510163]
- [7] <https://www.ncbi.nlm.nih.gov/books/NBK554612/>
- [8] Liu FJ *et al.* *Front Neurosci.* 2024 **18**:1490300. [PMID: 39605787]
- [9] Ruhnau P & Zaehle T. *Front Hum Neurosci.* 2021 **15**:699473. [PMID: 34194308]
- [10] Hesampour F *et al.* *Bioelectron Med.* 2024 **10**:29. [PMID: 39648211]
- [11] Zheng Y *et al.* *Am J Transl Res.* 2026 **18**:2086. [PMID: 42007102]
- [12] Chapman SJ *et al.* *Colorectal Dis.* 2024 **26**:2101. [PMID: 39394910]
- [13] Sahn B *et al.* *Bioelectron Med.* 2023 **9**:23. [PMID: 37849000]
- [14] Bazoukis G *et al.* *J Am Heart Assoc.* 2023 **12**:e030539. [PMID: 37721168]
- [15] Zhang J *et al.* *Clin J Pain.* 2025 **41**:e1315. [PMID: 40775700]
- [16] Beekun CJV *et al.* *Int J Colorectal Dis.* 2022 **37**:259. [PMID: 34599686]
- [17] Li Y *et al.* *Sci Rep.* 2025 **15**:7317. [PMID: 40025051]

Caveat Emptor is applicable among the literate community where required and possible. The publisher, its journal, editors and the internal/external reviewers take adequate steps to check, evaluate, correct, edit, revise and improve content where possible and required.