Pain Ther (2023) 12:707–722
https://doi.org/10.1007/s40122-023-00493-2

ORIGINAL RESEARCH

Transcutaneous Electrical Acupoint Stimulation Improves Postoperative Sleep Quality in Patients Undergoing Laparoscopic Gastrointestinal Tumor Surgery: A Prospective, Randomized Controlled Trial

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Received: January 6, 2023 / Accepted: February 24, 2023 / Published online: March 14, 2023

ABSTRACT

Introduction: This study was conducted to observe the effect of transcutaneous electrical acupoint stimulation (TEAS) on the postoperative sleep quality of patients undergoing gastrointestinal tumor surgery and to verify the possible mechanism.
Methods: Eighty-three patients were allocated to the TEAS or Sham group. Patients in the TEAS group received TEAS treatment (disperse-dense waves; frequency, 2/100 Hz) on bilateral Shenmen (HT7), Neiguan (PC6) and Zusanli (ST36) points for 30 min each time, total three times in the perioperative period. In the Sham group, electrodes were placed; however, no current was given. Sleep quality was assessed on the day before surgery (P1) and the first and third days after surgery (D1 and D3) using the Pittsburgh Sleep Quality Index (PSQI) and Athens Insomnia Scale (AIS). Postoperative pain was assessed using visual analog scale (VAS) 72 h postoperatively. The incidences of abdominal distension, dizziness, postoperative nausea and vomiting (PONV) and pulmonary complications were recorded. Serum levels of inflammatory cytokines and the expression of key factors of oxidative stress and key molecules of the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signal pathway were measured.
Results: TEAS ameliorated sleep quality at D1 and D3 (PSQI $P < 0.05$, AIS $P < 0.05$) and decreased postoperative pain as demonstrated by lower VAS scores compared to the Sham group ($P < 0.05$). The incidences of abdominal distension and PONV were also lower in the TEAS group. Markers of oxidative stress were increased ($P < 0.05$), and the serum concentration of interleukin-6 (IL-6) was significantly lower in the TEAS group. The key mediators of the Nrf2/ARE pathway were enhanced after TEAS.
Conclusion: Perioperative TEAS improved postoperative sleep quality, reduced postoperative pain and alleviated postoperative adverse effects in patients undergoing laparoscopic

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gastrointestinal tumor surgery resection. This may be associated with activating Nrf2/ARE signal pathway and decreasing its inflammatory actions.

Trial registration: Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx), ChiCTR2100054971.

Keywords: Transcutaneous electrical acupoint stimulation; Sleep quality; Gastrointestinal tumor; NRF2; Inflammation

Key Summary Points
Postoperative sleep disturbance (PSD) has many potential adverse effects. Improving sleep perioperatively is likely to be associated with improved well-being, surgical outcomes and patient safety
Transcutaneous electrical acupoint stimulation (TEAS) is a form of traditional Chinese medicine which replaces needles with electrical stimulation. TEAS has been studied in mastectomy and thoracic surgery
The aim of this study was to investigate the impact of TEAS at the acupoints of bilateral Shenmen (HT7), Neiguan (PC6) and Zusanli (ST36) on postoperative sleep quality in patients undergoing gastrointestinal tumor surgery
Perioperative TEAS improved postoperative sleep quality, reduced postoperative pain and alleviated postoperative adverse effects in patients undergoing laparoscopic gastrointestinal tumor surgery resection, which may be associated with activating the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signal pathway and decreasing its inflammatory actions

INTRODUCTION

Sleep quality plays a crucial role in maintaining normal physiological activities. Surgical patients typically suffer from profound sleep disturbance early in the postoperative period. The magnitude and duration of the surgical procedure have been shown to determine the degree of postoperative sleep disturbance (PSD) [1, 2]. A reduction in rapid eye movement (REM) and slow-wave sleep and a lack of inherent rhythmicity are more pronounced after major abdominal surgery compared to minor surgery [2]. Questionnaire studies showed that the greatest incidence of sleep disturbances was found after major surgical procedures [2–4]. PSD has many adverse effects including cognitive impairment (including delirium), altered pain perception, mood disturbances, metabolic derangements and proinflammatory changes [5–7]. Improving perioperative sleep quality and duration is likely to improve well-being, surgical outcomes and patient safety.

The surgical stress response is one of the main factors that influence postoperative sleep [8]. This response is secondary to both tissue trauma and anesthesia and activates the hypothalamic-pituitary-adrenal (HPA) axis. HPA activation has been recognized as a primary mechanism of stress related to brain damage [9]. Moreover, oxidative stress plays a critical role in the pathophysiology of sleep disturbance as brain free radicals accumulate during wakefulness and are removed during sleep [10]. Clinical studies have found increased levels of oxidative stress markers following laboratory-induced sleep deprivation and in patients with primary insomnia compared to those without sleep disturbances [11, 12]. Additionally, it has been reported that sleep deprivation leads to the accumulation of reactive oxygen species (ROS) and consequent oxidative stress in animal models [13, 14].

Anti-oxidative factors, including nuclear factor erythroid 2-related factor 2 (Nrf2), are also downregulated in the setting of sleep deprivation [15]. The transcription factor Nrf2 is best known as one of the main orchestrators of the cellular aerobic and oxidative stress response. Nrf2 induces the expression of antioxidant and cytoprotective genes under oxidative conditions including catalase (CAT), superoxide dismutase (SOD), glutathione S-transferases (GST), glutathione peroxidase (GSH-Px) and heme oxygenase-1 (HO-1) [16–18]. Moreover, Nrf2 is tightly regulated by sleep-related genes, suggesting an antioxidant and anti-inflammatory role of sleep through the regulation of Nrf2 signaling [19, 20]. Wang et al. demonstrated that corilagin ameliorates sleep deprivation and induces memory impairment by activating Nrf2 [21]. Other studies have shown that the expression of Nrf2 was reduced following oxidative stress after chronic sleep deprivation [15]. Whether Nrf2 plays a key role in PSD after gastrointestinal (GI) surgery and the underlying mechanisms remain unclear.

As traditional Chinese acupuncture therapy, transcutaneous electrical acupoint stimulation (TEAS) is a therapeutic technique that involves the application of low-frequency electrical currents to acupoints on the surface of the skin. It is a non-invasive form of electrotherapy that is widely used in clinical practice. Previous reports had described the use of TEAS for chronic pain after mastectomy [22] and demonstrated its utility in the reduction of postoperative ileus and enhancement of the recovery of GI function [23]. TEAS causes no adverse reactions such as those caused by acupuncture needles and has similar effects to electroacupuncture [24]. Several studies have shown that TEAS may adjust autonomic balance by enhancing vagal activity and suppressing sympathetic activity [25–27]. However, the effect of TEAS on PSD after GI surgery and its mechanisms remain to be determined.

In this study, we examined whether TEAS could ameliorate PSD. In addition, we analyzed the change in Nrf2 expression during GI surgery and evaluated its activity and downstream effects after TEAS intervention.

METHODS

Study Design and Participants

This was a multi-center, prospective, double-blind, randomized controlled trial at the Affiliated Hospital of Nanjing University of Chinese Medicine and Xuzhou Traditional Chinese Medicine Hospital Affiliated to Nanjing University of Chinese Medicine between December 2021 and August 2022. The study was conducted in accordance with the Helsinki Declaration and was approved by the ethics committee of Affiliated Hospital of Nanjing University of Chinese Medicine (no. 2021NL-199-02) and Xuzhou Traditional Chinese Medicine Hospital Affiliated to Nanjing University of Chinese Medicine (no. 09/2020). The study protocol was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx, ChiCTR2100054971). Informed consent was obtained from all participants.

The inclusion criteria were as follows: (1) patients undergoing elective laparoscopic GI tumor surgery, (2) age 18 to 75-years, (3) American Society of Anesthesiologists (ASA) grade I to III, (4) body mass index (BMI) 18.5–28 kg/m^2 and (5) preoperative clinical tumor-node-metastasis (TNM) staging: $cT_{is\text{-}3}N_{0\text{-}1}M_0$ as per the AJCC/UICC 8th edition. Exclusion criteria were as follows: (1) Pittsburgh Sleep Quality Index (PSQI) ≥ 7 points or Athens Insomnia Scale (AIS) ≥ 6 points before surgery, (2) sleep apnea or moderate or severe snoring, (3) a pacemaker in situ, preoperative sinus bradycardia (heart rate < 50 beats/min) or sinus node disease, second-degree or third-degree atrioventricular block, (4) long-term use of anticonvulsants, antidepressants or other psychotropic drugs, (5) severe sensitivity or allergy to the drugs or equipment in this study, (6) severe heart, liver or kidney disease, (7) participation in other clinical trials in the past 3 months, (8) hearing and/or language communication barriers, (9) pregnancy or breastfeeding, (10) fever (temperature $> 38.5°$ C) or clinical (hematological, radiographic and/or microbiological) evidence of infection before surgery and (11) patients who live with critically ill patients or are housed in a ward with > 3 patients. Patient demographic information was collected, including age, BMI and ASA grade. All investigators were trained according to the standardized acupoint technique and TEAS manipulation by a senior acupuncturist with 20 years of practicing experience.

Randomization, Blinding, Anesthesia and Surgery

All enrolled patients underwent standard laparoscopic radical gastrectomy for gastric cancer or laparoscopic radical resection for colorectal cancer. Patients' eligibility was assessed through a two-step screening for final enrollment and randomization. The initial screening, recruitment, final enrollment and randomization were conducted 1 day prior to surgery. Patients were assigned to either the TEAS group or the Sham group by a table of computer-generated random numbers. Group assignments were sealed in sequentially numbered opaque envelopes. Patients, attending surgeons, operating room nurses, data collectors and individuals who performed the final statistical analysis were blinded to group assignment.

Upon admission to the operating room, patients had their blood pressure (BP), electrocardiogram (ECG) and peripheral capillary oxygen saturation (SpO_2) routinely monitored. Venous access was obtained, and intravenous-inhalation compound anesthesia was administered. For induction of anesthesia, an intravenous bolus injection of midazolam 0.04 mg/kg, etomidate 0.3 mg/kg, sufentanil 0.4 μg/kg and vecuronium 0.08 mg/kg was used. Bispectral index (BIS) was monitored intraoperatively to maintain a range of 40–60. Continuous inhalation of 1%–2% sevoflurane and continuous infusions of propofol (5 $mg/kg^{-1}\cdot h^{-1}$) and remifentanil (0.2 $\mu g\ kg^{-1}\cdot min^{-1}$) were administered with guidance from muscle relaxation. Intermittent bolus injections of vecuronium bromide were provided to maintain muscle relaxation. Prior to closing the incision, 20 ml 0.25% ropivacaine was injected. Postoperatively, patients were transferred to the postanesthesia care unit (PACU) and then to the ward after extubation, ensuring full consciousness, and Aldrete score of ≥ 9 points.

Sample Size

Based on prior research and preliminary results, it was estimated that the incidence of PSD would be 90%, and a 30% reduction in incidence would be clinically significant. Using a two-sided test with $\alpha = 0.05$, $\beta = 0.10$ and power $(1 - \beta) = 0.90$, the calculated sample size for each group was 39 cases.

Study Protocol

TEAS was administrated a total of three times at each acupoint: (1) the night before surgery, (2) the night of the surgery and (3) the first night after surgery. TEAS was applied to three pairs of acupoints: bilateral Shenmen (HT7), Neiguan (PC6) and Zusanli (ST36) acupoints, which were identified according to the traditional anatomical localizations (Fig. 1). TEAS was performed using an electronic acupuncture apparatus (KD-2A, Beijing Yaoyang Kangda Medical Instrument Ltd. Co., Beijing, China) by trained and qualified nurses. A dense-disperse frequency of 2/10 Hz and intensity of 6–15 mA were used for 30 min. The optimal intensity was adjusted to maintain a slight twitching of the regional muscle according to the individual's maximum tolerance. In the Sham group, the patients were connected to the apparatus, and sham TEAS was provided with the same lamplight as real TEAS, but no electronic stimulation was applied.

Outcomes

Primary Outcome

The first primary outcome of the study was postoperative sleep quality, which was evaluated using both the PSQI and AIS. Sleep quality was assessed on the following days: (1) the first day before surgery (P1), (2) the first day after surgery (D1) and (3) the third day after surgery (D3). The PSQI is a widely used and validated scoring system that consists of 19 self-evaluation items and 5 other evaluation items. The score indicates the level of sleep quality and

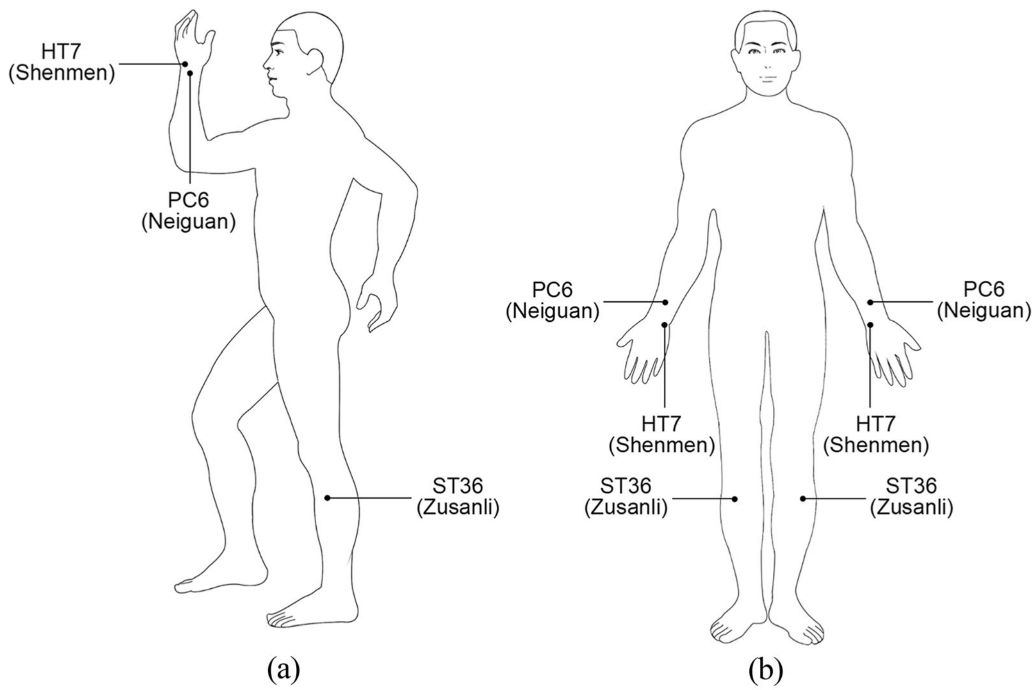


Fig. 1 Location of Shenmen (HT7), Neiguan (PC6) and Zusanli (ST36) acupoints. **a** Lateral view, **b** front view

severity of the sleep disorder [28]. The AIS is a self-assessed psychometric instrument that quantifies sleep difficulty based on the ICD-10 criteria and includes eight evaluation items [29].

Secondary Outcomes

The secondary outcomes include visual analog scale (VAS) scores at 24 h, 48 h and 72 h after surgery, cumulative doses of additional rescue analgesia, abdominal distension, dizziness, postoperative nausea and vomiting (PONV), and postoperative pulmonary complications (POPC) within 72 h after surgery.

Blood Sample Analysis

The levels of Nrf2, glutathione peroxidase 3 (GPX3), SOD and cortisol (COR) were measured on the first day before surgery (P1), 0.5 h postoperatively on the day of surgery (D0), the first day after surgery (D1) and the third day after surgery (D3). The levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10) were measured on the first day before surgery (P1) and the first, third and fifth days after surgery (D1, D3 and D5). The blood samples were measured with ELISA kits (Cloud-Clone Corp., Wuhan, China) in accordance with the manufacturer's instructions.

Statistical Analysis

The data were analyzed using SPSS 23.0 and GraphPad Prism 8.0 software. Measurement data were expressed as mean ± standard deviation (SD). Comparisons between two groups were performed using Student's *t* test. Continuous data were analyzed using one- or two-way analysis of variance, as appropriate. Categorical data were analyzed using the chi-square or Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

We assessed 98 patients for eligibility to participate in this study initially. Among them, seven patients did not meet the inclusion criteria, and three declined to participate. The remaining 88 patients were enrolled in the study. Later, three patients from the TEAS group and two from the

Sham group were excluded because of a protocol breach. In total, 83 patients completed the study, and their data were included in the analysis. The recruitment and follow-up of the trial participants are presented in Fig. 2.

Characteristics of Study Population

There was no significant difference in demographics, ASA, TNM staging, duration of surgery and anesthesia, intraoperative high/low blood pressure times, intraoperative fluid administration, intraoperative blood loss, urine output and time to first postoperative flatus between the two groups (Table 1, $P > 0.05$).

Primary Outcomes

Perioperative Sleep Quality

There was no significant difference in PSQI and AIS scores between the TEAS and Sham groups at P1 ($P > 0.05$, respectively). However, the PSQI and AIS scores in the two groups significantly increased at D1 and D3 ($P < 0.05$, respectively). Patients in the TEAS group had significantly lower PSQI and AIS scores than those in the Sham group at D1 and D3 ($P < 0.05$, respectively, Fig. 3a, b).

Secondary Outcomes

The TEAS group had significantly lower VAS scores during activity than the Sham group at 24, 48 and 72 h after surgery ($P < 0.05$, respectively, Fig. 4b). However, there was no significant difference in VAS scores at rest between the two groups 72 h after surgery ($P > 0.05$, Fig. 4a). These results indicated that TEAS may ameliorate pain during activity but not at rest.

Compared to the Sham group, the TEAS group had a significantly lower cumulative number of additional doses of rescue analgesia ($P = 0.011$). Additionally, the incidences of abdominal distension and PONV were significantly higher in the Sham group than in the TEAS group ($P = 0.009$ and $P = 0.004$, respectively). However, there was no significant

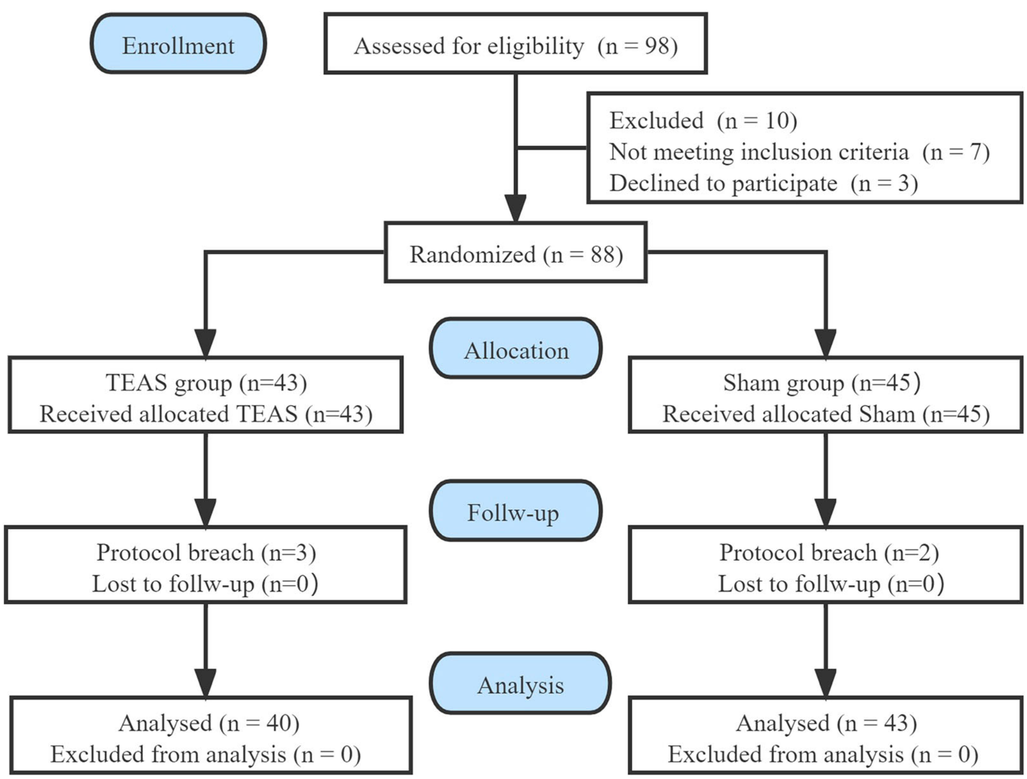


Fig. 2 CONSORT diagram for patients enrolled in the study. *TEAS* transcutaneous electrical acupoint stimulation

Table 1 Baseline patient characteristics and operative details

Characteristic	TEAS group (*n* = 40)	Sham group (*n* = 43)	*P* value
Age (year, mean ± SD)	58.20 ± 7.90	60.44 ± 9.64	0.252
BMI (kg/m^2, mean ± SD)	23.87 ± 2.85	23.73 ± 2.37	0.809
Education level (*n* (%))			
Primary education	9 (22.5%)	7 (16.3%)	0.623
Secondary education	21 (52.5%)	27 (62.8%)	
Tertiary education	10(25.0%)	9 (20.9%)	
Motion sickness (*n* (%))	3 (7.5%)	5 (11.6%)	0.524
ASA score (*n* (%))			
I	0 (0.0%)	0 (0.0%)	0.062
II	34 (85.0%)	29 (67.4%)	
III	6 (15.0%)	14 (32.6%)	
TNM staging (*n* (%))			
I	16 (40.0%)	12 (27.9%)	0.412
II	8 (20.0%)	13 (30.2%)	
III	16 (40.0%)	18 (41.9%)	
Duration of surgery (min, mean ± SD)	254.63 ± 62.57	239.53 ± 71.30	0.310
Duration of anesthesia (min, mean ± SD)	272.63 ± 59.45	254.21 ± 69.14	0.198
Intraoperative high/low blood pressure times (*n* (%))	0.58 ± 1.06	0.65 ± 1.11	0.750
Intraoperative fluid input volume (ml)	2307.75 ± 787.99	2137.67 ± 799.17	0.332
Intraoperative blood loss (ml)	61.00 ± 26.10	72.79 ± 33.48	0.079
Urine output (ml)	642.50 ± 305.62	593.49 ± 330.89	0.486
Time to first postoperative flatus (h, mean ± SD)	54.57 ± 16.62	60.70 ± 19.10	0.124
Postoperative hospitalizations (days, mean ± SD)	8.60 ± 3.86	8.65 ± 3.47	0.949

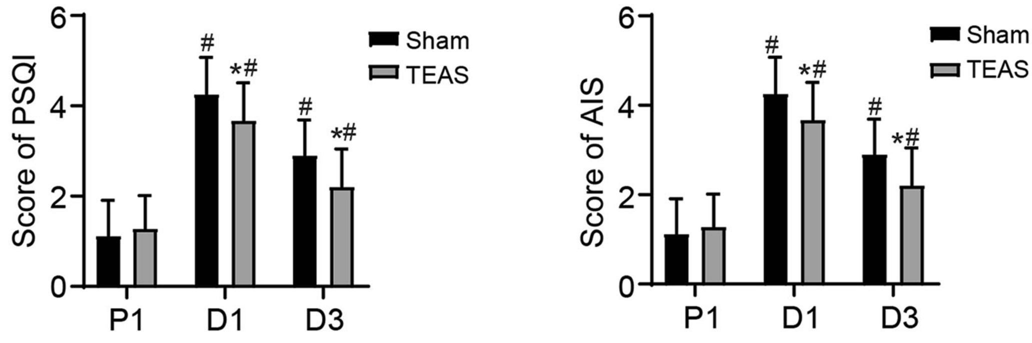
Values are presented as mean ± SD or *n* (%)
TEAS transcutaneous electrical acupoint stimulation, *SD* standard deviation, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *TNM* tumor-node-metastasis

difference in the incidences of dizziness or POPC between the two groups ($P = 0.231$ and $P = 0.175$, respectively, Table 2).

Blood Sample Biomarkers

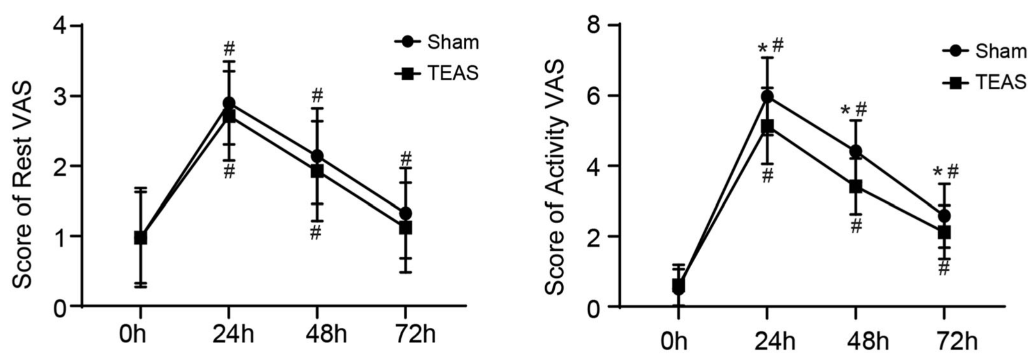
Compared to the Sham group, the TEAS group had significantly lower levels of IL-6 at D1, D3 and D5 ($P < 0.05$), while serum levels of TNF-α and IL-10 at D1, D3 and D5 were not significantly different ($P > 0.05$). The mean values of TNF-α and IL-10 in the TEAS group were lower than those in the Sham group at these points (Table 3).

As presented in Table 4, the TEAS group had higher concentrations of Nrf2, GPX3, SOD and COR compared to the Sham group after D1 ($P < 0.05$). Moreover, the serum levels of Nrf2, SOD and COR in the TEAS group were higher at



(a) (b)

Fig. 3 PSQI and AIS scores in the two groups. **a** PSQI, **b** AIS. *TEAS* transcutaneous electrical acupoint stimulation, *PSQI* Pittsburgh Sleep Quality Index, *AIS* Athens Insomnia Scale, *P1* first day before surgery, *D1* first day after surgery, *D3* third day after surgery. Data are presented as mean ± standard deviation. #$P < 0.05$ versus P1; *$P < 0.05$ versus the Sham group



(a) (b)

Fig. 4 Rest VAS and activity VAS scores in the two groups. **a** Rest VAS, **b** activity VAS. *TEAS* transcutaneous electrical acupoint stimulation, *VAS* visual analog scale. Data are presented as mean ± standard deviation. #$P < 0.05$ versus 0 h; *$P < 0.05$ versus the Sham group

D0 than those in the Sham group ($P < 0.05$) (Table 4).

DISCUSSION

In this study, we found that TEAS reduced PSD and improved sleep quality during the perioperative period in patients undergoing laparoscopic GI tumor resection. The underlying mechanism may be related to activation of the Nrf2 signal pathway.

PSD is a common issue that is often observed in surgical patients because of tissue trauma, anesthesia and the hospital environment [30]. Postoperative poor sleep quality worsens cognitive function and delays the recovery process [31]. Additionally, it can also trigger stress and immune inflammatory responses as well as postoperative pain. While pharmacological measures can improve sleep quality, they are not always satisfactory and may cause adverse effects, such as memory loss, disorientation, dizziness and falls [32]. Nonpharmacological therapy in Traditional Chinese Medicine (TCM) often uses acupuncture to treat insomnia [33], making it a popular research topic. TEAS is a new derivative of traditional acupuncture or

Table 2 Rescue analgesia and adverse events 72 h after surgery between the TEAS and Sham groups

Characteristic	TEAS group (n = 40)	Sham group (n = 43)	*P* value
Cumulative number of rescue analgesia (number, mean ± SD)	0.53 ± 0.55	0.98 ± 0.96	0.011*
Adverse events 72 h after surgery			
Abdominal distension (n (%))	11(27.5%)	24 (55.8%)	0.009*
Dizziness (n (%))	10(25.0%)	16(37.2%)	0.231
PONV (n (%))	6 (15.0%)	19 (44.2%)	0.004*
POPC (n (%))	7 (17.5%)	13(30.2%)	0.175

Values are presented as mean ± SD or n (%)
TEAS transcutaneous electrical acupoint stimulation, *SD* standard deviation, *VAS* visual analog scale, *POPC* postoperative pulmonary complications, *PONV* postoperative nausea and vomiting
*$P < 0.05$ versus the Sham group

Table 3 Serum levels of inflammatory cytokines in the TEAS and Sham groups

Characteristic	TEAS group (n = 40)	Sham group (n = 43)	*P* value
TNF-α (pg/ml, mean ± SD)			
P1	4.32 ± 3.72	3.93 ± 4.14	0.670
D1	13.81 ± 8.80	16.62 ± 9.84	0.211
D3	12.66 ± 6.34	13.99 ± 7.38	0.435
D5	3.76 ± 2.55	4.90 ± 4.55	0.184
IL-6 (pg/ml, mean ± SD)			
P1	3.27 ± 2.54	3.26 ± 2.06	0.995
D1	10.65 ± 4.94	15.59 ± 10.54	0.022*
D3	8.83 ± 3.72	14.19 ± 14.00	0.037*
D5	5.58 ± 4.01	11.16 ± 15.67	0.042*
IL-10 (pg/ml, mean ± SD)			
P1	2.31 ± 1.39	2.39 ± 1.90	0.830
D1	10.11 ± 8.35	11.81 ± 5.97	0.325
D3	8.10 ± 6.41	9.95 ± 5.47	0.204
D5	2.63 ± 1.43	3.21 ± 2.54	0.219

Values are presented as mean ± SD
TEAS transcutaneous electrical acupoint stimulation, *SD* standard deviation, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *IL-10* interleukin-10, *P1* first day before surgery, *D1* first day after surgery, *D3* third day after surgery, *D5* fifth day after surgery
*$P < 0.05$ versus the Sham group

electroacupuncture (EA) that may be a viable way to improve the sleep quality after surgery because of its potential to reduce pain and injury, lower infection incidence and improve patient tolerance. Some studies have demonstrated that TEAS can improve sleep quality after video-assisted thoracoscopic surgery and enhance recovery after laparoscopic gastric cancer surgery [34, 35]. However, the impacts of TEAS on postoperative GI cancer patients and its underlying mechanism are still unclear. Our study found that administering TEAS during the perioperative period was associated with better subjective sleep quality and reduced postoperative pain. Moreover, we discovered that TEAS treatment improved sleep quality partly by regulating the Nrf2/antioxidant response element (ARE) signaling pathway.

Postoperative factors, particularly pain, are associated with the development of sleep disturbances [36, 37]. Studies have shown that postoperative pain and sleep disturbance can have a reciprocal relationship. Pain can cause prolonged sleep latency and reduce total sleep time, while sleep disturbances can also increase pain sensitivity and lower pain thresholds [38, 39]. The most effective way to improve sleep quality and promote recovery after surgery is through adequate analgesia [8]. Multimodal

Table 4 Comparison of peripheral blood biomarkers of oxidative stress between the TEAS and Sham groups

Characteristic	TEAS group (n = 40)	Sham group (n = 43)	P value
Nrf2 (ng/ml, mean ± SD)			
P1	0.29 ± 0.16	0.29 ± 0.12	0.890
D0	1.18 ± 2.85	0.31 ± 0.15	0.049*
D1	1.16 ± 2.80	0.29 ± 0.12	0.047*
D3	0.39 ± 0.26	0.29 ± 0.12	0.039*
GPX3 (ng/ml, mean ± SD)			
P1	10,056.28 ± 6000.47	10,035.88 ± 5431.14	0.998
D0	14,916.37 ± 11,914.03	10,644.17 ± 6188.44	0.054
D1	14,374.61 ± 6061.14	10,846.83 ± 5865.99	0.016*
D3	13,212.81 ± 5575.85	9942.25 ± 5323.79	0.021*
SOD (ng/ml, mean ± SD)			
P1	68.17 ± 23.92	68.89 ± 15.25	0.886
D0	85.36 ± 27.52	73.51 ± 20.18	0.044*
D1	81.29 ± 22.18	69.21 ± 22.41	0.034*
D3	77.73 ± 22.43	67.99 ± 13.18	0.040*
COR (μg/dl, mean ± SD)			
P1	30.62 ± 19.22	30.22 ± 17.23	0.921
D0	26.25 ± 10.22	31.93 ± 12.94	0.038*
D1	34.40 ± 15.74	43.22 ± 16.15	0.022*
D3	31.20 ± 13.28	37.90 ± 13.94	0.037*

Values are presented as mean ± SD
TEAS transcutaneous electrical acupoint stimulation, *SD* standard deviation, *Nrf2* nuclear factor erythroid 2-related factor 2, *GPX3* glutathione peroxidase 3, *SOD* superoxide dismutase, *COR* cortisol, *P1* first day before surgery, *D0* 0.5 h postoperatively on the day of surgery, *D1* first day after surgery, *D3* third day after surgery
*$P < 0.05$ versus the Sham group

analgesia, which includes both opioid and non-opioid treatments, has been used to prevent and treat pain after major abdominal surgery. However, it is important to acknowledge that this approach may also have side effects, risks and limitations that cannot be entirely avoided [40].

In our study, the VAS scores and reduction in analgesic requirement 72 h after surgery revealed that perioperative TEAS played a potential important role in reducing acute postoperative pain. We also found that the TEAS group had lower scores on the PSQI and AIS, indicating that TEAS treatment may improve sleep quality during the postoperative period. Interestingly, repeated TEAS lowered pain intensity during activity, but not at rest. Our results were consistent with a previous trail, which suggested that transcutaneous electrical nerve stimulation could reduce pain intensity during activities such as walking and deep breathing, but has no effect on pain at rest [41].

We attributed this difference to the influence of different pain mechanisms during activity versus rest [42, 43].

Surgery can induce both local and systemic inflammation [44], and persistent sleep disturbance can lead to prolonged activation of the inflammatory cytokines and chemokines, which may be harmful to the body. Inflammatory cytokines can communicate with the central nervous system (CNS) through neural and cellular mechanisms, resulting in altered CNS activity and disrupted sleep regulation [45–47]. Preclinical studies have shown that sleep deprivation or disturbance can induce the release of inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and TNF-a in peripheral blood and various brain regions [48–50]. In animal models, interleukin-4 (IL-4) and IL-10, which are considered to be anti-inflammatory cytokines, have been found to reduce the amount of non-rapid eye movement (NREM) sleep [51]. This is consistent with evidence that the antagonism of inflammatory cytokines can also affect sleep in animals [52].

Our study found that the TEAS group had significantly lowered levels of IL-6 in the peripheral blood on D1, D3 and D5 compared with the Sham group, suggesting that TEAS may regulate the inflammatory response of the body. Interestingly, there was no significant difference in TNF-α levels between the two groups, although the mean levels of TNF-α in the TEAS group were lower than those of the Sham group at each time point after surgery, suggesting that TEAS may have some inhibitory effect on TNF-α. This might be because TNF-α reached its peak level in plasma 1.5 h after the onset of inflammatory reaction [53], and the first postoperative blood sample in our study was collected 24 h after surgery, which may have affected our findings. More clinical samples are needed to confirm this. Our study also found that perioperative TEAS did not affect peripheral blood IL-10 levels after surgery, and there was no consistent result on the effect of acupuncture on IL-10 in the literature. Previous studies have reported that electroacupuncture can increase the concentration of IL-10 in colonic tissue of mice with colitis and reduce the concentration of inducible nitric oxide synthase (iNOS), exerting an anti-inflammatory effect [54]. However, other studies have reported the opposite effect [55]. Additionally, it was found that electroacupuncture had no significant effect on peripheral blood IL-10 levels at all surgical time points in patients undergoing supratentorial craniotomy under general anesthesia [56]. We speculated that the different effects of acupuncture on IL-10 in peripheral blood reported in the literature may be related to different experimental conditions and acupoints selected. Further research is needed to confirm this.

Numerous clinical and experimental studies have shown that stress is associated with poor sleep quality [57, 58]. Traumatic stress leads to the production of excess reactive oxygen species (ROS), causing oxidative stress that can lead to sleep disturbances [59]. Moreover, oxidative stress is the major pathological mechanism that causes secondary brain injury [60]. Our study found that levels of Nrf2, GPX3 and SOD were higher in the TEAS group on the first and third day after surgery compared to the Sham group, while the COR level was lower. These findings suggested that TEAS treatment could activate Nrf2, followed by elevation of antioxidative factors such as SOD and GPX3 and downregulation of COR expression. Furthermore, our study found that sleep quality was improved in the TEAS group, which may be associated with the activation of the Nrf2/ARE signal pathway and reduction of stress response.

In addition, studies have shown that oxidative stress-induced accumulation of ROS plays a crucial role in the inflammatory response by activating proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6 and TNF-α [61, 62]. Depletion of Nrf2 in human monocytes has been reported to enhance TNF-induced inflammatory cytokines [63]. Activation of Nrf2 has been shown to prevent lipopolysaccharide (LPS)-induced transcriptional upregulation of pro-inflammatory cytokines, including IL-6 and IL-1β [64]. Furthermore, elimination of ROS suppresses inflammation in Nrf2-deficient mice [65]. Our study also showed that TEAS downregulated the expression of IL-6 in the early postoperative period, which may be related to the activation of Nrf2/ARE pathway.

We found that the TEAS group had significantly lower incidence of abdominal distension and PONV, which is consistent with findings from several previous studies [34, 35]. One possible mechanism for this effect is that acupuncture may increase the release of β-endorphin and promote the secretion of corticosteroids in the brain. Additionally, the release of endogenous glucocorticoid may reduce the incidence of PONV and mitigate the side effect of exogenous glucocorticoids [66]. However, we did not observe any benefits of TEAS for dizziness or POPC in our study.

There were some limitations to this study. Although the Nrf2/ARE signaling pathway played a crucial role in physiological activity in humans, further studies are needed to confirm the relationship between TEAS and other downstream target genes of this pathway. In addition, more large-scale and multicenter clinical research studies are warranted to confirm the effect of TEAS in patients undergoing laparoscopic GI tumor resection in the future.

CONCLUSION

In conclusion, our study suggested that TEAS could be an effective method to improve sleep quality, alleviate postoperative pain, suppress inflammation and decrease postoperative complications in patients undergoing laparoscopic GI tumor resection. The activation of the Nrf2/ARE signaling pathway may play a role in mediating the therapeutic effect of TEAS. However, further studies are necessary to fully elucidate the underlying mechanisms of TEAS on postoperative sleep quality in patients undergoing laparoscopic GI tumor surgery and to confirm our findings. These results provided new insights into the potential benefits of TEAS for postoperative recovery and supported its use as an adjuvant therapy in clinical practice.

ACKNOWLEDGEMENTS

We thank all the patients who participated in this study.

Funding. This study was supported by Project of National Clinical Research Base of Traditional Chinese Medicine in Jiangsu Province, China (JD2022SZ18), Xuzhou Science and Technology Innovation Project (KC19023, KC22181) and Key Subject Project of Jiangsu Province: Surgery of Traditional Chinese Medicine (js2251). The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Author Contributions. Conceptualization: Jun Wang, Fei-Fei Lu, Hong-Guang Quan, Zhi-Wei Jiang; Methodology: Jun Wang, Fei-Fei Lu; Formal analysis and investigation: Jun Wang, Fei-Fei Lu, Miao-Miao Ge, Li-Wen Wang, Wen-Zhuo Zhang; Writing–original draft preparation: Jun Wang, Fei-Fei Lu, Miao-Miao Ge; Writing–review and editing: Jun Wang, Fei-Fei Lu, Miao-Miao Ge, Fei-Long Ning, Zhi-Wei Jiang; Funding acquisition: Jun Wang, Fei-Fei Lu, Zhi-Wei Jiang; Resources: Gang Wang, Guan-Wen Gong, Xin-Xin Liu, Bao-He Chen, Yang Liu; Supervision: Hong-Guang Quan, Zhi-Wei Jiang. All authors reviewed the manuscript.

Disclosures. Jun Wang, Fei-Fei Lu, Miao-Miao Ge, Li-Wen Wang, Gang Wang, Guan-Wen Gong, Xin-Xin Liu, Wen-Zhuo Zhang, Fei-Long Ning, Bao-He Chen, Yang Liu, Hong-Guang Quan and Zhi-Wei Jiang declare that they have no conflict of interest.

Compliance with Ethics Guidelines. This study was approved by the ethics committee of Affiliated Hospital of Nanjing University of Chinese Medicine (no. 2021NL-199–02), Xuzhou Traditional Chinese Medicine Hospital Affiliated to Nanjing University of Chinese Medicine (no. 09/2020) and registered in the Chinese clinical trial registry (ChiCTR2100054971). Each participant provided written informed consent before initiating any study-related procedures. This study

was conducted in accordance with the Declaration of Helsinki.

Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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