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Research article

Perioperative transcutaneous electrical acupoint stimulations as part of an enhanced recovery after surgery protocol for living donors undergoing nephrectomy: A randomized, controlled clinical trial

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ABSTRACT

Objective: Living kidney donors (LKDs) experience perioperative anxiety. We designed the following study to evaluate the anxiolytic effect of transcutaneous electrical acupoint stimulation (TEAS) during the perioperative period in a group of LKDs undergoing laparotomy nephrectomy.
Methods: LKDs were randomly assigned to either the TEAS or control group. Participants in the TEAS group received 30min of intervention (6–15 mA, 2–100 Hz), at Yintang (EX-HN-3), bilateral Taichong (LR3) and Neiguan (PC6) one day before surgery (D_0), before induction of anesthesia (D_1) and one day after surgery (D_2). The participants in the control group received the same placement of electrodes but without electrical stimulation. Venous blood was collected before each intervention. Anxiety levels and recovery profiles were recorded.
Results: LKDs in the TEAS group had lower anxiety level than those in the control group at D_1, D_2 and three days after surgery (D_3). The percentage differences were: 33.3%, 25.0%, and 22.2%; [95% confidence interval (CI), (−55.1%, −11.6%), (−47.4%, −2.6%), and (−42.3%, −2.2%); $P = 0.005$, $P = 0.034$, and $P = 0.035$; respectively]. LKDs who received TEAS had better sleep quality and short-term recovery profiles than those in the control group. The plasma levels of 5-hydroxytryptamine (5-HT) and melatonin (MT) in the TEAS group were significantly higher than those in the control group at D_1 and D_2 (5-HT: $P = 0.001$, and $P < 0.001$; MT: $P = 0.006$, and $P = 0.001$). At the 3-month follow up, fewer LKDs in the TEAS group had incisional pain when compared to the control group ($P = 0.032$).
Conclusions: Perioperative TEAS decreased perioperative anxiety and facilitated postoperative recovery in the LKDs, and potential decreased the development of chronic pain. Trial Registration: Registered at ChiCTR2000029891, http://www.chictr.org.cn/listbycreater.aspx.

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1. Background

Kidney transplantation has significantly improved the life expectancy and quality of life in patients with end-stage renal disease. Because of the scarcity of cadaver donors, living kidney donations have gradually increased worldwide. Current guidelines endorse selection of donors in good health [1]. However, many living kidney donors (LKDs) confront perioperative psychological and physical stresses similar to those experienced by general surgical patients [2,3]. Previous studies indicated that approximately 6%–67% of LKDs suffered perioperative mental distress, but only 10% of them sought psychological consultation [4–6].

Anxiety is known to lead to adverse consequences during the perioperative period [7,8]. Hence, it is important to decrease anxiety in these LKDs. Recent anesthesia practice has focused on utilizing multi-modal analgesia, regional techniques and non-pharmacologic interventions to facilitate the recovery of surgical patients [9,10]. Transcutaneous electrical acupoint stimulation (TEAS) is a noninvasive form of acupuncture interventions which applies electrical stimulation onto acupuncture points using transcutaneous electrodes. TEAS has been used successfully in reducing anxiety [11] and is well-received by patients without adverse effects [12].

We designed this randomized-controlled clinical trial (RCT) to evaluate the anxiolytic effect of perioperative TEAS in a group of LKDs undergoing laparotomy nephrectomy.

2. Material and methods

The Clinical Trial Ethics Committee of the First Affiliated Hospital of University of Sciences and Technology (USTC-Hefei, Anhui) of China approved this study protocol. This protocol was registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/listbycreater.aspx; ChiCTR2000029891; principal investigator: Juan Li; date of registration: February 16, 2020). Registration was completed before initiating enrollment. Potential candidates were identified from the operating room schedule at Anhui Provincial Hospital. Prior to the scheduled surgery, a research assistant met with these candidates and provided them with both a standard verbal[2] and a written description of this study. All participants signed informed consent forms prior to participating in this study. The report of this study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines [13] and adhered to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [14].

All participants underwent nephrectomy, through laparotomy, performed by the same surgical team in the period from September 2020 to December 2020. The inclusion criteria were as follows: (1) age 18–65 years, (2) body mass index (BMI) 18–30 kg/m^2, (3) relatively healthy, American Society of Anesthesiologists physical status I-II (ASA I-II), (4) able to read and sign consent, and (5) no prior acupuncture treatment. The exclusion criteria were as follows: (1) history of acupuncture treatment or current treatment with acupuncture, (2) significant medical co-morbidity, ASA III-IV, (3) pacemaker placement, (4) infection or unhealed wound near the chosen acupoints, (6) current use of sedatives, analgesics, or anti-anxiety drugs, (7) current psychological/psychiatric treatment, and (8) inability to read and sign consent.

2.1. TEAS and control interventions

Based on Traditional Chinese Medicine (TCM) and available clinical trials, five acupoints [Yingtang (EX-HN3), bilateral Taichong (LR3) [15,16] and Neiguan (PC6) [15,17] [please refer to Fig. S1]; and foot note[3] were selected for TEAS intervention aimed at reducing patient anxiety. TEAS was performed for 30 min at one day before surgery (D_0), before the induction of anesthesia (D_1), and one day after surgery (D_2) i.e., a total of three treatment over a three-day period. The first author YH, who has extensive acupuncture training and who has been in practice for 2 years, performed the assigned TEAS intervention on every LKD based on this/her group assignment. The group assignment was written in a piece of paper and placed in a sealed envelope. All participants were asked to remain in a supine position for and during the intervention. The skin at the selected acupoints and area was cleaned and prepped with 75% isopropyl alcohol. The surface electrodes (3 × 3cm) (see supplement) were placed onto these acupoints. Yingtang point pairing electrode patch was placed on the skin located at right mid-subclavicular area. All electrodes were then connected to a Hwato electronic stimulator (model SDZ-V, Suzhou Medical Appliances Co. Ltd, Suzhou, China). The mode of electrical stimulation was dense-disperse, alternated 2Hz/100 Hz frequencies; the intensity was adjusted according to individual tolerance, generally between 6 and 15 mA. Participants in TEAS could sense vibration following activation of the stimulator for a total of 30 min [18]. Participants assigned to the control group had the same electrode placements, but the stimulator was disabled without any transmission of electricity. This method had been used to blind the participants successfully in a previous study [19].

2.2. Intraoperative and postoperative management

All participants received the same intraoperative and postoperative management. On the day of surgery, all LKDs received intravenous (IV) pantoprazole (80 mg) and methylprednisolone (40 mg) preoperatively. Once ASA standard monitors and a bispectral

[2] "We are going to test the effects of an acupuncture-like electrical stimulations being integrated into routine perioperative care and the intensity of electrical stimulation is very low so you may or may not be able feel the stimulations."

[3] Yintang (EX-HN3, located in the root of the nose, and between the eyebrows.) and bilateral Neiguan (PC6, located 2 cun* up the transverse wrist, between the palmaris longus tendon and the radial carpal flexor tendon.) and Taichong (LR3, located in the depression of the first two metatarsal unions). * Unit of Chinese measurement.

index monitor (BIS) were placed, general anesthesia was induced with IV sufentanil 0.3–0.5 μg kg^{-1} and propofol 0.2–0.3 mg kg^{-1}. When the BIS number reached between 40 and 60, IV cisatracurium 0.2–0.3 mg kg^{-1} was administered and a laryngeal mask airway (Male: I-gel® 4, Female: I-gel® 3, Berman, Germany) was placed. All participants received volume-controlled mechanical ventilation with tidal volume of 8 ml kg^{-1} body weight. Bilateral transversus abdominis plane block (TAP block) was performed under ultrasound guidance and a total of 30 ml of 0.375% ropivacaine was injected via 0.7 × 90 mm block needles (15 ml each side). All LKDs received continuous target-controlled infusion (TCI) of propofol (modified Marsh model, Cp 2.0–3.0 μg ml^{-1}) and remifentanil (modified Marsh model, Cp 2.0–3.0 ng ml^{-1}). In addition, 1% sevoflurane was used to maintain the BIS between 40 and 60. Based on the standard protocol, IV phenylephrine and/or atropine were administered to ensure adequate blood perfusion to the kidney at the time of harvest. Intravenous muscle relaxant (IV cisatracurium 0.05–1 mg kg^{-1}) was administered when T1 twitch height reached 25% of baseline detected by a Train of Four (TOF) monitor (Veryark-TOF, Guangxi, China). Sevoflurane and TCI (propofol and remifentanil mixture) were discontinued 30 min before the end of surgery. Fifteen minutes before the end of surgery, IV droperidol (1 mg) and flurbiprofen (100 mg) were administered to prevent postoperative nausea and vomiting (PONV) and pain. At the end of surgery, IV 50 μg kg^{-1} neostigmine and 20 μg kg^{-1} atropine were administered to reverse the effect of muscle relaxant. Participants were transferred to the Post Anesthesia Care Unit (PACU), and I-gel® was removed when the participant met the clinical criteria [20]. A patient-controlled intravenous analgesia pump [sufentanil (1 μg ml^{-1}), azasetron (0.4 mg ml^{-1}) and droperidol (0.01 mg ml^{-1}); flow rate (2 ml h^{-1}); bolus (4 ml); lock time (30min)] was connected to the PACU for 48 h postoperatively. At D_3, if a visual analogue scale–pain (VAS-P) score ≧ 30 and 50 mg of IV flurbiprofen was used as rescue analgesic.

2.3. Outcomes measurements (please refer to Table 1)

(a) *Hospital Anxiety and Depression Scale - Anxiety (HADS-A):* HADS-A is a reliable and validated instrument for assessing the psychological status of non-psychiatric inpatients. It consists of 7 items for anxiety. Items are classified using a 4-point Likert scale with scores from 0 to 3 and the total scores for anxiety ranging from 0 to 21 [21]. For the Chinese version of HADS-A, please refer to the Appendix in the supplemental document.

(b) *The Insomnia Severity Index (ISI):* The ISI is a 7-items self-reporting questionnaire assessing the nature, severity, and impact of insomnia. The dimensions evaluated are severity of sleep onset, sleep maintenance, and early morning awakening problem, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problem by others and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item, and a score higher than 14 has been accepted as the optimal cut off for insomnia [22].

(c) *The Quality of Recovery-15(QoR-15):* The QoR-15 scale is a validated measure to evaluate the quality of a patient's recovery. The scale consists of 15 items assessing patient-reported health status in five domains: pain intensity, physical independence, physical satisfaction, psychological and emotional state. Each item is rated on a scale of 0–10; 150 is the maximum score and 0 is the minimum score. The quality of recovery has been classified based on the scores assessed by QoR-15 into excellent, good, moderate, and poor; they are 136–150, 122–135, 90–121, and 0–89, respectively [23].

(d) *Visual Analogue Scale for Pain (VAS-P):* The VAS-P scale is a unidimensional measure of pain intensity. It consists of a line with left side "0" representing "no pain" and right side "100" representing "extreme pain".

(e) *Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS):* LANSS comprises of a 7 items pain scale including 5 items for the sensory descriptors and 2 items for sensory examination. The primary purpose of this test is to assess whether the pain experienced is predominantly caused by nerve damage or not. The LANSS scale is the only scale with validity for discriminating the origin of pain (neuropathic vs. nociceptive) [24].

(f) *Blood Samples for Biomarkers:* Three milliliter of venous blood samples were collected in anticoagulant tubes before every TEAS treatment. Blood samples were immediately centrifuged at 4000r min^{-1} for 10min, and the plasma was transferred to Eppendorf tubes and stored in a $-80\ ^{\circ}C$ freezer until analyses. Concentrations of plasma 5-hydroxytryptamine (5-HT), melatonin (MT), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) were measured using commercial ELISA kits (Hefei Nuozhuo Biological Technology). These biomarkers were chosen because 5-HT and MT are neurotransmitters closely related to anxiety and the sleep cycle [25,26]. IL-1β and TNF-α are pro-inflammatory cytokines closely related to the intensity of pain and pathogenesis of chronic pain [27].

2.4. Primary outcome and recovery profiles

The primary outcome was the difference of anxiety levels in LKDs who received or did not receive TEAS. We also collected recovery profiles including sleep quality (ISI) and postoperative recovery (e.g., incidence of PONV, usage of rescue analgesics, severity of postoperative pain, postoperative recovery index, etc.). In addition, blood samples were collected at D_0, D_1, and D_2 to determine plasma levels of biomarkers (5-HT, melatonin, IL-1β and TNF-α).

2.5. Sample size calculation

Using PASS 15.0 (NCC, Kaysville, Utah, United States), the required sample size was calculated based on existing data that indicates approximately 65% of LKDs experienced anxiety [6] and nearly 32% of surgical patients had anxiety despite TEAS treatment [28]. Assuming a two-sided type I error (α) of 0.05 and a power of 80%, a total of 66 LKDs were needed. To allow for a 10% drop out rate, the sample size needed to be 74 LKDs.

2.6. Randomization and blinding

The participants were randomized into either TEAS (n = 37) or control (n = 37) group in a 1:1 ratio based on a randomization number generated by an independent researcher using IBM®SPSS 25.0 (Armonk, New York USA). The randomization number was placed in a sealed envelope and was not revealed until the first intervention. Only the acupuncturist performing the intervention knew which intervention the assigned number represented. No participant, surgeon, anesthesiologist, data collector, or outcome assessor knew the allocation of participants.

2.7. Statistical analysis

Categorical variables were expressed as n (%) and were analyzed using the χ^2 test or Fisher's exact test. Continuous variables were presented as means ± standard deviations (SD) or median [interquartile range (IQR)] and the Shapiro-Wilk test was used to verify the normality of the distribution. Continuous variables were compared using the independent sample *t*-test or Wilcoxon rank-sum test. Rank variables were compared using Wilcoxon rank-sum test. The Hodges-Lehmann estimator was used to calculate the median and 95% CI differences. Two-way repeated-measurements ANOVA was used to determine the effect of factors at different time points. Bonferroni correction was applied. A logistic regression model was used to assess whether anxiety was associated with any or all plasma biomarkers tested (5-HT, MT, IL-1β and TNF-α levels). *P* values < 0.05 were considered statistically significant. All analyses were performed using IBM®SPSS 25.0 (Armonk, New York USA).

3. Results

A total of 74 LKDs were recruited but two LKDs withdrew from the study for personal reasons (Fig. 1). Therefore, only 72 LKDs completed the study and were included in the final data analyses. There were no differences in baseline characteristics between the groups (Table 2). There were also no significant differences in the duration of surgery and anesthesia, time to removal of LMA, intraoperative consumption of remifentanil and propofol, blood loss and urine output between the groups (Table 3).

3.1. Primary outcome

At D_0 and D_4 (at the time of discharge), there were no differences in anxiety levels between the TEAS and control groups. However,

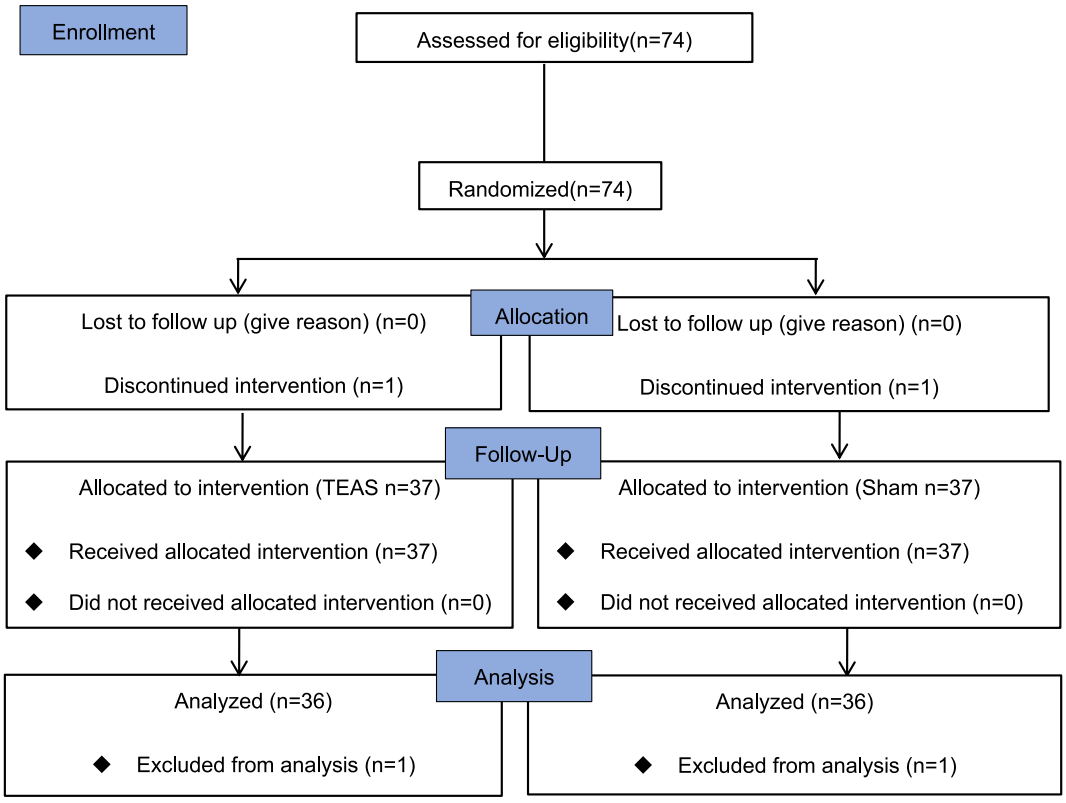

Fig. 1. Study flow diagram.

anxiety levels of the LKDs were significantly lower in the TEAS groups than those of the control group at D_1, D_2, and three days after surgery (D_3), please refer to Table 4 and Table S1.

3.2. Recovery profiles

There were no differences in sleep quality between the two groups at D_0 and D_4 (Table 4). All LKDs regardless of groups had worsening of sleep quality immediately following surgery as compared to before surgery (D_0) but LKDs in the TEAS group had significantly better quality of sleep than those in the control group at D_2 and D_3 ($P = 0.025$, and $P = 0.030$, respectively, Table 4). Similarly, there were no differences in plasma levels of 5-HT and MT between the two groups at baseline. Interestingly, both 5-HT and MT levels increase in the TEAS group and reaches statistically significance at D_1 {5-HT:589.1 ± 92.6 vs 485.7 ± 95.6, differences in means: 103.5 [95% confidence interval (CI): 59.2–147.7], $P < 0.001$; MT: 11.8 ± 2.0 vs 9.5 ± 2.0, differences in means: 2.4 [95%CI: 1.4–3.3], $P < 0.001$} and D_2 {5-HT: 589.4 ± 94.0 vs 456.1 ± 71.0, differences in means: 133.4 [95% CI: 94.2, 172.5], $P < 0.001$; MT: 11.9 ± 2.3 vs 8.4 ± 1.3, differences in means: 3.5 [95%CI: 2.7, 4.4]; $P < 0.001$} as compared to those of the control group [Fig. 2(A-B)]. A logistic regression analysis revealed that plasma level of MT and anxiety were closely related (OR = 0.771,95%CI 0.609–0.977, $P = 0.031$, Table S2).

LKDs who received TEAS reported less postoperative pain than those in the control group at D_2 and D_3 but there were no significant differences in VAS-P scores between the two groups at D_4 ($P = 0.001$, $P = 0.014$, and $P = 0.145$; respectively, Table 4). Correspondingly, LKDs in the TEAS group received a lower amounts of rescue analgesics postoperatively ($P = 0.002$, Table 3). LKDs in the TEAS group experienced fewer episodes of PONV ($P = 0.023$) and earlier recovery of bowel activities ($P = 0.002$) than those of the control group (Table 3). The postoperative recovery index (QoR-15) between the TEAS and control groups indicated more LKDs in the TEAS group reported moderate level of recovery at D_2 and D_3 ($P = 0.009$, and $P = 0.001$, Table 4). However, there were no differences between the groups at D_4 ($P = 0.402$). At M_3 (3-month postoperative follow up) 16 (44.4%) LKDs in the TEAS group and 25 (69.4%) in the control group still experienced pain (VAS-P ≧30) ($P = 0.032$, Table 3). Of the LKDs that reported still having pain at M_3, 7 (19.4%) in the TEAS group and 15 (41.7%) in the control group were found to have neuropathic pain, i.e., LANSS≧12 ($P = 0.041$, Table 3).

There were no differences of IL-1β and TNF-α levels at the baseline D_0 between the two groups ($P = 0.915$, and $P = 0.594$, respectively.). However, the plasma IL-1β level was significantly suppressed in LKDs who received TEAS as compared to those did not receive TEAS at D_1 [55.9 ± 12.3 vs 63.7 ± 13.0; differences in means:7.8 (95% CI:1.8–13.7; $P = 0.011$, and at D_2 55.1 ± 15.6 vs 73.8 ± 12.9; differences in means: 18.7 (95% CI: 12.0–25.5); $P < 0.001$][Fig. 2(C)]. Similar suppression of plasma levels of TNF-α at D_1 and D_2 in LKDs who received TEAS were also detected. The differences in plasma levels of TNF-α between the two groups reached statistical significance at D_2 [54.1 ± 12.0 vs 72.1 ± 10.3; differences in means: 18.0 (95%CI: 12.8–23.3); $P < 0.001$] [Fig. 2(D)].

4. Discussion

Perioperative anxiety is common among surgical patients. More than 70% of surgical patients experience preoperative anxiety which peaks on the day of surgery [8]. It is well established that the level of anxiety correlates with postoperative complications [29]. The result of this pilot study indicated that perioperative TEAS at Ying Tang (EX-HN3), bilateral Tai Chong (LR3) and Neiguan (PC6) can reduce perioperative anxiety similar to the results seen in previous clinical studies [15,30,31].

Although the mechanism of the anxiolytic effect of TEAS is unclear, a study has shown that acupuncture regulates the release of neurotransmitters, e.g. 5-HT, enkephalin, endorphin, etc., leading to various psychological and physiological responses [32]. Indeed, a study showed that acupuncture triggered the release of 5-HT and enkephalin in patients with psychological illness [33]. However, we were not able to find a correlation between anxiety and plasma levels of 5-HT in this pilot study. Instead, we discovered there might be an association between anxiety and plasma levels of MT ($P < 0.05$). Inhalation or intravenous anesthetics may cause interruption of normal sleep-wake cycle and alter sleep quality [34]. Studies have shown that both anesthetic techniques cause a rapid decrease of MT immediately post-surgery then a gradually return to baseline [35,36]. Song et al. found perioperative TEAS improved postoperative sleep quality in a group of patients undergoing video-assisted thoracoscopic surgery [37]. Spence and colleagues found that acupuncture increased nocturnal MT secretion and reduced the level of anxiety and severity of insomnia in a group of anxious patients [38]. Huang and colleagues also demonstrated that preoperative TEAS increased plasma levels of MT in patients who received sevoflurane general anesthesia [39]. We also found that LKDs who received perioperative TEAS had better postoperative sleep quality than those in the control group. We speculated that these anti-insomnia effects of TEAS might occur through the regulation of MT

Table 1
The outcomes assessment schedule.

Assessment Schedule	D_0	D_1	D_2	D_3	D_4	M_3
Hospital Anxiety and Depression Scale-Anxiety	X	x	x	x	x	
Insomnia Severity Index	X		x	x	x	
The Quality of Recovery −15	X			x	x	
Visual Analogue Scale for Pain			x	x	x	x
Blood Sample for Biomarker	X	x	x			
LANSS						x

Abbreviations: D_0, one day before surgery; D_1, before the induction of general anesthesia; D_2, one day after surgery; D_3, three days after surgery; D_4, at the time of discharge; M_3, at 3-month after surgery; LANSS, Leeds assessment of neuropathic symptoms and signs scale.

Table 2
Patients characteristics.

Parameter	Control group (N = 36)	TEAS group (N = 36)	*P*-value
Age [yr; mean ($_{SD}$)]	54.6 (8.0)	54.0 (5.8)	0.722
Body mass index [kg m^{-2}; mean ($_{SD}$)]	24.0 (3.2)	24.1 (2.0)	0.943
Sex [n (%)]			0.306
Male	9 (25.0)	13 (36.1)	
Female	27 (75.0)	23 (63.9)	
ASA [n (%)]			0.471
Ⅰ	23 (63.9)	20 (55.6)	
Ⅱ	13 (36.1)	16 (44.4)	
Education levels [yr; n (%)]			0.617
≦6	23 (63.9)	25 (69.4)	
≧6	13 (36.1)	11 (30.6)	
Donation relationship [n (%)]			0.934
Mother	25 (69.4)	23 (63.9)	
Father	7 (19.4)	9 (25.0)	
Others	4 (11.1)	4 (11.1)	

Notes: Values are presented as means ($_{SD}$), or *n* (%).
Abbreviations: ASA, American society of anesthesiologists; SD, standard deviation.

Table 3
Intraoperative characteristics and postoperative complications.

Intraoperative and postoperative parameters	Contol group (N = 36)	TEAS Group (N = 36)	*P*-value
Intraoperative propofol [mg; median (IQR)]	550 (406, 645)	490 (430, 600)	0.417
Intraoperative remifentanil [μg; median (IQR)]	1000 (881, 1144)	950 (750, 1238)	0.572
Intraoperative bleeding [ml; median (IQR)]	175 (150, 200)	175 (150, 200)	0.087
Intraoperative urine volume [ml; median (IQR)]	1000 (600, 1200)	800 (525, 1075)	0.088
Time to safe removal of LMA [mins; median (IQR)]	35 (30, 45)	30 (20, 44)	0.421
Anesthesia time [mins; mean ($_{SD}$)]	174 (31)	167 (26)	0.305
Surgical time [mins; mean ($_{SD}$)]	146.6 (30.1)	139.4 (26.8)	0.284
PONV [n (%)]	12 (33.3)	4 (11.1)	0.023
Time to first bowel movement [days; mean ($_{SD}$)]	2.2 (0.7)	1.7 (0.6)	0.002
Rescued Analgesics [n (%)]	28 (77.8)	15 (41.7)	0.002
Pain (VAS-P ≧30) at M3 [n (%)]	25 (69.4)	16 (44.4)	0.032
LANSS≧12 at M3 [n (%)]	15 (41.7)	7 (19.4)	0.041

Notes: Values are presented as means (SD), n (%), or median (IQR).
Abbreviations: ASA, American society of anesthesiologists; LMA, laryngeal mask anesthesia; PONV, postoperative nausea and vomit; IQR, interquartile range; SD, standard deviation.

released from the central nervous system. Future studies are warranted to explore such coordination.

Continuous perioperative TEAS intervention was associated with decreased intraoperative opioid consumptions and improved postoperative recovery in a group of patients undergoing video-assisted thoracoscopic lobectomy and patients received sinusotomy [40,41]. In contrast to these studies, we did not observe any reduction in intraoperative remifentanil consumption. Because of our hospital policy, all LKDs without major complications regardless of their recovery profile can only be discharged at 12 days postoperatively, thus there were no differences in the duration of hospitalization between the two groups.

Surgery itself could lead to a host of deleterious effects e.g., inflammatory, hormonal, and genomic responses [42]. Neuroimmune-endocrine responses can adversely affect postoperative recovery [43]. We found that perioperative TEAS reduced plasma levels of proinflammatory cytokines (TNF-α and IL-1β) as compared to those in the control groups. This might explain why LKDs in the TEAS group had less postoperative pain, PONV, required a lower amounts of rescue analgesics, and had earlier recovery of bowel activities. Our study results also showed that fewer LKDs in the TEAS group had continuing pain at the 3-month follow up than those in the control group. As mentioned previously, pro-inflammatory cytokine (TNF-α and IL-1β) are found to be closely associated with the intensity of chronic pain [43]. Unfortunately, our study was not designed to confirm or deny such a correlation. Lastly, the results of this study indicated that LKDs who had received perioperative TEAS had better recovery profiles than those without perioperative TEAS, which is similar to results from a previous study conducted in a group of women undergoing laparoscopic gynecological surgery [18].

There are several limitations to this pilot study: (1) we did include a no-intervention control (standard care) group because we were concerned about the potential for causing disappointment that may result in a negative psychological impact in LKDs assigned in this group; (2) we did not include a "believing assessment test" at the inception of this study, as belief in a treatment might affect the outcomes of the treatment, (3) we did not perform the range of electrical stimulation frequencies and/or duration of TEAS that are optimal for the maximum anxiolytic effect, and (4) our sample size was small and only a single population of surgical patients was included in this study. However, the results of this study will serve as a model for future large multicenter clinical trials which may include other surgical populations, e.g., breast cancer patients, etc. In summary, perioperative TEAS was able to reduce anxiety levels

Table 4
The Comparison of HADS-A, ISI, VAS-P and QoR-15 in the two study groups.

Measurements	Control group (n = 36)	TEAS Group (n = 36)	Difference (95% CI)	*P*-value
HADS-A [scores, median, (IQR)]				
D_0	6.0 (3.0,10.0)	7.0 (6.0,10.0)	0.0 (-2.0, 3.0)	0.251
D_1	9.5 (6.3,13.0)	7.0 (6.0,8.0)	4.0 (2.0, 6.0)	<0.001
D_2	9.0 (6.3,11.0)	7.0 (7.0,8.0)	2.0 (0.0, 3.0)	0.009
D_3	7.0 (6.0,10.0)	5.0 (4.0,6.0)	4.0 (2.0, 5.0)	<0.001
D_4	4.0 (3.0,6.0)	4.0 (3.0,6.0)	0.0 (-1.0, 1.0)	0.674
ISI [scores, median,(IQR)]				
D_0	6.5 (4.0, 10.0)	7.0 (4.0, 11.0)	−0.5 (−2.0, 2.0)	0.901
D_2	16.5 (10.5, 20.5)	13.0 (7.0, 17.0)	3.5 (0.0, 6.0)	0.025
D_3	12.5 (7.0, 19.0)	8.5 (7.0, 12.0)	4.0 (0.0, 6.0)	0.030
D_4	6.5 (4.0, 8.8)	6.0 (4.0, 11.0)	0.5 (−2.0, 2.0)	0.856
VAS-P [scores, median,(IQR)]				
D_2	55.0 (40.0, 60.0)	30.0 (30.0, 47.5)	25.0 (10.0, 20.0)	0.001
D_3	40.0 (30.0, 50.0)	30.0 (30.0, 30.0)	10.0 (0.0, 10.0)	0.014
D_4	30.0 (20.0, 30.0)	30.0 (20.0, 30.0)	0.0 (0.0, 10.0)	0.145
M_3	30.0 (20.0, 40.0)	20.0 (20.0, 30.0)	10.0 (0.0, 10.0)	0.010
QoR-15 [scores; mean ($_{SD}$)]				
D_2	99.1 ± 10.0	104.5 ± 7.0	−5.4 (−9.5, −1.4)	0.009
D_3	100.9 ± 10.7	108.5 ± 7.4	−7.6 (−11.9, −3.2)	0.001
D_4	112.4 ± 11.6	114.3 ± 6.4	−1.9 (−6.3, 2.5)	0.402

Notes: Values are presented as means (SD), n (%), or median (IQR).
Abbreviations: D_0, one day before surgery; D_1, before the induction of general anesthesia; D_2, one day after surgery; D_3, three days after surgery; D_4, at the time of discharge; HADS-A, hospital anxiety depression scale-anxiety; ISI, insomnia severity index; QoR-15, quality of recovery-15; CI, confidence interval; SD, standard deviation.

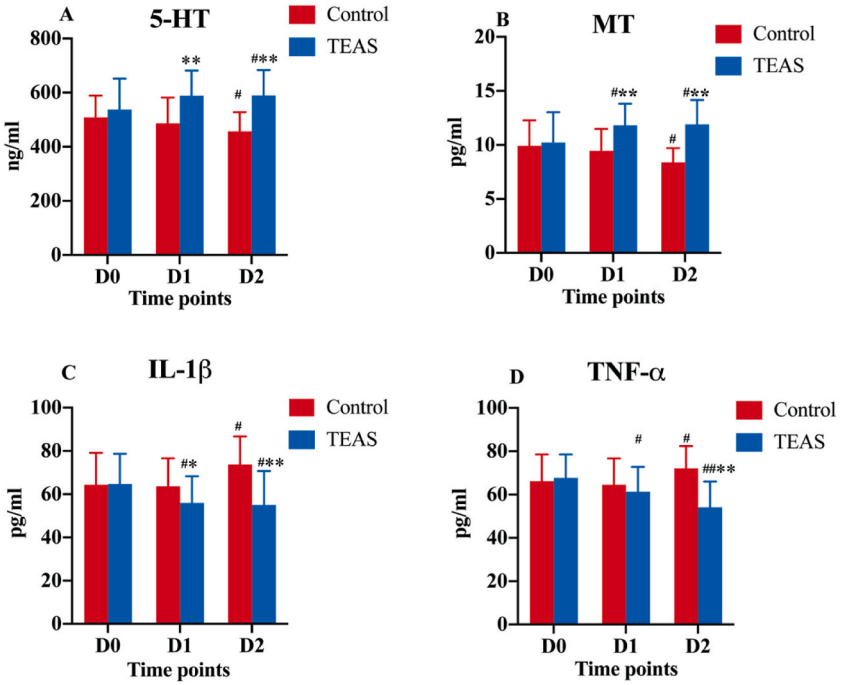

Fig. 2. Serum 5-HT, MT, IL-β, and TNF-α levels (n = 36) A:5-hydroxytryptamine(5-HT); B: melatonin (MT); C: interleukin-1β (IL-1β); D: tumor necrosis factor-α(TNF-α); D_0, A day before surgery; D_1, On the day of surgery prior to induction of general anesthesia; D_2, One day after surgery. Compare to D_0, $^{\#}P < 0.05$, $^{\#\#}P < 0.001$ Compare to Control, $^{*}P < 0.05$, $^{**}P < 0.001$.

and facilitate recovery of a group of kidney donors who underwent nephrectomy.

Data sharing statement

The data supporting this study are available from the corresponding author for a reasonable request.

Ethics approval

The current study was accordance with Declaration of Helsinki and approved by the Chinese Clinical Trial Registry (http://www.chictr.org.cn/listbycreater.aspx; ChiCTR2000029891; principal investigator: Juan Li; date of registration: February 16, 2020).

Author contribution statement

Yu Hou: Performed the experiments; Wrote the paper.

Fang Kang; Hongtao Liu; Chengwei Yang; Xiang Huang; Xiaohong Guan: Conceived and designed the experiments; Analyzed and interpreted the data.

Mingming Han: Contributed reagents, materials, analysis tools or data.

Shu-Ming Wang: Analyzed and interpreted the data; Wrote the paper.

Juan Li: Conceived and designed the experiments; Wrote the paper.

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Data availability statement

Request from the author Prof. Li juan (huamuzi1999@qq.com).

Declaration of interest's statement

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e14423.

Abbreviations

TEAS	transcutaneous electrical acupoint stimulation
LKDs	living kidney donors
PONV	postoperative nausea and vomiting
Neiguan	PC6
Taichong	LR3
Yintang	EX-HN3
HADS-A	hospital anxiety and depression scale-anxiety
VAS-P	100-mm visual analogue scale for pain
ISI	insomnia severity index
QoR-15	quality of recovery-15
LANSS	Leeds assessment of neuropathic symptoms and signs scale
D0	one day before surgery
D1	before induction of anesthesia
D2	one day after surgery
D3	three day after surgery
D4	discharge from the hospital
M3	at 3-month after surgery
RCT	randomized controlled trail
BIS	bispectral index monitor
BMI	body mass index
TCI	target-controlled infusion
ASA	American Society of Anesthesiologists
LMA	laryngeal mask anesthesia

TCM	Traditional Chinese Medicine
5-HT	5-hydroxytryptamine
MT	melatonin
IL-1β	interleukin-1β
TNF-α	tumor necrosis factor-α
CONSORT	Consolidated Standards of Reporting Trials
CI	confidence interval

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