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Original Article

Randomized controlled trial of TEAS with different acupoints combination on opioids consumption in patients undergoing off-pump coronary artery bypass grafting

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Abstract: We conducted this prospective, double-blinded, randomized controlled trial to compare the opioid sparing effect of transcutaneous electric acupoint stimulation (TEAS) on the distal-proximal acupoints combination and regional acupoints combination. 186 adults scheduled for elective off-pump coronary artery bypass grafting (OP-CABG) surgery were randomized to TEAS with distal-proximal acupoints combination (LI4 and CV17), regional acupoints combination (CV17 and CV14) and control (non-acupoints) groups. The primary endpoint was intraoperative sufentanil consumption. Secondary endpoints included perioperative hemodynamics, duration of mechanic ventilation, length of cardiac care unit (CCU) and postoperative hospital stay, incidence and the duration of re-intubation, re-admission to CCU, placement of intra-aortic balloon counter pulsation (IABP) or ventricular assisted device (VAD), postoperative cardiac function, incidence of postoperative complications, and all cause mortality by day 30. The cumulative consumption of sufentanil was significantly reduced in the distal-proximal acupoints combination group when compared with those in the regional acupoints combination and control groups (255.0 ± 106.1 μg vs 300.4 ± 106.9 μg and 305.9 ± 119.1 μg, $P = 0.027$). No significant differences among the three groups were found as refer to all of the secondary endpoints. TEAS with distal-proximal acupoints combination has better efficacy in reducing intraoperative opioid consumption in patients undergoing OP-CABG surgery.

Keywords: Transcutaneous electric acupoint stimulation, coronary artery bypass grafting, opioids, randomized controlled trial

Introduction

Transcutaneous electric acupoint stimulation (TEAS) is reported to reduce intraoperative opioids consumption and alleviate postoperative side effects in surgical patients [1]. A number of trials suggested that TEAS is an effective adjunct to anesthesia and analgesia, and thus enhance postoperative recovery [2, 3]. However, questions remain to be answered before promoting the clinical application of TEAS such as the selection of acupoints and the patterns of acupionts combination. According to traditional Chinese Medicine (TCM) theory, the effects of acupuncture vary when different acupoints or different combination of acupoints are targeted. Compelling evidence has supported that stimulation on combination of acupoints trumps that of single acupoint [4, 5]. There are certain rules regard to acupoints combination in clinical practice, including anterior-posterior acupoints combination, superior-inferior acupoints combination, distal-proximal acupoints combination, regional acupoints combination and superficies-interior acupoints combination. The stimulation on distal-proximal acupoints combination exerts better effects than those of regional acupoints combination in TCM theory and clinical practice.

High dose of long-acting opioids during off-pump coronary artery bypass grafting (OP-

CABG) surgery is associated with predictable risks of postoperative complications, including increased postoperative morphine consumption, pain and hyperalgesia [6], respiratory depression, prolonged mechanic ventilation, increased risk of myocardial ischemia and infarction [7], and delayed bowel movement recovery [8]. Few studies investigated the effects of distal-proximal acupoints combination versus regional acupoints combination on opioids consumption in cardiac surgery. Although empirical evidence of TCM and clinical experiences suggested that stimulation on distal-proximal acupoints combination (acupoints distal and adjacent to lesion position) has synergistic effects and produces greater efficacy than those of regional combination of acupoints [1, 9-11], the experimental evidence is yet to be obtained.

In this prospective, double-blinded, randomized controlled trial, the effects of TEAS with different combination of acupoints on opioids consumption in patients undergoing OP-CABG surgery were investigated. Because acupuncture was proven to have many other benefits, therefore, the endpoints such as hemodynamics, cardiac function, incidence of postoperative complications and mortality were also included in this clinical trial.

Methods

Trial design

This prospective, double-blinded, randomized controlled trial was conducted in Xijing Hospital and Tianjin Chest Hospital in China (ClinicalTrials.gov number, NCT02443220). The trial was approved by the institutional ethics review committees at both centers, and the study protocol conformed to the principles outlined in the Declaration of Helsinki. The patient data were de-identified. Patients were screened and underwent randomization during the period from August 2014 through February 2015 at the Xijing and Tianjin Chest hospitals. The study was partly funded by the National Key Basic Research Program of China (973 Program, 2014CB543202) and National Natural Science Foundation of China (81370011), which were not involved in the design of the protocol, the conduct of the trial, or the analysis or reporting of the data. Independent statisticians at the Clinical Trial Center of Xijing Hospital performed all the analysis. The site investigators were unaware of the study group assignments until the data were unblinding in March 2015. All authors had full and independent access to all the data and vouch for the integrity, accuracy, and completeness of the data and the fidelity of the study to the protocol. Staff at the Clinical Trial Center of Xijing Hospital monitored the trial data.

In this prospective, double-blinded, randomized controlled clinical trial, 186 patients undergoing off-pump CABG surgery were enrolled. Randomization was performed centrally at the Clinical Trial Center of Xijing Hospital. The conduct of the trial and the safety of the participants were overseen by the steering committee.

Patients

Patients above 18 years old who were scheduled for elective off-pump CABG surgery and provided written informed consent were eligible for enrollment. Exclusion criteria included ASA physical status of IV, emergency and urgent surgery, life expectancy < 1 year at the time of enrollment, hemodynamic instability as defined by a SBP < 90 mmHg, preoperative intra-aortic balloon counter pulsation (IABP) or ventricular assisted device (VAD), severe hepatic or renal dysfunction, history of thoracotomy, mediastinal fiber thickening or severe pleural adhesions, severe systemic infection, with contraindications to the use of TEAS such as skin damage or infection at acupoints, suffering from nervous system diseases or abnormal mental state, participating in other clinical trial within 3 months of enrollment. Patients who were transferred to cardiopulmonary bypass (CPB), had severe adverse reactions, and could not follow the study protocols were withdrawn from the study.

Intervention and blinding

Patients were randomized to TEAS with distal-proximal acupoints combination (distal-proximal group), regional acupoints combination (regional group) and non-acupoints combination (control group). The TEAS was lasted for 30 minutes before anesthesia by appointed staff, who ware unaware of the study group assignments. Based on the theory of traditional Chinese medicine (TCM), *Hegu* (LI4) and *Danzhong* (CV17) were chosen as the distal-proximal acupoints for combination while *Danzhong*

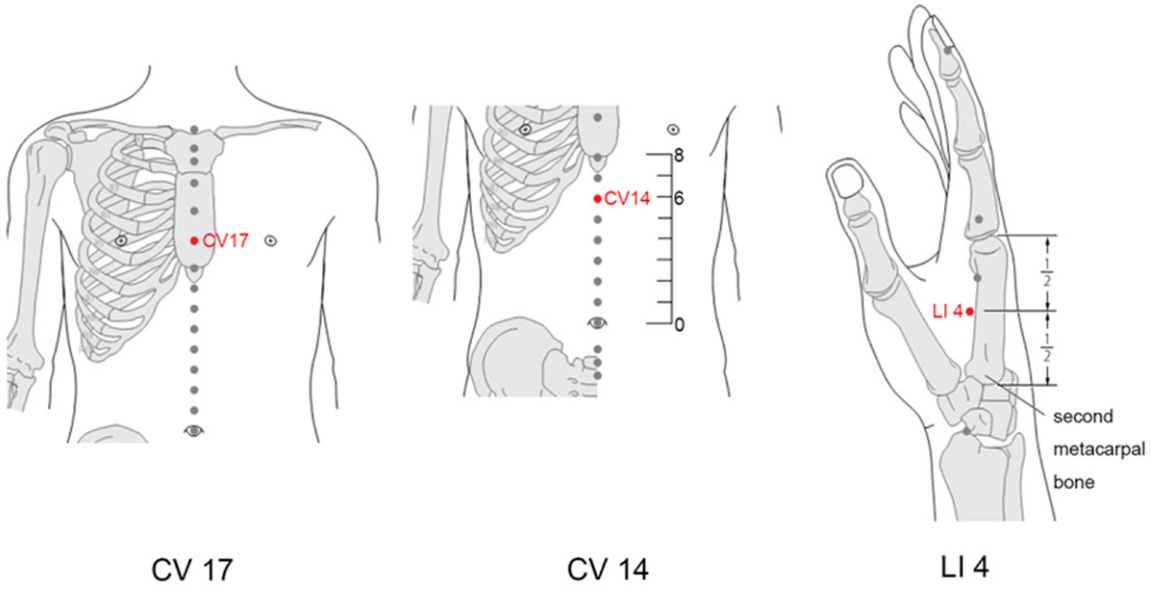

Figure 1. Localization of acupoints. From left to right: Danzhong (CV17): In the anterior thoracic region, at the same level as the fourth intercostal space, on the anterior median line; Juque (CV14): On the upper abdomen, 6 B-cun superior to the centre of the umbilicus, on the anterior median line; Hegu (LI4), on the dorsum of the hand, radial to the midpoint of the second metacarpal bone.

(CV17) and *Juque* (CV14) were chosen as regional acupoints for combination. In patients assigned to control group, 2 cm parallel to the right of the regional acupoints (CV17 and CV14) were chosen to be stimulated. The acupoints were identified according to the traditional anatomic localization (see **Figure 1**). Gel electrodes were applied to the skin after cleaned with alcohol pad. The acupoints were then stimulated electrically with an intensity of 7-11 mA and dense-disperse frequency of 2/10 Hz for 30 min before the anesthesia induction, using the *Hwato* electronic acupuncture treatment instrument (model No. SDZ-V, Suzhou Medical Appliances Co., Ltd, Suzhou, China). The stimulating intensity was adjusted to maintain a slight twitching of the local muscles based on individual maximum tolerance, indicating the so-called "*De-Qi*" sensations of heaviness, numbness, and swelling. To ensure double blinding, all of the patients were stimulated, and surgical drapes were used to cover the patients. The patients, the staff involved in intraoperative care (anesthesia and the cardiac surgical team) and postoperative care (the CCU physicians), the investigators who obtained and documented data and performed follow-up assessment, and the clinical endpoint committee were unaware of the study group assignments.

Identical surgical team at each center performed surgical procedures for the enrolled patients at each participant Clinical Trial Center. Anesthesia was induced with bolus injection of 0.03 mg/kg midazolam, target-controlled infusion (TCI) of propofol with plasma concentration of 1.0-2.0 ug/ml (Marsh model [12]) and sufentanil with initial effect site concentration of 0.2 ng/ml (Gepts model [13]) and increased 0.2 ng/ml per minute according to the bispectral index. When the consciousness of patients were lost, rocuronium was administered at 0.6 mg/kg to facilitate endotracheal intubation. During the surgery, the bispectral index was maintained at 40 to 60. The effect site concentration of sufentanil was adjusted based on hemodynamics, BIS and the experience of anesthetist while the plasma concentration of propofol was relatively stable. Swan-Ganz catheter was placed after induction for monitoring of hemodynamics and cardiac function (Edwards Lifesciences LLC, One Edwards Way, Irvine, USA). Patients were mechanically ventilated in a volume-controlled mode with a tidal volume of 6 ml/kg, 12 times/min and FiO_2 of 50%.

Hemodynamic parameters were recorded at the following 11 time points: before the anesthesia induction (baseline, T0), loss of con-

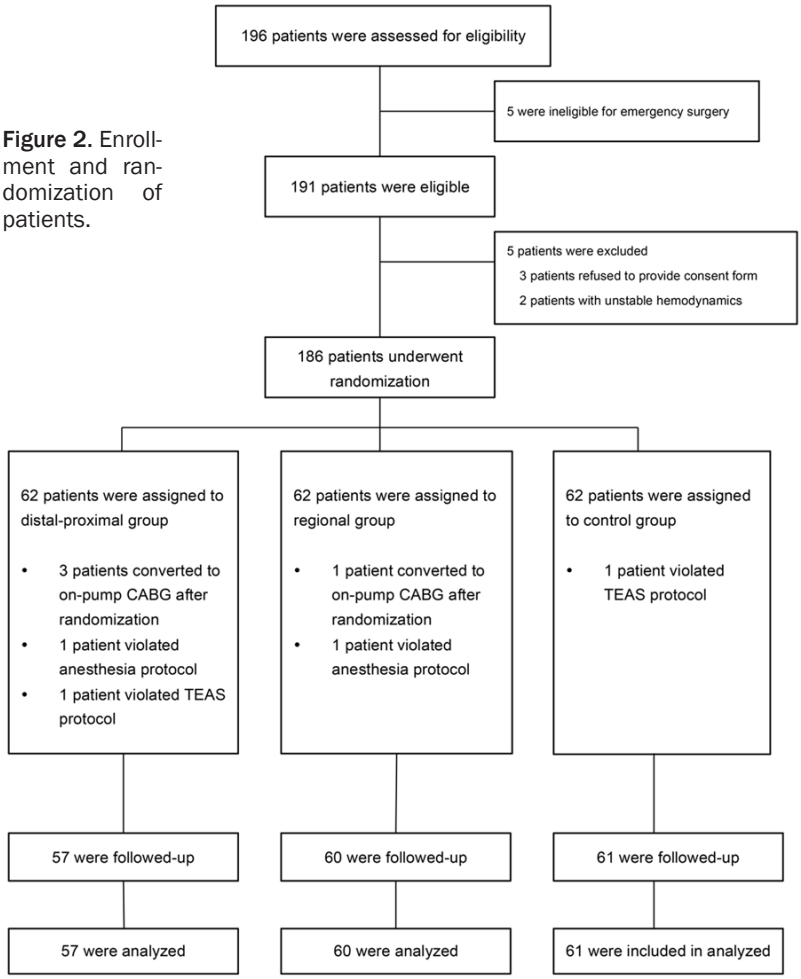

Figure 2. Enrollment and randomization of patients.

sciousness (T1), before intubation (T2), one minute after intubation (T3), initiation of surgery (T4), after the sternotomy (T5), after dissection of internal mammary artery (T6), at clamping (T7) and unclamping (T8) the aorta, 5 minutes after revascularization (T9), closure of sternum (T10), end of surgery (T11).

Primary and secondary endpoints

The primary endpoint was intraoperative sufentanil consumption. The secondary endpoints were the intraoperative hemodynamics and cardiac functional parameters, the duration of mechanic ventilation, the length of CCU stay, the incidence and the duration of re-intubation, re-admission to CCU, the incidence of IABP or VAD, the length of postoperative hospital stay, postoperative cardiac function as reflected by serum cardiac troponin I levels and inotrope scores, the incidence of postoperative complications and all cause mortality at day 30.

Statistical analysis

The trial was conducted to determine whether TEAS on distal-proximal acupoints combination was better in reducing intraoperative opioids consumption in patients undergoing OP-CABG surgery as compared to those of regional acupoints combination and control groups. To estimate the sample size, a pilot study was conducted, in which the sufentanil consumption was measured in 15 patients undergoing OP-CABG surgery. The overall sufentanil consumption was 351 ± 88 μg in the preliminary data. Anticipating a overall intraoperative sufentanil consumption of 351 ± 88 μg and assuming a 15% dropout rate, we originally determined that enrollment of 186 patients would give the study 80% power to detect a 15% reduction of the primary endpoint with distal-proximal acupoints combination group than with control group with the use of One-Way ANOVA with continuity correction, at a significance level of 0.05.

The measurement data with normal distribution are expressed as mean and standard deviations (SD) or standard error of the mean (SEM). Discrete data are expressed as numbers and percentages. Baseline clinical and demographic characteristics and procedural data were compared among the three groups by the Student's t-test or t-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables whenever appropriate. The differences in time course of effect-site concentration of sufentanil, hemodynamics, cardiac function parameters, postoperative serum cardiac troponin I and inotrope scores among study groups and among time points within each group were analyzed by repeated measures analysis of variance. For each indi-

Table 1. Characteristics and surgical details of patients

Characteristics	Control (n = 61)	Distal-Proximal (n = 57)	Regional (n = 60)	*P* Value
Age (years)	61.3 ± 6.6	61.0 ± 6.3	59.8 ± 7.9	0.503
Male sex-no. (%)	48 (78.7%)	47 (82.5%)	48 (80.0%)	0.873
BMI (kg/m^2)	25.4 ± 3.1	25.8 ± 3.5	25.0 ± 5.1	0.567
Preexisting conditions-no. (%)	39 (63.93%)	42 (73.68%)	40 (66.67%)	0.507
Diabetes	23 (37.70%)	18 (31.58%)	19 (31.67%)	0.718
Cerebrovascular disease	8 (13.11%)	9 (15.79%)	7 (11.67%)	0.804
Chronic pulmonary disease	2 (3.28%)	2 (3.51%)	0	0.352
Ulcer disease	3 (4.92%)	1 (1.75%)	1 (1.67%)	0.469
Peripheral vascular disease	2 (3.28%)	1 (1.75%)	3 (5%)	0.623
Preoperative inotrope scores	0.44 ± 0.96	0.19 ± 0.61	0.47 ± 0.97	0.163
Preoperative Laboratory findings				
Hb (g/L)	141.2 ± 15.6	141.9 ± 16.9	137.0 ± 17.7	0.246
Scr (umol/L)	86.3 ± 18.7	90.3 ± 18.2	84.6 ± 17.3	0.244
Troponin (ng/mL)	0.55 ± 3.52	2.84 ± 17.86	4.17 ± 29.08	0.606
SV (ml)	54.0 ± 12.8	62.0 ± 19.6	56.7 ± 13.0	0.245
EF				
≥55%	44 (72.13%)	41 (71.93%)	45 (75%)	0.915
30-55%	17 (27.87%)	16 (28.07%)	15 (25%)	0.915
EDV (ml)	97.3 ± 22.4	112.6 ± 42.7	101.5 ± 25.2	0.261
LAD (mm)	64.7 ± 14.8	63.1 ± 15.1	63.9 ± 14.6	0.837
ASA Status				0.13
II	9 (14.75%)	14 (24.56%)	18 (30%)	
III	52 (85.25%)	43 (75.44%)	42 (70%)	
Surgical details				
Propofol dosage (mg)	784.0 ± 255.4	826.0 ± 270.4	796.8 ± 263.1	0.674
Time of anaesthesia (min)	200.2 ± 49.8	208.4 ± 57.6	206.3 ± 43.4	0.657
Time of surgery (min)	171.5 ± 40.6	183.0 ± 51.9	179.1 ± 40.0	0.358
Intraoperative inotrope score	3.13 ± 2.28	3.30 ± 2.17	3.46 ± 2.99	0.776
No. of bypassed vessels	2.8 ± 0.8	2.7 ± 0.8	2.7 ± 0.7	0.789

NOTE. Data are presented as number (%) or mean ± standard deviation. There was no significant difference in any parameters ($P < 0.05$). Abbreviations: BMI, body mass index; Hb, hemoglobin; Scr, serum creatinine; SV, stroke volume; EF, ejection fraction; EDV, end-diastolic volume; LAD, lef t atrial diameter.

vidual, missing values were replaced by the last observed variable value (last observation carried forward). SPSS software package version 19.0 (SPSS, Chicago, IL) was used for data analysis. A p value < 0.05 was considered statistically significant.

Results

Study population

A total of 196 patients were assessed for eligibility, 191 patients were eligible while 5 patients were ineligible for enrollment as those were subjected to emergency surgery. Five patients was not randomized although eligible for the trial, 3 of them refused to provide consent form and 2 of them was hemodynamic unstable after entering the operating room. 186 patients underwent randomization and received the intervention according to the randomization assignment. 178 patients fulfilled the criteria for the full analysis set (61 in control group, 57 in distal-proximal group, 60 in regional group). Eight patients (one in control group, five in distal-proximal group, two in regional group) were not included in the full analysis set. Among them, three patients in distal-proximal group and one patient in regional group were transferred to CPB; one patient in distal-proximal group and one patient in regional group violated the standard anesthesia protocol by

Table 2. Results of endpoints analysis

Endpoints	Control (n = 61)	Distal-Proximal (n = 57)	Regional (n = 60)	*P* Value
Primary endpoint				
Sufentanil (μg)	305.9 ± 119.1	255.0 ± 106.1*	300.4 ± 106.9	0.027
Secondary endpoints				
APACHE II score	18.0 ± 0.9	18.1 ± 1.0	17.9 ± 0.7	0.743
Duration of Ventilation (h)	23.0 ± 29.9	19.0 ± 13.3	20.8 ± 18.1	0.608
Length of CCU stay (h)	62.3 ± 35.3	59.4 ± 28.2	58.2 ± 33.4	0.793
Re-intubation (%)	4 (6.56%)	2 (3.51%)	3 (5.1%)	0.752
Re-admission to CCU (%)	1 (1.64%)	0 (0)	4 (6.67%)	0.073
Length of secondary CCU stay (h)	70.0 ± 0	-	63.5 ± 59.1	0.928
IABP or VAD	0 (0)	0 (0)	0 (0)	1.000
Postoperative hospital stay (day)	8.8 ± 3.4	8.8 ± 2.7	8.8 ± 3.5	0.990
Reoperation (%)	3 (4.92%)	1 (1.75%)	6 (10%)	0.147
Readmission to Hospital (%)	1 (1.64%)	0 (0)	4 (6.67%)	0.093

NOTE. Data are presented as number (%) or mean ± standard deviation. *$P < 0.05$ compared with control group and regional group. Abbreviations: APACHE, Acute Physiology, Age, Chronic Health Evaluation; CCU, cardiac care unit; IABP, intra-aortic balloon counter pulsation; VAD, ventricular assisted device.

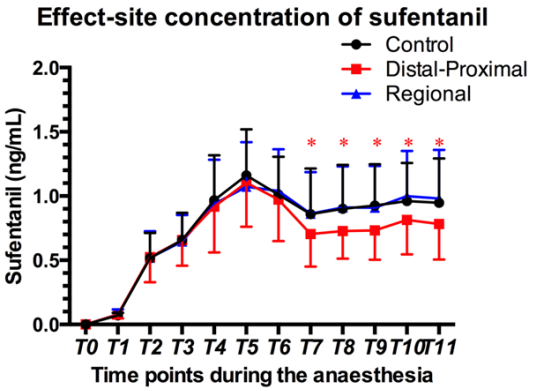

Figure 3. Continuous monitoring of sufentanil effect-site concentration in patients receiving control, distal-proximal and regional TEAS. Data were presented as mean ± standard deviation (range bars); *$P < 0.05$ compared with the control group and regional group. The time points are before the anesthesia induction (baseline, T0), loss of consciousness (T1), before intubation (T2), one minute after intubation (T3), initiation of surgery (T4), after the sternotomy (T5), after dissection of internal mammary artery (T6), at clamping (T7) and unclamping (T8) the aorta, 5 minutes after revascularization (T9), closure of sternum (T10), end of surgery (T11).

using different sufentanil TCI model; one patient in control group and one patient in distal-proximal group violated the standard TEAS protocol by not starting 30 minutes before anesthesia (see **Figure 2**). Baseline demographic and clinical characteristics are shown in **Table 1**. There were no relevant imbalances among groups at the baseline.

Endpoints results

The cumulative intraoperative consumption of sufentanil in the distal-proximal group (255.0 ± 106.1) was significantly less than those in the regional group (300.4 ± 106.9) and control group (305.9 ± 119.1) ($P = 0.027$, **Table 2**). There was no significant difference in sufentanil effect-site concentration at time points before internal mammary artery dissection (T1-T6). Effect-site concentration of sufentanil was significantly lower in distal-proximal group than those in regional and control groups at the time points of T7-T11, which is from the end of internal mammary dissection to the end of operation (**Figure 3**, $P < 0.05$). There was no significant difference in intraoperative propofol consumptions among the groups ($P = 0.674$). The intraoperative variables as refer to the time of surgery, intraoperative inotrope scores, and the number of vascularized vessels were comparable among groups (**Table 1**).

There were no significant differences with respect to the secondary endpoints among three groups. The postoperative clinical recovery parameters including APACHE II score, the duration of mechanic ventilation, the length of CCU stay, the incidence and the duration of re-intubation, re-admission to CCU, the incidence of IABP or VAD, the length of postoperative hospital stay, re-operation and re-admission to hospital were comparable among groups (**Table 2**). No TEAS related adverse events were observed.

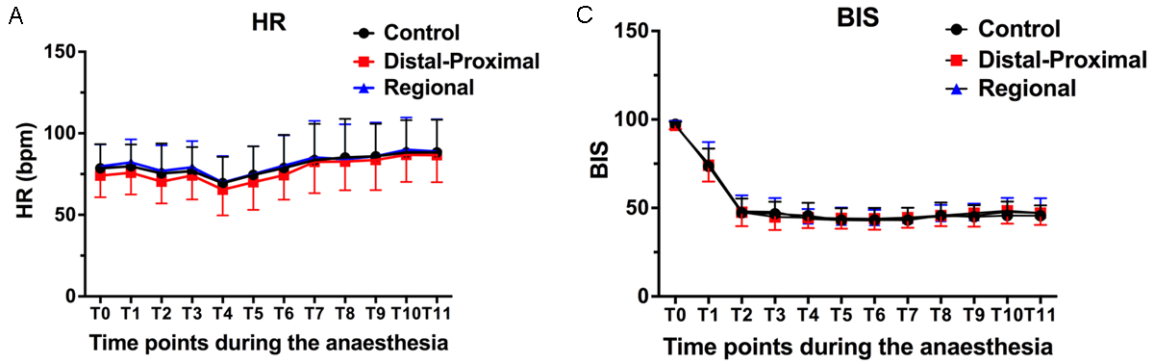

Figure 4. Continuous monitoring of hemodynamics during anesthesia induction and maintenance of off-pump coronary artery bypass grafting in patients receiving control, distal-proximal and regional TEAS. Data were presented as mean ± standard deviation (range bars); A. Heart rate (HR); B. MAP (mean arterial pressure); C. Bispectral index (BIS). Time points during the anesthesia: T0: the onset of anesthesia (baseline), T1: at the time of loss of consciousness, T2: at the time before intubation, T3: 1 minute after intubation, T4: at the start of surgery, T5: after the sternotomy, T6: after the separation of Internal mammary artery, T7: before clamping the aorta, T8: at the time of releasing lateral forceps, T9: 5 minutes after revascularization, T10: at the time of closure, T11; at the end of surgery.

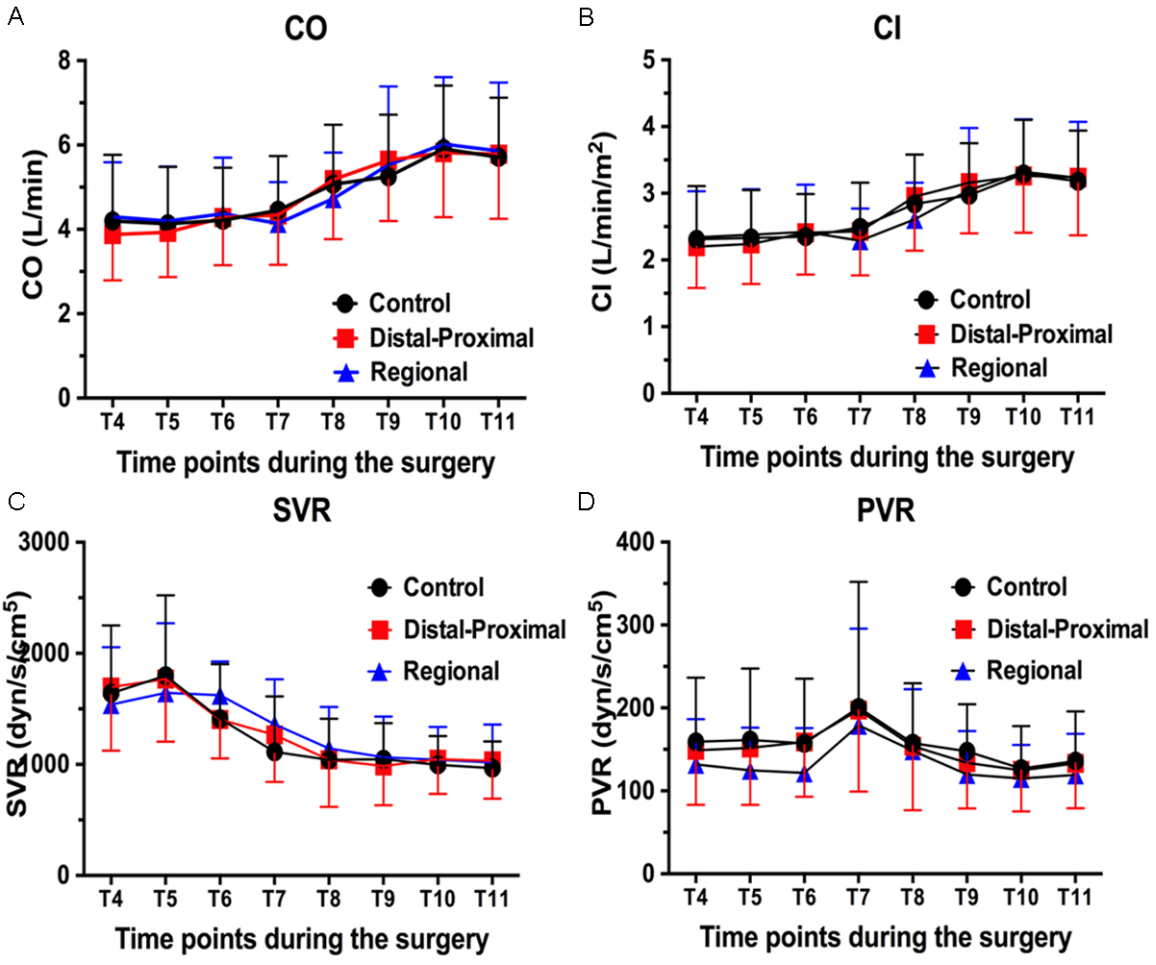

Figure 5. Continuous monitoring of cardiac functional parameters during the surgery of off-pump coronary artery bypass grafting in patients receiving control, distal-proximal and regional TEAS. Data were presented as mean ± standard deviation (range bars); A. Cardiac output (CO); B. Cardiac index (CI); C. SVR (systemic vascular resistance); D. Pulmonary vascular resistance (PVR). Time points during the surgery: T4: at the start of surgery, T5: after the sternotomy, T6: after the separation of Internal mammary artery, T7: before clamping the aorta, T8: at the time of releasing lateral forceps, T9: 5 minutes after revascularization, T10: at the time of closure, T11; at the end of surgery.

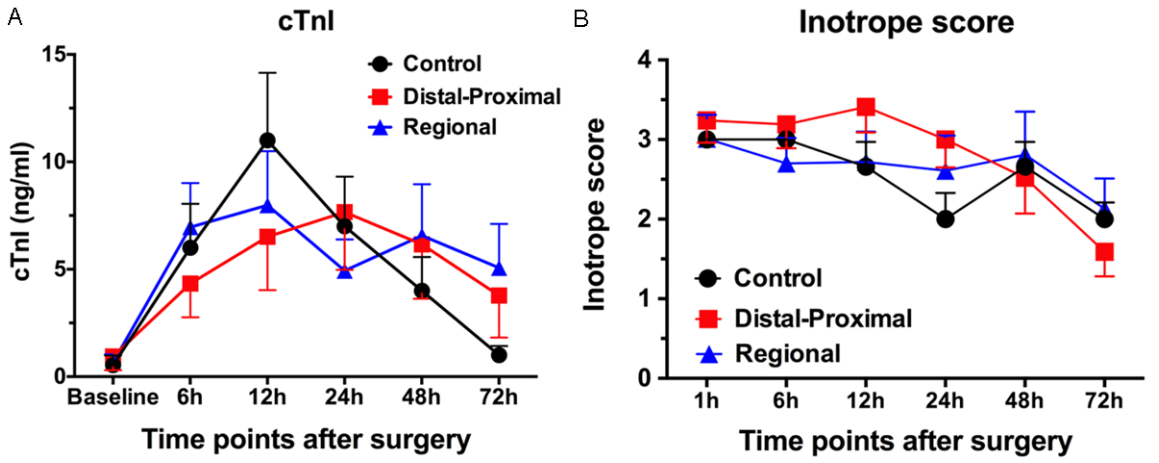

Figure 6. A. Continuous monitoring of serum cardiac troponin I (cTnI) at the time points of 6 hours, 12 hours, 24 hours, 48 hours and 72 hours after surgery of off-pump coronary artery bypass grafting in patients receiving control, distal-proximal and regional TEAS. Data were presented as mean ± standard error (range bars). B. Continuous monitoring of inotrope scores at the time points of 1 hour, 6 hours, 12 hours, 24 hours, 48 hours and 72 hours after surgery of off-pump coronary artery bypass grafting in patients receiving control, distal-proximal and regional TEAS. Data were presented as mean ± standard error (range bars). The inotrope score is presented as ug/(kg-minutes) and was calculated as dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) + isoprenaline (×100).

The hemodynamics was maintained stable during the whole process (see **Figures 4** and **5**). The level of postoperative serum cardiac troponin I release was associated with surgical procedure but did not differ significantly among groups (see **Figure 6A**). In addition, the postoperative cardiac function as measured by the use of cardiac supportive medicine (inotrope scores) did not differ significantly among groups (see **Figure 6B**). Also, there was no significant difference with respect to any other secondary endpoints, as refer to postoperative complications and all cause mortality at day 30 among groups (**Table 3**).

Discussion

In this prospective, double-blinded, randomized controlled trial in patients scheduled for elective off-pump CABG surgery under total intravenous anesthesia at two medical centers, we demonstrated that TEAS with distal-proximal acupoints combination significantly reduced intraoperative sufentanil consumption. The study was the first to compare the opioid sparing effect of TEAS between distal-proximal acupoints combination and regional acupoints combination in patients undergoing off-pump CABG surgery. The result provides the new evidence for the combination of acupoints if the TEAS or acupuncture-drug balanced anesthesia [14] is applied to clinical practice.

The potent analgesic effects of acupuncture make it be increasingly used during surgery to assist anesthesia [1, 2]. Accumulating evidence suggested that acupuncture alleviated pain and regulated the physiological functions of the body [15, 16]. TEAS combines traditional Chinese acupuncture and modern electrical techniques, which is non-invasive, safer and more acceptable to patients and clinical doctors [17]. It was reported that acupuncture, electro-acupuncture (EA) and TEAS were all effective in reducing perioperative analgesic demand and in relieving postoperative pain [1, 18, 19]. However, few studies have investigated the opioid sparing effects of TEAS with different acupoints combination.

Table 3. Postoperative complications & mortality (no. (%))

Postoperative complications	Control (n = 61)	Distal-Proximal (n = 57)	Regional (n =60)	*P* Value
Overall	42 (68.85%)	45 (78.95%)	41 (68.33%)	0.357
Sterile wound dehiscence	1 (1.64%)	0 (0)	4 (6.67%)	0.073
Respiratory complications				
ALI	17 (27.87%)	13 (22.81%)	10 (16.67%)	0.336
ARDS	4 (6.56%)	4 (7.02%)	7 (11.67%)	0.538
Pneumothorax	0 (0)	0 (0)	1 (1.67%)	0.372
Atelectasis	1 (1.64%)	2 (3.51%)	4 (6.67%)	0.356
Pleural effusion	5 (8.20%)	1 (1.75%)	6 (10%)	0.176
Pulmonary infection	9 (14.75%)	14 (24.56%)	13 (21.67%)	0.392
Respiratory failure	1 (1.64%)	1 (1.75%)	1 (1.67%)	0.999
Time of ventilation > 48 h	4 (6.56%)	5 (8.77%)	6 (10%)	0.788
Cardiovascular complications				
Ventricular fibrillation	0 (0)	1 (1.75%)	4 (6.67%)	0.072
Heart failure	3 (4.92%)	0 (0)	1 (1.67%)	0.184
New onset of MI	0 (0)	0 (0)	2 (3.33%)	0.137
Hydropericardium	0 (0)	0 (0)	1 (1.67%)	0.372
Hemorrhagic shock	0 (0)	0 (0)	2 (3.33%)	0.184
Neurologic complications				
Delirium	0 (0)	0 (0)	2 (3.33%)	0.184
Stroke	1 (1.64%)	0 (0)	0 (0)	0.381
Urinary complications				
AKI (Acute kidney injury)	14 (22.95%)	16 (28.07%)	12 (20%)	0.584
AKI I	10 (16.39%)	16 (28.07%)	7 (11.67%)	0.064
AKI II	4 (6.56%)	0 (0)	4 (6.67%)	0.139
AKI III	0 (0)	0 (0)	1 (1.67%)	0.372
Haematological complications				
Thrombopenia	0 (0)	0 (0)	1 (1.67%)	0.372
Gastrointestinal complications				
Acute hepatic injury	20 (32.79%)	26 (45.61%)	30 (50%)	0.138
Death	5 (8.20%)	1 (1.75%)	4 (6.67%)	0.287

NOTE. Data are presented as number (%). There was no significant difference in any parameters ($P < 0.05$). Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; MI, myocardial infarction; AKI, acute kidney injury.

Among the parameters and factors, by which the effects of TEAS are determined, the specificity of acupoints and different acupoints combination are of the paramount importance. Based on the TCM theory and outcomes from previous studies, different acupoints are selected for different purposes [20]. *Hegu* (LI4) is an important acupoint for analgesia as proved in various animal models [21, 22]. In clinical trials, TEAS at *Hegu* (LI4) significantly decreased intraoperative sufentanil requirements, enhanced pain relief postoperatively and thus improved postoperative recovery for patients subjected to supratentorial tumour resection [18] and sinusotomy [1]. *Danzhong* (CV17) and *Juque* (CV14) acupoints are located on the Ren meridian, which exert therapeutic effects on coronary heart diseases (angina pectoris) according to Huangdi Neijin (the Yellow Emperor's Classic). Also, a meridian that passes through or close to the surgical area is usually selected in order to achieve the analgesic effects. Therefore, these three acupoints were selected in the present clinical trial.

Different acupoints combination is the other key determinant of the clinical efficacy of acupuncture. Reza et al [4] demonstrated stimulation at PC6 and LI4 combination profoundly decreased the incidence of postoperative nausea and vomiting when compared to those stimulation at single acupoint PC6 in a double-

blinded, randomized controlled trial involving 227 surgical patients. Eighty (69.6%) of 115 patients in the combined acupoints group complained nausea and vomiting compared with 96 (85.7%) in the single acupoint group. In cardiac surgery, EA bilaterally at regional combination of *ZhongFu* (LU1), *LieQue* (LU7), and *XiMen* (PC4) acupoints for 15-20 min prior to surgical incision to the end of surgery which discontinued during cardiopulmonary bypass and restarted as the cardiopulmonary bypass pump flow down to 1.5 L/min consumed only 13% of the fentanyl required in the control group without EA [23]. Empirical evidence of TCM suggested the combination of distal-proximal acupoints produces greater efficacy [9, 11]. Clinical practice demonstrated acupuncture on distal-proximal acupoints combination had positive therapeutic effects on peripheral facial paralysis [11] and advanced osteoarthritis of the knee [24]. In a prospective, randomized, placebo-controlled trial, TEAS with distal -proximal acupoints combination for 30 min versus no stimulation at the same acupoints before anesthesia significantly reduced intraoperative remifentanil consumption and alleviated postoperative side effects in patients undergoing sinusotomy [1]. Up to now, few studies have compared the effects of distal-proximal acupionts combination to the other acupoints combination patterns. Therefore, experimental evidence supporting the superiority of TEAS on distal-proximal acupoints combination to the regional acupoints combination is yet to be obtained. It was demonstrated in the present clinical trial that stimulation on distal-proximal combination of *Hegu* (LI4) and *Danzhong* (CV17) consumed less sufentanil than those in regional and control groups in patients undergoing OP-CABG.

Patients' perception and expectations to treatment are one of the central elements to the efficacy of analgesia and that these elements may contribute to self-reinforcing effects in acupuncture treatment. To avoid possible bias and to blind the patients, stimulation at non-acupoints (2 cm parallel to the right of regional acupoints) was served as control in the present study. However, the dosage of sufentanil in the regional and control groups was still much lower than those reported in other clinical trial (468 ± 41 μg) [25] and our preliminary study (351 ± 88 μg). In fact, non-acupoint stimulation exhibited efficacy was demonstrated in other study [26]. In a largest clinical study for knee pain [27], acupuncture was found to be not different from sham acupuncture treatment at non-acupoints. This was probably due to the fact that the therapeutic effect of the acupuncture at non-acupoints does exist or because of the individuals modify or improve their behavior in response to the awareness of being observed (Hawthorne effect). Besides, there is persistent uncertainty about the size and area of acupoints. The acupoint was considered as an area instead of a single point according to TCM theory. Use of electrical stimulation may make it difficult to separate activation of acupoints from non-acupoints since the electrical current spreads between acupoints, which may explain the positive effect of the non-acupoints in this study. Moreover, a randomized study [28] showed that patients who believed they received active acupuncture had lower pain levels than those who believed they received placebo acupuncture, which backed up the theory of Hawthorne effect. In recent years, the acupoint sensitization phenomenon was observed [29]. That is when the function of internal organs is damaged, the size of acupoints' receptive fields and the sensitivity of acupoints changed accordingly. This may also explain the therapeutic effect of controlled non-acupoints stimulation when acupoint sensitization phenomenon happened.

Our study has several limitations. As mentioned above, stimulation at non-acupoints close to the regional acupoints as a control might blunt the anesthetic sparing effects of TEAS. The other effects of distal-proximal acupoints combination of TEAS on postoperative recovery were inexplicit as well. This may be the potential explanation for failure to detect any differences as refer to the postoperative complications or mortality among three groups. In addition, the small sample size in present trial may be underpowered to detect any significant benefits of TEAS on postoperative outcomes. A large-scale trial is needed to clarify the benefits of TEAS with distal-proximal acupoints combination including long-term outcome after surgery.

In conclusion, in this prospective, double-blinded, randomized controlled trial, significant reduction of intraoperative sufentanil consumption was observed in TEAS with distal-proximal acupoints combination compared to regional acupoints combination in OP-CABG surgery. Future studies should focus on effects

of TEAS with distal-proximal acupoints combination on long-term outcome of patients undergoing cardiac surgery.

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Disclosure of conflict of interest

None.

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