

**Electrical Acupoint Stimulation for Postoperative Recovery in Elder Patient Undergoing**

**Knee Arthroplasty: Study Protocol and Statistical Analysis Plan**

**( Code name : LINGSHU )**

**Clinical trial protocol**

**Responsible party : Affiliated Hospital of Shandong University of Traditional Chinese**

**Medicine**

**Study main investigator: Su Fan**

**Anticipated data: may 1, 2018**

**Protocol number : SZH-A-20170501-R2**

## **Electrical Acupoint Stimulation for Postoperative Recovery in Elder Patient Undergoing Knee Arthroplasty: Study Protocol and Statistical Analysis Plan**

Wei-Liang Zhang

### **Methods/design:**

#### **Design**

This is a single-center, double-blind, clinical, randomized controlled study. It was approved by Ethical Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine on 15 June 2017 (Approval No. 2017-13th-KY) and registered at the ClinicalTrials.gov (ID. NCT03249701) before recruiting participant. The trail will base on the Consolidated Standards of Reporting Trials (CONSORT 2010) guidelines, and Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA). As the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and corresponding checklist, the participants will be recruited among inpatients who will receive total knee arthroplasty under epidural anesthesia between May 1, 2018 to Oct 1, 2018 at Department of Joint Orthopedics, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, attended by Dr.lv. All potential patients will be identified from operating schedule following the inclusion and exclusion criteria as below, and an appointed researcher will go to the ward for application of selective strategy.

#### **Participants**

All participants will be randomly assigned to experimental group (group E), placebo group (group

P) and control group (group C) at a ratio of 1:1 on the basis of digital random numbers generated by SPSS.17.0 software. For reducing the selection bias, an appointed researcher (W.Z) will be responsible for randomization.

### **Study subject**

The study subject is elder inpatient who will be undergoing elective total knee arthroplasty under epidural anesthesia, age from 65 to 85 years old, ASA physical status of I-III, and agree to the informed consent form. The exclusion criteria are the subject (1) refuse to participate in the study; (2) already participate in other clinical studies; (3) is not available due to severe physical status, like ASA classification of IV; (4) required emergency patient; (5) is not suitable to TEAS requirement, e.g. pace maker or metal implant; (6) has deficiency in cognition and literacy and medical history of mental disorder, deep venous thrombosis, or history of drug abuse and acupuncture. Subject should be removed if he/she: (1) switch to general anesthesia; (2) refuses to continuous TEAS administration without any excuse; (3) gets serious adverse reactions in treatment period (e.g. cardiac arrest, comatose); (4) can't accomplish the follow-up visit; (5) acupuncturist changed; (6) low compliance patient.

### **Outcome Measures**

Primary outcome measure: The primary outcome is the Quality of Recovery-40 questionnaire (QoR-40). It was specifically designed to evaluate quality of recovery in subject after surgery with including five aspects: emotional state, physical comfort, psychological support, physical independence and pain. There are 40 items in total, each adding 1-5 points to the score. Thus, the highest possible score is 200 points; higher scores indicate better quality of recovery. The QoR-40 will be evaluated at preoperative day 1 and postoperative day 1, 3, 7, respectively.

Secondary outcome measures: a. Incidence of postoperative complications: we will assess incidence of postoperative complications when initially find by participant or accompanying family members and diagnosed through examination or scale. Any complication after surgery will be recorded and filled in the case report form. When subject send back to ward, we will require the accompanying family members to record any complaint from subject. Assessment of incidence of postoperative complications will be going on three times and occur at postoperative day 1, 3, 7, respectively. b. The length of hospital stay (LOH): The LOH = the day of patient discharge from hospital – the day of patient admit to hospital, which is calculated base on the Hospital Information System. c. Level of stress response: The Adrenocorticotropic Hormone (ACTH), Cortisol (COR) are chosen to address the level of perioperative stress response. Blood sample taken intravenously and collected at the time of 1 day before surgery (baseline) and 1st day, 3rd day after surgery, respectively. d. Level of inflammatory response: In clinic, the C Reactive Protein and Neutrophil-lymphocyte ratio are well-known to represent the level of perioperative inflammatory response [27, 28]. Blood sample taken intravenously and collected at the time of 1 day before surgery (baseline) and 1st day, 3rd day after surgery, respectively.

### Sample Size Calculation

This trail contains two groups. A sample size estimation formula can be used to calculate the numbers of subjects in each group, base on two-groups, randomly, controlled design.

$$n = \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \cdot (\sigma_1^2 + \sigma_2^2)}{\delta^2}$$

where  $n$ ,  $\sigma$ ,  $\delta$  represent the sample size in each group, standard deviation, mean difference of two groups, respectively. In a condition of  $\alpha = 0.05$ ,  $\beta = 0.1$  with a two sided test, we obtain  $Z_{1-\alpha} = 1.96$  and  $Z_{1-\beta} = 1.282$ . According to previous data by Bai et al, the primary outcome of QoR-40

in the article is  $176.9 \pm 11.1$  vs.  $164.3 \pm 13.7$  as compare experimental group to control group ( $p = 0.006$ ), the sample size for each group was 21 cases and the final sample size estimated in each group was 26 cases with adding a 20% dropout rate. Totally 54 subjects are needed.

### **Randomization**

According to the digital random numbers generated by SPSS.17.0 software, all participants will be assigned to experimental group (group E), placebo group (group P) and control group (group C) randomly and equally. For minimal risk bias of selection and others, a specific appointed researcher (W.Z) will be in charge of the process of randomization. A sequence number will be allotted to an ensured qualified subject and a sealed envelope method is used to reduce allocation bias: the envelope is dark and opaque, sealed, content inside can't be seen even under bright light.

### **Blind method**

In this trail, the TEAS operator (F.Y), statistician (S.W), data collector (H.S), trail administrator (W.Z) work independently and follow the blind method. All investigators will only perform his/her assign task and there will not be direct communication between all investigators privately regarding this proposed study. The group assignments are only aware of by TEAS operator (F.Y). For the test of blinding to participant, a survey about how they are think about their treatment received will be achieved to determine whether single- or double-blind of this trail is.

### **Intervention**

Surgical day, the subject will be transferred into operation room and calms down for few minutes with a supine position lying on the surgical bed. Acupoint stimulation administered at 30 min before epidural administration and 30 min after wound closed 2/10 HZ and the intensity adjust to maximal tolerance by participant until end of treatment. The acupuncture points are selected on

the basis of WHO Standard International Acupuncture Nomenclature, and zusanli (ST36, downward 3 inches to the hollow of patellar ligament lateral, Fig.2 a), sanyinjiao (SP6, 3 inches above the top of malleolus medialis, Fig.2 b), neiguan (PC6, 2 inches to the midpoint of wrist skin crease, Fig.2 c), quchi (LI11, the lateral end of the elbow crease when elbow flex 90 degree, Fig.2 d) are located specifically as figure.2 shown. After acupoint area disinfected by 75% alcohol, a medical electrode will be placed on the acupuncture points and connecting to an electro-acupuncture stimulator (SDZ-V, Suzhou medical technology Co. Ltd., Suzhou, China).

### **Experimental group**

TEAS uses unilaterally. When TEAS administered in group E, a maximal stimulus intensity need to find out by a test of each personal tolerance before anesthesia and keep the intensity through the entire surgery. Check the TEAS treatment discontinuously and guarantee all procedures normal. The operator has to observe the condition of patient because the TEAS may cause to some side effects, an emergency actions will be used when necessary.

### **Placebo group**

EAS uses unilaterally. When EAS administered in group P, a maximal stimulus intensity need to find out by a test of each personal tolerance before anesthesia and keep the intensity through the entire surgery. Check the EAS treatment discontinuously and guarantee all procedures normal. The operator has to observe the condition of patient because the EAS may cause to some side effects, an emergency actions will be used when necessary.

### **Control group**

The subject in group C will obtain a sham stimulation, which means the medical electrode adheres to the same acupuncture points as experimental group without actual electrical stimulus (or

attached to an inactive electrical stimulator). All other procedures else are same as the participant in group E except for stimulation intensity.

### **Study protocol**

All participants will fill a demographic information sheet (including age, gender, height, weight, ASA classification status, education level, income, previous anesthesia experience/complications, medical history, anxiety and depression, preoperative examination and based line functional ability). The first assessment of patient status will take place at 1 day before surgery (baseline), and repeat at 1st day, 3rd day, 7th day after surgery.

**Safety Assessment:** We will define an adverse event as an event if more than three subjects suffer a same symptom, such as local skin rash, dizziness, and low blood sugar during the treatment-evaluation period. These events will be statistically analyzed, and treatment safety is evaluated in accordance with the research protocol. If serious adverse events occur, we will report it immediately and take actions accordingly.

### **Data collection**

For data collection, the case report form (CRF) is established, in which demographic information, medical history, clinical characteristics, primary and secondary outcome measures, recovery assessment, follow-up, safety assessment are arranged and covered. All investigators are asked to follow the requirement of the CRF instruction, as well as complete the form in a timely and precise way.

### **Statistical Analysis**

1. Content of statistical analysis: a. Dropout sample: the accuracy numbers lost and dropout rate of subjects are described, and reasons for the dropout is given. b. Balance comparison: The

comparability of subjects in two groups are compared via the baseline information assessing. c. Efficacy analysis: we will treat the QoR-40 as the primary outcome to evaluate the efficacy of TEAS treatment in improving the postoperative recovery after total knee arthroplastic, a mean and deviation as the expression of primary outcome and compared between groups using one-way ANOVA (SNK method), however, before statistic performed, a test of normal distribution of data should be used to determine whether the data are suitable for analysis using the one-way ANOVA. Additional four composite outcome measures (incidence of any postoperative complication, length of hospital stay, level of stress response, level of inflammatory response) are also used as secondary outcomes to determine the efficacy of

### **Methods of Statistical Analysis**

According to the principle of intention-to-treat (ITT), our data will contain all subjects enrolled. Efficacy and safety measures will be analyzed in accordance with protocol strictly, thus, only subjects who completed the entire trial and followed the protocol requirements should be analyzed. Quantitative and qualitative variables are described statistically with  $X \pm SD$  and count numbers, separately. Quantitative variables will be analyzed by one-way ANOVA (SNK method) in statistic, a normal data distribution needed before performance. Qualitative variables will be analyzed using either  $\chi^2$  test or Fisher' s exact test. All statistical tests are two-sided, and P value  $< 0.05$  will be considered to be statistically significant. Statistical analysis will be performed using SPSS 17.0 software for application.