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Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

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Keywords:	electroacupuncture, postoperative pain, total knee arthroplasty, the study protocol

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Manuscripts

1 **Application of electroacupuncture for postoperative pain management after total**
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6 **2 knee arthroplasty: a study protocol for a single-blinded, randomised**
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8 **3 placebo-controlled trial**

10 4 Sheng Zhong, Hai Huang, Jun Xie, Ling Zhao, Xiu-ling Song, Yue-lai Chen, Lian-bo
11
12
13 5 Xiao

15 **6 Author Affiliations:**

17 7 Sheng Zhong, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
18
19
20 8 Medicine, Shanghai, China, drcyan@foxmail.com

22 9 Hai Huang, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
23
24
25 10 Medicine, Shanghai, China, haichuan880@163.com

27 11 Jun Xie, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
28
29
30 12 Medicine, Shanghai, China, leoxie199@126.com

32 13 Ling Zhao, PhD, Shanghai University of Traditional Chinese Medicine, Shanghai,
33
34
35 14 China, zhao099@hotmail.com

37 15 Xiu-ling Song, MD, Shanghai University of Traditional Chinese Medicine, Shanghai,
38
39
40 16 China, songxiuling2007@163.com

42 17 Yue-lai Chen, PhD, Shanghai University of Traditional Chinese Medicine, Shanghai,
43
44
45 18 China, chenylai@163.com

47 19 Lian-bo Xiao, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
48
49
50 20 Medicine, Shanghai, China, 13701888178@163.com

52 **21 Corresponding Author:**

54 22 Lian-bo Xiao, PhD, Guanghua Hospital, Shanghai University of Traditional Chinese
55
56
57
58
59
60

1
2
3 23 Medicine, No. 540 Xinhua Road, Changning District, Shanghai (CN 200052), China,
4
5

6 24 13701888178@163.com, +8613701888178
7

8 25 Yue-lai Chen, PhD, Shanghai University of Traditional Chinese Medicine, No. 540
9

10 26 Cailun Road, Pudong District, Shanghai (CN 201203), China, chenyuelai@163.com,
11
12

13 27 +8613020193726
14

15 28 Lian-bo Xiao and Yue-lai Chen contributed equally to this paper.
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20 30 **Author Contributions**

21
22 31 SZ and LBX conceived the study while HH, JX, LZ, XLS designed the study. The
23
24

25 32 study protocol was drafted by SZ and LBX, and was revised by YLC. All authors
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28 33 approved the final manuscript of this study protocol.
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41
42 39 The authors declared that there are no potential conflicts of interest with respect
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45 40 to the research, authorship, and/or publication of this study.
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3 **42 Abstract:**

4 **43 Introduction:** The purpose of this study is to assess the efficacy of electroacupuncture
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7 **44** to relief pain and promote functional rehabilitation after total knee surgery.

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9 **45** Methods and analysis: We propose a single-blinded, randomised placebo-controlled
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11
12 **46** trial to evaluate the efficacy of electroacupuncture. Osteoarthritis patients (aged 55 to
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14
15 **47** 80 years) undergoing unilateral total knee arthroplasty will be included in the trial.

16
17 They will be randomised to receive either electroacupuncture or
18
19 **49** sham-electroacupuncture. A total of 110 patients will receive electroacupuncture and
20
21
22 **50** sham-electroacupuncture for three days after TKA. Postoperative pain will be
23
24
25 **51** measured using VAS score, and the need for an additional dose of opioid and
26
27 **52** analgesics will be recorded as the primary outcome. Secondary outcomes include
28
29 **53** knee function and swelling, postoperative anxiety, postoperative nausea and vomiting
30
31
32 **54** among other complications.

33
34 **55** Ethics and dissemination: This study has been approved by the ethics committee, and
35
36
37 **56** subsequent modifications of the protocol will be reported and approved by it. Written
38
39 **57** inform content will be obtained from all of the participants or their authorized agents.

40
41 **58** Trial registration number: ChiCTR1800016200

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43
44 **59** Keywords: electroacupuncture, postoperative pain, total knee arthroplasty, the study
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47 **60** protocol

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51 **62 Article Summary**

52
53 **63** *Strengths and limitations of this study*

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55
56 **64** The study is the first single-blinded, randomised placebo-controlled trial in China
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4 65 to assess the efficacy of electroacupuncture to relief pain and promote functional
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6 66 rehabilitation after total knee surgery.
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8 67 The study will use an efficient sham-electroacupuncture method that makes it
9
10 68 hard for patients with acupuncture treatment experience to distinguish between both
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13 69 treatments.
14

15 70 The study is rigorously designed, which includes adequate sample size, proper
16
17
18 71 randomization and allocation concealment, and prospective trial registration to reduce
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21 72 selection and confounding bias.
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23 73 Yet, the placebo effect cannot be eliminated due to the unblinded surgeons and
24
25 74 acupuncturists.
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28 75

30 76 **Introduction**

31
32 77 Total knee arthroplasty (TKA) is the most frequently performed surgical
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34
35 78 procedure for end-stage osteoarthritis and rheumatoid arthritis. Moderate to severe
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38 79 postoperative pain is a major complaint in most patients. Acute and subacute
39
40
41 80 postoperative pain is highly associated with persistent post-surgical pain (PPSP),
42
43 81 especially when the acute pain is not treated with effective analgesia.¹ A recent study
44
45 82 showed that 10%-34% and 7%-23% of patients reported severe pain after TKA and
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47
48 83 total hip arthroplasty (THA), respectively, which indicates that TKA patients are more
49
50 84 likely to develop PPSP.² Multimodal analgesia has been used for 20 years and it is
51
52
53 85 considered to be the most effective strategy for PPSP. Abuse of analgesic drugs has
54
55 86 increased exposure of the public to the side effects of non-steroidal anti-inflammatory
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3 87 drugs (NSAIDs) and opioids.^{3,4} Drug-free interventions to reduce pain or opioid
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6 88 consumption are more consistent with the principles of enhanced recovery after
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9 89 surgery (ERAS).

10
11 90 According to the theories of Traditional Chinese Medicine (TCM), acupuncture
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13 91 can help dredge the meridians and correct imbalance of flow of energy. Clinical trials
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16 92 and systematic reviews have shown that acupuncture is effective against many
17
18 93 different types of acute and chronic pain.⁵⁻⁷ Electroacupuncture (EA) has been proved
19
20 94 to be beneficial for postoperative pain after TKA.⁸ Studies on the mechanism of
21
22
23 95 electroacupuncture analgesia indicated that it activates many bioactive chemicals
24
25
26 96 through peripheral, spinal, and supraspinal mechanisms.⁹ We hypothesize that EA
27
28 97 may active the descending pain regulation of the periaqueductal grey (PAG) and the
29
30 98 rostral ventromedial medulla (RVM).¹⁰⁻¹² Besides, the placebo effect is highly
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32
33 99 associated with both areas of the brain.¹³ Strict blinding is required to rule out the
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35 100 effects of the placebo effect on outcomes.

36
37
38 101 The purpose of this study is to assess the efficacy of electroacupuncture on pain
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40 102 relief and promoting functional rehabilitation after total knee surgery. We will use a
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43 103 large sample size and an effective electroacupuncture blind method to ensure a
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45 104 credible conclusion.

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48 49 50 106 **Methods and analysis**

51 52 107 *Study Context*

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55 108 This study will be a parallel randomised controlled trial performed at the inpatient
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4 109 ward of Shanghai University of Traditional Chinese Medicine Guanghua Hospital,
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6 110 Shanghai, China. The annual surgical number of total knee arthroplasty for
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8 111 osteoarthritis was about 600 in 2017. In this study, there will be 7 investigators,
9
10 112 including a chief orthopaedic surgeon (LBX) with 20 years of clinical experience, two
11
12 113 orthopaedic physicians (JX and SZ), two Chinese medicine acupuncturists (HH and
13
14 114 YLC), and two outcome assessors (LZ, and XLS). ERAS programme will be
15
16 115 performed by trained nurses and physiotherapists at the inpatient ward. The schedule
17
18 116 and the study flow diagram is shown in Table1 and Figure 1.
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23 117 *Sample size calculation*

24
25 118 In a previous meta-analysis study in which pain relief was compared between EA
26
27 119 groups and controls, the minimal mean difference of the two groups based on the VAS
28
29 120 score was -1.14 (95% CI, -1.90 to -0.38), and the standard deviation was estimated to
30
31 121 be 2.⁸ Considering a dropout rate of 10%, 110 patients are required to yield a power
32
33 122 of 80% with a significance level of 0.05.¹⁴
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38 123 *Randomisation and allocation concealment*

39
40 124 One hundred and ten patients will be divided into EA and Sham-EA groups with a
41
42 125 ratio of 1:1. An independent biostatistician will generate a random sequence using the
43
44 126 R (version 3.4.4). A sequence of numbers will be prepared and sealed in an opaque
45
46 127 envelope. Only the acupuncturist will be allowed to open the envelope to obtain the
47
48 128 grouping code.
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51 129 *Single-blinding*

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55 130 The acupuncturist will be blinded to the grouping information in advance, and the
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3 131 treatment method according to the grouping information contained in envelopes. All
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5
6 132 participants, orthopaedic surgeons, and relevant healthcare staff will be blinded to the
7
8 133 study. The outcome assessor will not be aware of the treatment that patients received
9
10
11 134 and will only instruct the patient to fill in the scales. The independent biostatistician
12
13 135 will also be blinded when performing the statistical analyses. To maximize the
14
15 136 blinding of patients, an effective sham electroacupuncture method will be applied
16
17 137 with adhesive pads, a dull-tipped placebo needle, and a sham electrical stimulation
18
19
20 138 device. Details of the sham operation design are described in the following part.

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22
23 139 *Eligibility criteria*

24
25 140 *Eligible*

26
27
28 141 (1) Aged 55 to 80 years; (2) Meet the 1995 American College of Rheumatology
29
30 142 (ACR) diagnostic criteria for osteoarthritis; (3) Undergoing unilateral total knee
31
32 143 arthroplasty under general anaesthesia without surgical contraindications; (4)
33
34
35 144 American Society of Anesthesiologists (ASA) Grade I or II.

36
37 145 *Ineligible*

38
39
40 146 (1) The area of acupuncture points has skin damage and cannot perform
41
42 147 acupuncture; (2) Preoperative deep venous thrombosis or swelling of the lower
43
44 148 extremities; (3) Severe arrhythmia, heart failure, chronic obstructive pulmonary
45
46
47 149 disease, epilepsy, mental disease; (4) Received treatment of acupuncture in past 1
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49
50 150 month.

51
52 151 *Study interventions*

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55 152 *EA group*

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4 153 Patients will receive early acupuncture analgesia once a day from 24 to 72 hours
5
6 154 after surgery. The first session of acupuncture treatment will be performed at 24 hours
7
8 155 postoperatively. Firstly, the adhesive pads will be put on the acupoints of bilateral
9
10 156 *Futu* (Stomach 32, ST32), *Zusanli* (Stomach 36, ST36), *Yanglingquan* (Gall Bladder
11
12 157 34, GB34), and *Yinlingquan* (Spleen 9, SP9). 1.5 *cun* acupuncture needles
13
14 158 (0.25×40mm, Huatuo Inc.) will be manually inserted into the skin through the
15
16 159 adhesive pads (Figure. 2). When *De-qi* sensation is achieved, subsequent electrical
17
18 160 stimulation with a frequency of 2Hz, a continuous wave and tolerable intensity by the
19
20 161 patient will be applied to the four acupoints (GB 34 to ST32 and ST36 to SP9).
21
22 162 Needles with electrical stimulation will be retained for 20 minutes in each session.
23
24 163 The patients will receive a total of 3 treatments which were given once a day.
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30 164 *Sham-EA group*

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32
33 165 Similar to the EA group, three sessions of acupuncture will be provided at the
34
35 166 same time. An adhesive pad will be put on the sham-acupoint which is 20 mm distal
36
37 167 to the real acupoint (Figure. 3). The placebo needle has a blunt-tip and it will be
38
39 168 manually inserted into the adhesive pads but without skin penetration to provide
40
41 169 participant-blinding effects (Figure. 2). The sham electrical stimulation device will
42
43 170 have a connecting cord with a broken inner wire with no actual current output.
44
45 171 Needles will also be retained for 20 minutes in each session. The patients will receive
46
47 172 a total of 3 sham treatments which were given once a day. This Sham-EA method was
48
49 173 proved to be effective in a previous study.¹⁵
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54 174 *Postoperative analgesia*

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4 175 All patients will receive the same analgesic procedure. Fentanyl
5
6 176 patient-controlled analgesia (PCA) will be used at a continuous infusion rate of 0.25
7
8 177 $\mu\text{g}/(\text{kg}\cdot\text{h})$ and a bolus of 0.15 $\mu\text{g}/\text{kg}$ with a 10-minute lockout time. Patients will be
9
10 178 allowed to use Celebrex 200 mg per day. Besides, additional rescue doses of
11
12 179 analgesics will be provided upon demand for patients with a VAS score above 60.

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16 180 *Discontinuing criteria*

17
18 181 (1) Acupuncture cannot be tolerated after surgery or patients that cannot be
19
20 182 implemented according to the protocol; (2) Severe physiological and pathological
21
22 183 changes were found during surgery and it is not appropriate to receive acupuncture
23
24 184 treatment; (3) Patients in which the trial arrangement cannot be completed or the
25
26 185 safety judgment is affected due to surgical factors after the test; (4) Severe adverse
27
28 186 reactions, severe complications, and patients with rapid deterioration.

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34
35 188 *Outcome*

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37 189 *Primary outcome*

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39 190 *Pain*

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41
42 191 When the patients are discharged from the operating room, this will be recorded
43
44 192 as 0 hours. Outcome assessors will record VAS at 6, 24, 48, and 72 hours after surgery.
45
46 193 Patients can use a 100 mm visual analogue scale to assess the pain of their knee (from
47
48 194 no symptoms to very severe). Additional PCA dose requirement will be evaluated in
49
50 195 this study to reflect the degree of pain. Patients will be trained to adjust the PCA to
51
52 196 obtain an additional dose of analgesia depending on the degree of pain. This will be
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3 197 recorded 48 hours after surgery. Patients will be given an additional dose of analgesia
4
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6 198 upon demand if the VAS score is above 60. The additional use of analgesics within 2
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8
9 199 weeks after surgery will be recorded in the case report forms.

10 200 *Secondary outcome*

11
12
13 201 *Knee function and swelling*

14
15 202 Knee function will be measured based on Hospital for Special Surgery Knee
16
17
18 203 Score (HSS score) at one day before surgery and three days after surgery. All patients
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21 204 will first educated about the HSS score by a trained researcher until they fully
22
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24 205 understand the questionnaire, then asked to complete the form according to their
25
26 206 actual conditions. At 24 hours after surgery, the outcome assessor will remove the
27
28 207 elastic bandage and measure the circumference of the knee at the superior patellar
29
30 208 pole. A second measurement will be performed 72 hours after surgery. According to
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32
33 209 previous reports, electroacupuncture has the potential to promote functional
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35 210 rehabilitation.

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38 211 *Perioperative anxiety*

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40 212 Perioperative anxiety will be measured by the Hamilton Anxiety Scale (HAMA)
41
42
43 213 at one day before surgery and three days after surgery. HAMA has 14 levels to assess
44
45 214 the severity of a patient's anxiety, and it divides anxiety into physical (7~13) and
46
47 215 spiritual (1~6 and 14).

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50 216 *Postoperative nausea and vomiting (PONV)*

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52 217 PONV will be measured according to vomiting symptoms scores in 4-time points,
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55 218 including on the day of surgery and 1, 2, 3 days after surgery.¹⁶ Functional Living
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4 219 Index-Emesis is used to evaluate the effect of PONV on the quality of life, and it will
5
6 220 be measured 3 days after surgery.¹⁷
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8 221 *Postoperative complications and adverse events*
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10 222 All expected and unexpected adverse events will be measured during the
11
12
13 223 allocated intervention process and during the entire study period. Common adverse
14
15
16 224 events are fainting, needle sticking or breaking during acupuncture and acupuncture
17
18 225 hematomas. Other postoperative complications including incision infection, urinary
19
20
21 226 retention, deep vein thrombosis, and postoperative persistent pain will be recorded 6
22
23 227 weeks after surgery. All serious adverse events (SAEs) will be reported immediately
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25
26 228 to the sponsor to allow further investigations into their causes.
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28 229 *Data management*
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30 230 Data entry will be conducted by two independent trained research assistants using
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33 231 paper CRFs to record the research data after completion of final data collection. As
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36 232 acupuncture has known minimal risks, a formal data monitoring committee will not
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38 233 be required.^{6,18} Independent investigators of the hospital staff will monitor and audit
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40
41 234 the data periodically.
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43 235 *Statistical analysis*
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45 236 According to the intention to treat (ITT) principle, full analysis set (FAS) and
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48 237 per-protocol set (PPS) will be used for primary analysis. Safety set (SS) will not be
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51 238 required since acupuncture has minimal risks.^{6,18} Sensitivity analysis will be
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53 239 performed to determine the impact of incomplete records on results. Missing data will
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55 240 not be imputed. Statistical analysis will be performed using R (version 3.4.4). The
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4 241 difference between the two groups will be calculated and compared using the t-test if
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6 242 the Shapiro-Wilk test showed that the data is normally distributed, otherwise the
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8 243 Mann-Whitney U test will be used. A Pearson χ^2 or Fisher's exact test will be used to
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11 244 calculate the differences in the enumeration data. Mixed effects models will be used
12
13 245 to analyze the trend of changes in VAS scores with two factors of groups and time.¹⁹

15 246 *Ethics and dissemination*

17
18 247 This study has been approved by the ethics committee of Shanghai Guanghua
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20 248 Hospital of Integrated Chinese and Western Medicine (approval number AF13v2-2),
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22
23 249 and any modification of the protocol will be reported and approved by it. Written
24
25 250 inform consent will be obtained from all participants or their authorized agents. All
26
27
28 251 electroacupuncture treatments will be free and the research data will be strictly
29
30 252 confidential. The result of the trial will be presented on the website of the Chinese
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32
33 253 Clinical Trial Registry and published in peer-reviewed journals.

34 254 *Patient and Public Involvement*

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37 255 Patient and public were not involved in the design of this study. The participants
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40 256 will be informed of the result of this study during the follow-up visit. Besides, we will
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43 257 enlist their help in disseminating the research findings.

44 258 **Discussion**

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47 259 Multiple evidence-based ERAS strategies for TKA have been shown to reduce
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50 260 postoperative complications and improve the prognosis and patient satisfaction.
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52 261 Postoperative pain after TKA is mostly caused by postoperative functional exercise.
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55 262 Drug-free interventions, especially EA, are highly effective in pain relief and
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3 263 promoting functional rehabilitation. The minimal clinically important difference
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6 264 (MCID) is a measure that is used to evaluate the clinical significance of an
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9 265 intervention. In the case of standardized multimodal analgesia, the MCID for VAS of
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11 266 postoperative pain after TKA is -2.26, and the MCID can be used to evaluate the
12
13 267 effect of Sham-EA.²⁰ Further research is required to determine whether a single EA
14
15
16 268 without multimodal analgesia may provide enough analgesia for the patients after
17
18 269 TKA. We suggest incorporation of EA as a routine treatment in ERAS strategies for
19
20
21 270 TKA. EA may also be used as a new analgesia to replace opioids usage.
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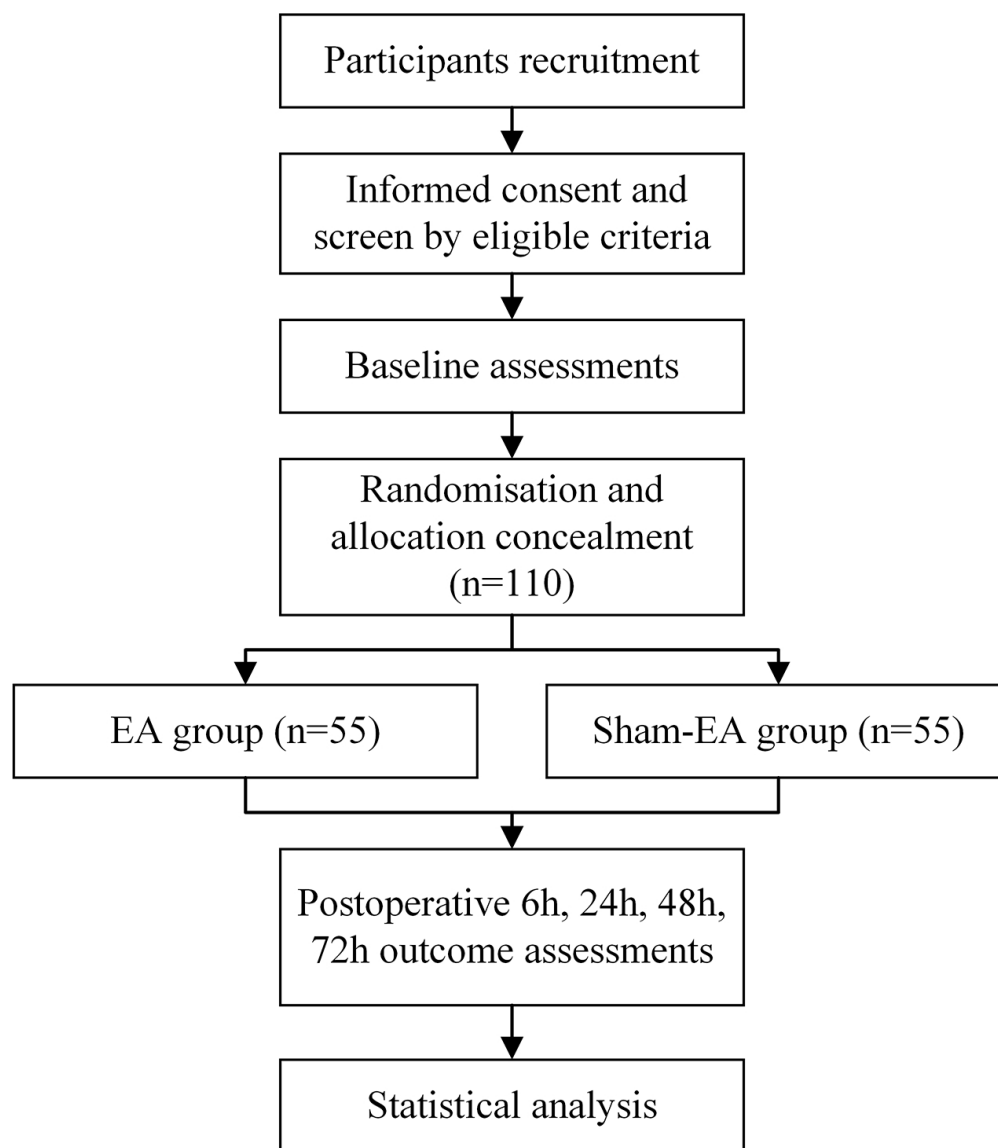
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Table 1. The schedule of trial enrolment, interventions and assessments

	Enrolment	Intervention period			
	Pre-OP	6 hours	24 hours	48 hours	72 hours
Enrolment					
Informed consent	•				
Assessment of eligibility	•				
Randomisation	•				
Interventions					
EA	•	•	•	•	•
Sham-EA	•				
Assessments					
VAS	•	•	•	•	•
Additional dose released by PCA				•	
HSS score	•				•
HAMA score	•				•
PONV		•	•	•	•
COK			•		•
Additional use of analgesics	•				•
Postoperative complications and adverse events		•	•	•	•

OP, operation; EA, electroacupuncture; VAS, Visual Analogue Score; PCA, patient controlled analgesia; HSS, hospital for special surgery; HAMA, Hamilton Anxiety Scale; PONV, post-operative nausea and vomiting; COK, circumference of knee

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43 Figure 1. Study flow diagram, including participants recruitment, eligibility, screening, randomization,
44 allocation concealment, and outcome assessments. EA, electroacupuncture.

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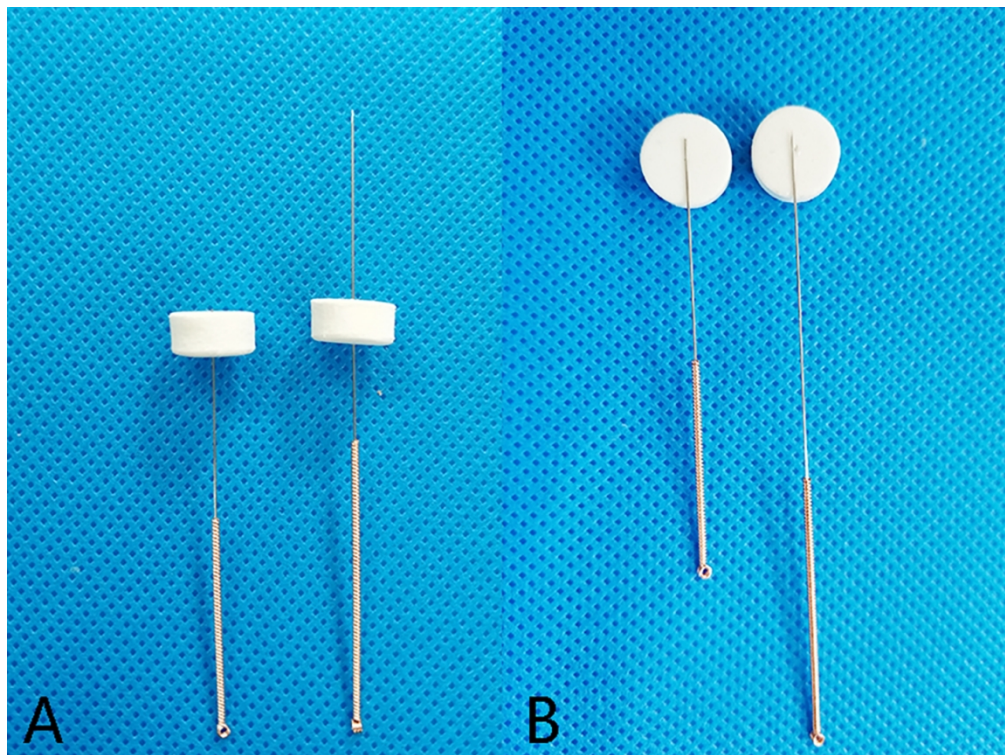


Figure 2. The difference between acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

119x90mm (300 x 300 DPI)

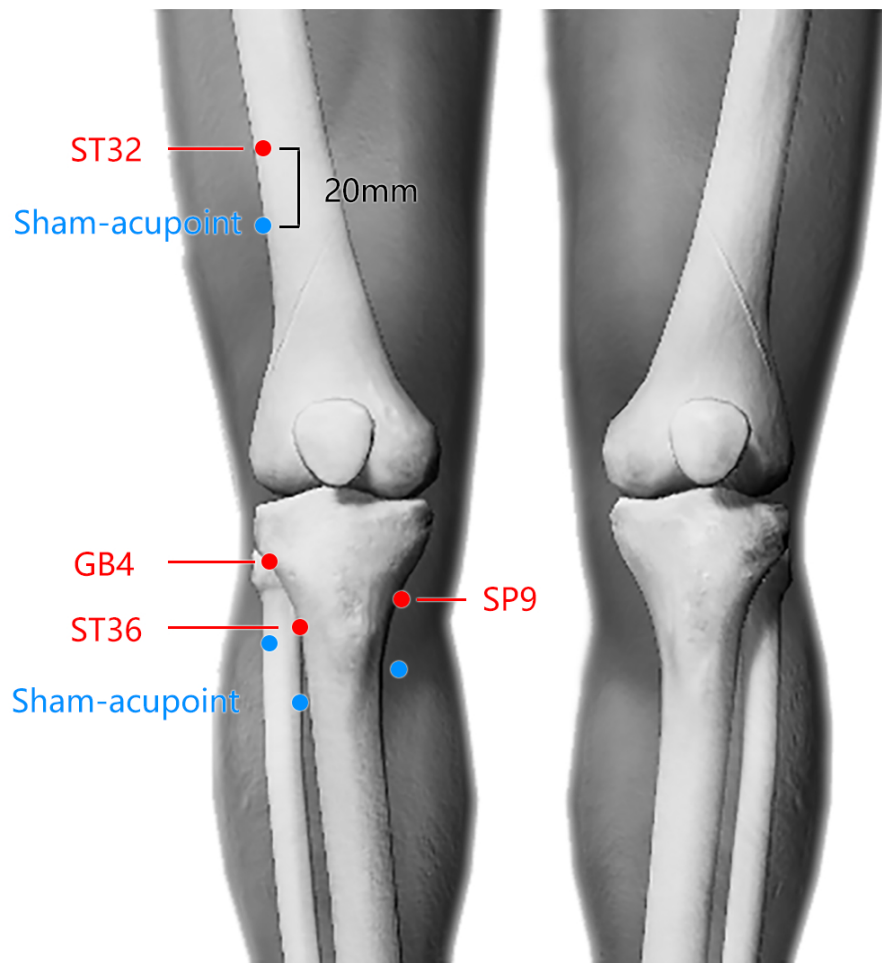


Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

94x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	13
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
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11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	4
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	3
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	3
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
40				
41				
42	Study setting	#9	Description of study settings (eg, community clinic,	5-6
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	7
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
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53				
54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-8
55	description		replication, including how and when they will be	
56			administered	
57				
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	9
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7				
8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	9
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
11				
12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	9
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
25				
26				
27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	17
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	6
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
44				
45				
46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
59				
60				

1	mechanism		envelopes), describing any steps to conceal the sequence	
2			until interventions are assigned	
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	6
5	implementation		participants, and who will assign participants to	
6			interventions	
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6-7
10			trial participants, care providers, outcome assessors, data	
11			analysts), and how	
12				
13				
14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	6-7
15	emergency		permissible, and procedure for revealing a participant's	
16	unblinding		allocated intervention during the trial	
17				
18				
19				
20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	11
21			and other trial data, including any related processes to	
22			promote data quality (eg, duplicate measurements, training	
23			of assessors) and a description of study instruments (eg,	
24			questionnaires, laboratory tests) along with their reliability	
25			and validity, if known. Reference to where data collection	
26			forms can be found, if not in the protocol	
27				
28				
29				
30				
31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	11
32	retention		up, including list of any outcome data to be collected for	
33			participants who discontinue or deviate from intervention	
34			protocols	
35				
36				
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38	Data management	#19	Plans for data entry, coding, security, and storage, including	11
39			any related processes to promote data quality (eg, double	
40			data entry; range checks for data values). Reference to	
41			where details of data management procedures can be	
42			found, if not in the protocol	
43				
44				
45				
46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
47			outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
49				
50				
51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
52	analyses		adjusted analyses)	
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
56	population and		adherence (eg, as randomised analysis), and any statistical	
57	missing data		methods to handle missing data (eg, multiple imputation)	
58				
59				
60				

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	n/a
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	11
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
20				
21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	11
22			and whether the process will be independent from	
23			investigators and the sponsor	
24				
25				
26				
27	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
28	approval		review board (REC / IRB) approval	
29				
30				
31	Protocol	#25	Plans for communicating important protocol modifications	12
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	12
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	12
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	12
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	2
56	interests		investigators for the overall trial and each study site	
57				
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59	Data access	#29	Statement of who will have access to the final trial dataset,	12
60				

		and disclosure of contractual agreements that limit such access for investigators	
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4	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care, and for	12
5	trial care	compensation to those who suffer harm from trial	
6		participation	
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8			
9	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial	12
10	trial results	results to participants, healthcare professionals, the public,	
11		and other relevant groups (eg, via publication, reporting in	
12		results databases, or other data sharing arrangements),	
13		including any publication restrictions	
14			
15			
16			
17	Dissemination policy:	#31b Authorship eligibility guidelines and any intended use of	12
18	authorship	professional writers	
19			
20			
21	Dissemination policy:	#31c Plans, if any, for granting public access to the full protocol,	12
22	reproducible	participant-level dataset, and statistical code	
23	research		
24			
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26			
27	Informed consent	#32 Model consent form and other related documentation given	n/a
28	materials	to participants and authorised surrogates	
29			
30			
31	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	n/a
32		biological specimens for genetic or molecular analysis in the	
33		current trial and for future use in ancillary studies, if	
34		applicable	
35			
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BMJ Open

Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026084.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Dec-2018
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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Research methods
Keywords:	electroacupuncture, postoperative pain, total knee arthroplasty, the study protocol

SCHOLARONE™
Manuscripts

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4 1 **Application of electroacupuncture for postoperative pain management after total**
5
6 2 **knee arthroplasty: a study protocol for a single-blinded, randomised**
7
8 3 **placebo-controlled trial**
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11 4 Sheng Zhong, Hai Huang, Jun Xie, Ling Zhao, Xiu-ling Song, Yue-lai Chen, Lian-bo
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14 5 Xiao

16
17 6 **Author Affiliations:**

18
19 7 Sheng Zhong, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
20
21
22 8 Medicine, Shanghai, China, drcyan@foxmail.com

23
24 9 Hai Huang, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
25
26
27 10 Medicine, Shanghai, China, haichuan880@163.com

28
29
30 11 Jun Xie, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
31
32
33 12 Medicine, Shanghai, China, leoxie199@126.com

34
35 13 Ling Zhao, PhD, Shanghai University of Traditional Chinese Medicine, Shanghai,
36
37
38 14 China, zhao099@hotmail.com

39
40 15 Xiu-ling Song, MD, Shanghai University of Traditional Chinese Medicine, Shanghai,
41
42
43 16 China, songxiuling2007@163.com

44
45 17 Yue-lai Chen, PhD, Shanghai University of Traditional Chinese Medicine, Shanghai,
46
47
48 18 China, chenyuelai@163.com

49
50 19 Lian-bo Xiao, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
51
52
53 20 Medicine, Shanghai, China, 13701888178@163.com

54
55
56 21 **Corresponding Author:**

57
58 22 Lian-bo Xiao, PhD, Guanghua Hospital, Shanghai University of Traditional Chinese
59
60

1
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4 23 Medicine, No. 540 Xinhua Road, Changning District, Shanghai (CN 200052), China,
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14
15
16
17 24 13701888178@163.com, +8613701888178
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28 25 Lian-bo Xiao and Yue-lai Chen contributed equally to this paper.
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27 **Author Contributions**

28 SZ and LBX conceived the study while HH, JX, LZ, XLS designed the study.

29 The study protocol was drafted by SZ and LBX, and was revised by YLC. All authors

30 approved the final manuscript of this study protocol.

31 **Word Count:**2190

32 **Funding**

33 This work will be supported by Project of Shanghai University of Traditional

34 Chinese Medicine Grant (Y201812).

35 **Conflicts of Interests**

36 The authors declared that there are no potential conflicts of interest with respect

37 to the research, authorship, and/or publication of this study.

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2
3 **Abstract:**
4

5 40 Introduction: The purpose of this study is to assess the efficacy of electroacupuncture
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8 41 to relieve pain and promote functional rehabilitation after total knee surgery.
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10 42 Methods and analysis: We propose a single-blinded, randomised placebo-controlled
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13 43 trial to evaluate the efficacy of electroacupuncture. Patients with osteoarthritis (aged
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16 44 55 to 80 years) undergoing unilateral total knee arthroplasty will be included in the
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18 45 trial. They will be randomised to receive either electroacupuncture or
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21 46 sham-electroacupuncture. A total of 110 patients will receive electroacupuncture and
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23 47 sham-electroacupuncture for three days after TKA. Postoperative pain will be
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26 48 measured using VAS score, and the need for an additional dose of opioid and
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29 49 analgesics will be recorded as the primary outcome. Secondary outcomes include
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31 50 knee function and swelling, postoperative anxiety, postoperative nausea and vomiting
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34 51 among other complications.
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36 52 Ethics and dissemination: This study has been approved by the ethics committee, and
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39 53 subsequent modifications of the protocol will be reported and approved by it. Written
40
41
42 54 inform content will be obtained from all of the participants or their authorized agents.
43

44 55 Trial registration number: ChiCTR1800016200
45

46 56 Keywords: electroacupuncture, postoperative pain, total knee arthroplasty, study
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49 57 protocol
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54 **Article Summary**
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57 60 *Strengths and limitations of this study*
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60 61 1. The study is the first single-blinded, randomised placebo-controlled trial in China
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4 62 to assess the efficacy of electroacupuncture to relieve pain and promote functional
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7 63 rehabilitation after total knee surgery.

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9 64 2. The study will use an efficient sham-electroacupuncture method that makes it hard
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12 65 for patients with electroacupuncture treatment experience to distinguish between both
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15 66 treatments.

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17 67 3. The study is rigorously designed, which includes adequate sample size, proper
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20 68 randomization and allocation concealment, and prospective trial registration to reduce
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23 69 selection and confounding bias.

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25 70 4. There is still bias in the implementation of blind method due to the unblinded
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28 71 acupuncturists.

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31 32 73 **Introduction**

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35 74 Total knee arthroplasty (TKA) is the most frequently performed surgical
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38 75 procedure for end-stage osteoarthritis and rheumatoid arthritis. Moderate to severe
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41 76 postoperative pain is a major complaint in most patients. Acute and subacute
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44 77 postoperative pain is highly associated with persistent post-surgical pain (PPSP),
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47 78 especially when the acute pain is not treated with effective analgesia.¹ A recent study
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50 79 showed that 10%-34% and 7%-23% of patients reported severe pain after TKA and
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53 80 total hip arthroplasty (THA), respectively, which indicates that TKA patients are more
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56 81 likely to develop PPSP.² Multimodal analgesia has been used for 20 years and it is
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59 82 considered to be the most effective strategy for PPSP. Abuse of analgesic drugs has
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62 83 increased exposure of the public to the side effects of non-steroidal anti-inflammatory

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4 84 drugs (NSAIDs) and opioids.^{3,4} Drug-free interventions to reduce pain or opioid
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6 85 consumption are more consistent with the principles of Enhanced Recovery After
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9 86 Surgery (ERAS).

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11 Clinical trials and systematic reviews have shown that the efficacy of
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14 88 electroacupuncture or acupuncture analgesia is controversial.⁵⁻⁸ Electrotherapy and
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17 89 acupuncture have been proved to be potentially beneficial for postoperative pain after
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20 90 TKA.⁹ Studies on the mechanism of electroacupuncture analgesia indicated that it
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23 91 activates many bioactive chemicals through peripheral, spinal, and supraspinal
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26 92 mechanisms.¹⁰ The supraspinal mechanisms showed EA analgesia is highly associated
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29 93 with descending pain regulation of the periaqueductal grey (PAG) and the rostral
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32 94 ventromedial medulla (RVM).^{10,11} The PAG-RVM system is recognized as the central
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35 95 site of action of analgesic agents including opioids, cyclooxygenase inhibitors, and
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38 96 cannabinoids.¹²⁻¹⁴ We hypothesize that EA may exert an analgesic effect by activating
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41 97 the PAG-RVM system. Besides, the placebo effect is highly associated with both
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44 98 areas of the brain.^{15,16} Strict blinding is required to rule out the effects of the placebo
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47 99 effect on outcomes.

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51 100 The purpose of this study is to assess the efficacy of electroacupuncture on pain
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54 101 relief and promoting functional rehabilitation after total knee surgery. We will use a
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57 102 large sample size and a reliable blind method of electroacupuncture to ensure a
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60 103 credible conclusion.

104 105 **Methods and analysis**

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4 106 *Study Context*
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6 107 This study will be a single-blinded, randomised placebo-controlled trial
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9 108 performed at the inpatient ward of Shanghai University of Traditional Chinese
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12 109 Medicine Guanghua Hospital, Shanghai, China. The annual surgical number of total
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14 110 knee arthroplasty for osteoarthritis was about 600 in 2017. We planned to begin
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17 111 recruiting patients from June 2018 and patients preparing for unilateral TKA will be
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19
20 112 recruited. In this study, there will be 7 investigators, including a chief orthopaedic
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22 113 surgeon (LBX) with 20 years of clinical experience, two orthopaedic physicians (JX
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24 114 and SZ), two Chinese medicine acupuncturists (HH and YLC), and two outcome
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27 115 assessors (LZ, and XLS). ERAS programme (Table 1) will be performed by trained
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30 116 nurses and physiotherapists at the inpatient ward. The ERAS programme is routinely
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33 117 applied, but electroacupuncture has been added to analgesia. The schedule and the
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35 118 study flow diagram is shown in Table 2 and Figure 1.
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38 119 *Sample size calculation*
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40 120 In a previous meta-analysis study in which pain relief was compared between EA
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43 121 groups and controls, the minimal mean difference of the two groups based on the
44
45 122 VAS score (on a scale of 0-10) was -1.14 (95% CI, -1.90 to -0.38), and the standard
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48 123 deviation was estimated to be 2.⁹ Considering a dropout rate of 10%, 110 patients
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50
51 124 are required to yield a power of 80% with a significance level of 0.05.¹⁷
52

53 125 *Randomisation and allocation concealment*
54

55
56 126 One hundred and ten patients will be divided into EA and Sham-EA groups with
57
58
59 127 a ratio of 1:1. An independent biostatistician will generate a random sequence using
60

1
2
3
4 128 the R (version 3.4.4). A sequence of numbers will be prepared and sealed in an
5
6
7 129 opaque envelope. Only the acupuncturist will be allowed to open the envelope to
8
9 130 obtain the grouping code.

11 131 *Single-blinding*

12
13
14 132 The acupuncturist will be blinded to the grouping information in advance, and the
15
16
17 133 treatment method according to the grouping information contained in envelopes. All
18
19
20 134 participants, orthopaedic surgeons, and relevant healthcare staff will be blinded to the
21
22
23 135 study. The outcome assessor will not be aware of the treatment that patients received
24
25
26 136 and will only instruct the patient to fill in the scales. The independent biostatistician
27
28
29 137 will also be blinded when performing the statistical analyses. To maximize the
30
31
32 138 blinding of patients, an effective sham electroacupuncture method will be applied
33
34
35 139 with adhesive pads, a dull-tipped placebo needle, and a sham electrical stimulation
36
37
38 140 device. Details of the sham operation design are described in the following part.

39 141 *Eligibility criteria*

40 142 *Eligible*

41
42
43 143 (1) Aged 55 to 80 years; (2) Meet the 1995 American College of Rheumatology
44
45
46 144 (ACR) diagnostic criteria for osteoarthritis; (3) Undergoing unilateral total knee
47
48
49 145 arthroplasty under general anaesthesia without surgical contraindications; (4)
50
51
52 146 American Society of Anesthesiologists (ASA) Grade I or II.

53 147 *Ineligible*

54
55
56 148 (1) The area of acupuncture points has skin damage and cannot perform
57
58
59 149 acupuncture; (2) Preoperative deep venous thrombosis or swelling of the lower
60

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3
4 150 extremities; (3) Severe arrhythmia, heart failure, chronic obstructive pulmonary
5
6
7 151 disease, epilepsy, mental disease; (4) Received treatment of acupuncture in past 1
8
9 152 month.

10
11
12 153 *Study interventions*

13
14 154 *EA group*

15
16
17 155 Patients will receive early acupuncture analgesia once a day from 24 to 72 hours
18
19 156 after surgery. The first session of acupuncture treatment will be performed at 24 hours
20
21 157 postoperatively. Firstly, the adhesive pads will be put on the acupoints of bilateral
22
23 158 *Futu* (Stomach 32, ST32), *Zusanli* (Stomach 36, ST36), *Yanglingquan* (Gall Bladder
24
25 159 34, GB34), and *Yinlingquan* (Spleen 9, SP9). 1.5 *cun* acupuncture needles
26
27 160 (0.25×40mm, Huatuo Inc.) will be manually inserted into the skin through the
28
29 161 adhesive pads (Figure. 2). When *De-qi* sensation is achieved, subsequent electrical
30
31 162 stimulation with a frequency of 2Hz, a continuous wave and tolerable intensity by the
32
33 163 patient will be applied to the four acupoints (GB 34 to ST32 and ST36 to SP9) using a
34
35 164 Hwato SDZ-V electrical stimulation device (Suzhou Medical Appliance Factory,
36
37 165 Suzhou, China). Needles with electrical stimulation will be retained for 20 minutes in
38
39 166 each session. The patients will receive a total of 3 treatments which were given once a
40
41 167 day.

42
43
44 168 *Sham-EA group*

45
46
47 169 Similar to the EA group, three sessions of acupuncture will be provided at the
48
49 170 same time. An adhesive pad will be put on the sham-acupoint which is 20 mm distal
50
51 171 to the real acupoint (Figure. 3). The placebo needle has a blunt-tip and it will be
52
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4 172 manually inserted into the adhesive pads but without skin penetration to provide
5
6 173 participant-blinding effects (Figure. 2). The sham electrical stimulation device will
7
8
9 174 have a connecting cord with a broken inner wire with no actual current output.
10
11
12 175 Needles will also be retained for 20 minutes in each session. The patients will receive
13
14 176 a total of 3 sham treatments which were given once a day. This Sham-EA method was
15
16
17 177 proved to be effective in a previous study.¹⁸

178 *Postoperative analgesia*

179 All patients will receive the same analgesic procedure. Fentanyl
180 patient-controlled analgesia (PCA) will be used at a continuous infusion rate of 0.25
181 $\mu\text{g}/(\text{kg}\cdot\text{h})$ and a bolus of 0.15 $\mu\text{g}/\text{kg}$ with a 10-minute lockout time. Patients will be
182 allowed to use Celebrex 200 mg per day. Besides, additional rescue doses of
183 analgesics will be provided upon demand for patients with a VAS score above 60.

184 *Discontinuing criteria*

185 (1) Acupuncture cannot be tolerated after surgery or patients that cannot be
186 implemented according to the protocol; (2) Severe physiological and pathological
187 changes were found during surgery and it is not appropriate to receive acupuncture
188 treatment, such as anaesthesia accidents, cardiac-cerebrovascular accidents, nerve or
189 vascular injury during surgery; (3) Patients in which the trial arrangement cannot be
190 completed or the safety judgment is affected due to surgical factors after the test; (4)
191 Severe adverse reactions, severe complications, such as deep vein thrombosis,
192 pulmonary embolism and severe allergic reactions.

193

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4 194 *Outcome*

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6 195 *Primary outcome*

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8
9 196 *Pain*

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11 197 When the patients are discharged from the operating room, this will be recorded
12
13
14 198 as 0 hours. Patients will put a mark on a 100 mm visual analogue scale to assess the
15
16
17 199 pain of their knee (from no pain to very severe) at 6, 24, 48, and 72 hours after
18
19
20 200 surgery, then assessors record it. Additional PCA dose requirement will be evaluated
21
22 201 in this study to reflect the degree of pain. Patients will be trained to adjust the PCA to
23
24 202 obtain an additional dose of analgesia depending on the degree of pain. This will be
25
26
27 203 recorded 48 hours after surgery. Patients will be given an additional dose of analgesia
28
29
30 204 upon demand if the VAS score is above 60. The additional use of analgesics within 2
31
32
33 205 weeks after surgery will be recorded in the case report forms.

34
35 206 *Secondary outcome*

36
37 207 *Knee function and swelling*

38
39
40 208 Knee function will be measured based on Hospital for Special Surgery
41
42 209 Knee-Rating Scale ¹⁹ (HSS scale) (Supplemental file) at one day before surgery and
43
44
45 210 three days after surgery. All patients will first be educated about the HSS scale by a
46
47
48 211 trained researcher until they fully understand the questionnaire, then asked to
49
50
51 212 complete the form according to their actual conditions. At 24 hours after surgery, the
52
53
54 213 outcome assessor will remove the elastic bandage and measure the circumference of
55
56
57 214 the knee at the superior patellar pole. A second measurement will be performed 72
58
59
60 215 hours after surgery.

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4 216 *Perioperative anxiety*

5
6 217 Perioperative anxiety will be measured by the Hamilton Anxiety Scale
7
8
9 218 (HAMA)²⁰ (Supplemental file) at one day before surgery and three days after surgery.
10
11
12 219 HAMA has 14 levels to assess the severity of a patient's anxiety, and it divides
13
14 220 anxiety into physical (7~13) and spiritual (1~6 and 14).

15
16
17 221 *Postoperative nausea and vomiting (PONV)*

18
19 222 PONV will be measured according to vomiting symptoms scores in 4-time points,
20
21
22 223 including on the day of surgery and 1, 2, 3 days after surgery.²¹ Functional Living
23
24 224 Index-Emesis (FLIE)²² (Supplemental file) is used to evaluate the effect of PONV on
25
26
27 225 the quality of life, and it will be measured 3 days after surgery.

28
29
30 226 *Postoperative complications and adverse events*

31
32 227 All expected and unexpected adverse events will be measured during the
33
34
35 228 allocated intervention process and during the entire study period. Acupuncture-related
36
37
38 229 adverse events are hematoma and syncope during acupuncture. Other postoperative
39
40
41 230 complications including incision infection, urinary retention, deep vein thrombosis,
42
43 231 and postoperative persistent pain will be recorded 6 weeks after surgery. All serious
44
45
46 232 adverse events (SAEs) will be reported immediately to the sponsor to allow further
47
48
49 233 investigations into their causes.

50
51 234 *Data management*

52
53 235 Data entry will be conducted by two independent trained research assistants using
54
55
56 236 paper CRFs to record the research data after completion of final data collection. As
57
58
59 237 acupuncture has known minimal risks, a formal data monitoring committee will not
60

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4 238 be required.^{8,23} Independent investigators of the hospital staff will monitor and audit
5
6 239 the data periodically.
7

8 9 240 *Statistical analysis*

10
11 241 According to the intention to treat (ITT) principle, full analysis set (FAS) and
12
13 242 per-protocol set (PPS) will be used for primary analysis. Safety set (SS) will not be
14
15 243 required since acupuncture has minimal risks.^{8,23} Sensitivity analysis will be
16
17 244 performed to determine the impact of incomplete records on results. Missing data will
18
19 245 not be imputed. Statistical analysis will be performed using R (version 3.4.4). The
20
21 246 difference between the two groups will be calculated and compared using the t-test if
22
23 247 the Shapiro-Wilk test showed that the data is normally distributed, otherwise the
24
25 248 Mann-Whitney U test will be used. A Pearson χ^2 or Fisher's exact test will be used to
26
27 249 calculate the differences in the count data. Mixed effects models will be used to
28
29 250 analyze the trend of changes in VAS scores with two factors of groups and time.²⁴
30
31
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37 251 *Ethics and dissemination*

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39
40 252 This study has been approved by the ethics committee of Shanghai Guanghua
41
42 253 Hospital of Integrated Chinese and Western Medicine (approval number AF13v2-2),
43
44 254 and any modification of the protocol will be reported and approved by it. Written
45
46 255 informed consent will be obtained from all participants or their authorized agents. All
47
48 256 electroacupuncture treatments will be free and the research data will be strictly
49
50 257 confidential. The result of the trial will be presented on the website of the Chinese
51
52 258 Clinical Trial Registry and published in peer-reviewed journals.
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58 259 *Patient and Public Involvement*

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260 Patient and public were not involved in the design of this study. The participants
261 will be informed of the result of this study during the follow-up visit. Besides, we will
262 enlist their help in disseminating the research findings.

263 Discussion

264 Drug-free interventions, especially EA, have been proven effective in pain relief
265 and promoting functional rehabilitation,^{25,26} and they will have good prospects for
266 relieving opioid abuse or overuse of NSAIDs. However, the effect and mechanism of
267 acupuncture analgesia are not clear, and the placebo effect is considered to play an
268 important role.⁸ This study has enough samples to obtain reliable results and we have
269 improved the implementation of blinding to reduce the placebo effect. We hope that
270 the results of the study will provide new evidence for electroacupuncture treatment of
271 postoperative pain in TKA. Another question is to determine if the statistical
272 difference between the two groups is clinically conscious. The minimal clinically
273 important difference (MCID) is a measure that is used to evaluate the clinical
274 significance of an intervention. In the case of standardized multimodal analgesia, the
275 MCID for VAS of postoperative pain after TKA is -22.6 (on a scale of 0-100), and the
276 MCID can be also used to evaluate the difference of EA and sham.²⁷

277 Multiple evidence-based ERAS strategies for TKA have been shown to reduce
278 postoperative complications and improve prognosis and patient satisfaction.
279 Postoperative analgesia is an important part of ERAS. This study is based on add-on
280 design, electroacupuncture and sham are applied to two groups of patients who used
281 standard multimodal analgesia to evaluate the benefits of electroacupuncture on

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4 282 postoperative pain in TKA. We recommend EA and more non-drug therapies as a
5
6 283 routine treatment in ERAS programme of TKA if results of the study prove that it
7
8
9 284 really works.
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Table 1. Enhanced Recovery After Surgery Programme

Preoperative

- 1 Preoperative education
 - 2 Carbohydrate loading preoperatively and avoidance of prolonged starving
 - 3 Use of preoperative probiotics
 - 4 No mechanical bowel preparation
 - 5 No premedication
 - 6 Preemptive analgesia
-

Intraoperative

- 7 Maintenance of normothermia
 - 8 Goal-directed perioperative fluid administration
 - 9 Minimally invasive incision
 - 10 Avoidance of nasogastric tubes and deep vein catheterization
 - 11 Avoidance of bladder catheter, if necessary early removal of bladder catheter
 - 12 Use of tranexamic acid
 - 13 Periarticular local injection analgesia
-

Postoperative

- 14 Multimodal analgesia: PCA analgesia, NSAIDs; Avoidance of opioid analgesia
 - 15 Use of postoperative antiemetic and laxatives
 - 16 Enforced early mobilisation
 - 17 Enforced early postoperative oral feeding
-

PCA, patient controlled analgesia; NSAIDs, non-steroidal antiinflammatory drugs

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Table 2. The schedule of trial enrolment, interventions and assessments

	Enrolment		Intervention period		
	Pre-OP	6 hours	24 hours	48 hours	72 hours
Enrolment					
Informed consent	•				
Assessment of eligibility	•				
Randomisation	•				
Interventions					
EA		•	•	•	•
Sham-EA		•	•	•	•
Assessments					
VAS	•	•	•	•	•
Additional dose released by PCA				•	
HSS scale	•				•
HAMA score	•				•
PONV		•	•	•	•
COK			•		•
Additional use of analgesics	•				•
Postoperative complications and adverse events		•	•	•	•

OP, operation; EA, electroacupuncture; VAS, Visual Analogue Score; PCA, patient-controlled analgesia; HSS, hospital for special surgery; HAMA, Hamilton Anxiety Scale; PONV, post-operative nausea and vomiting; COK, circumference of knee

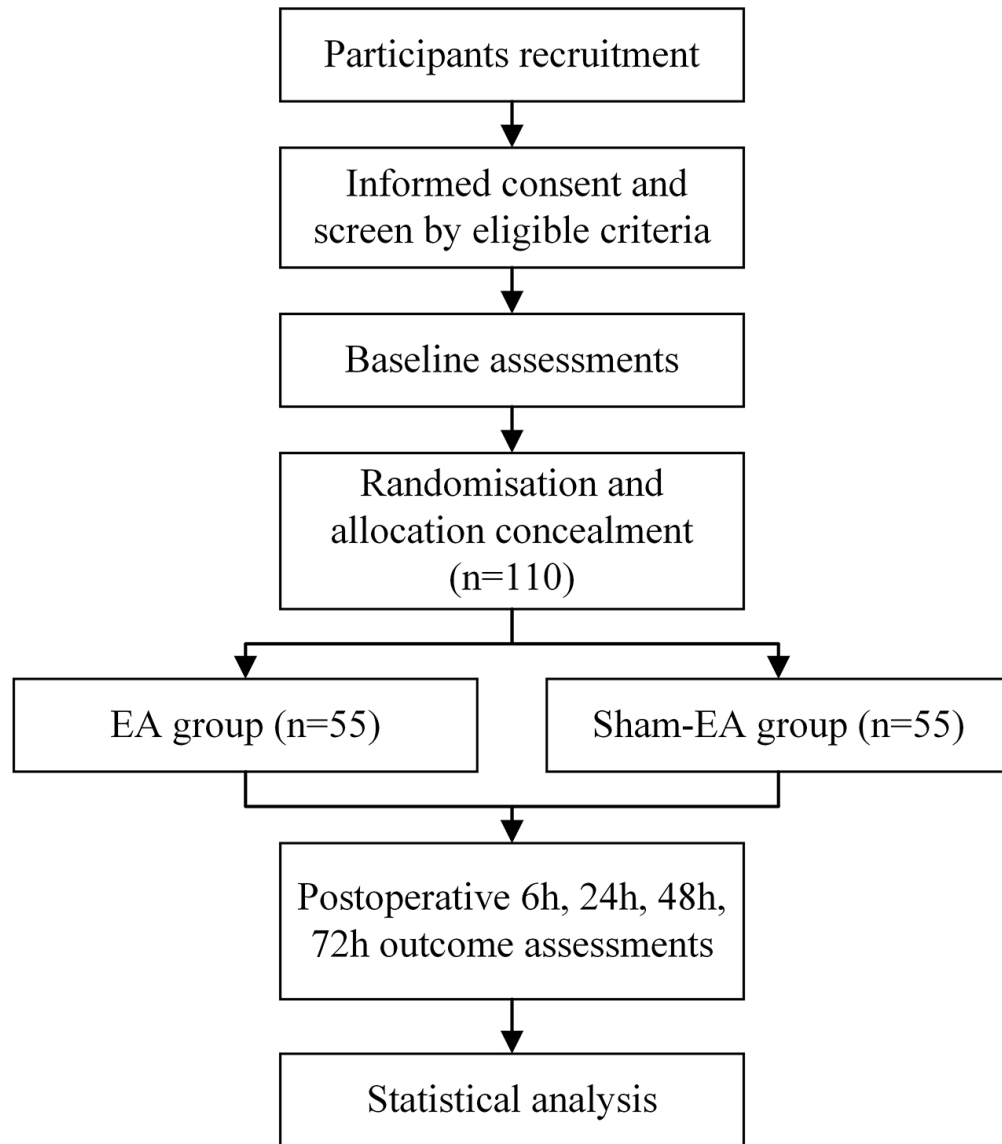
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4 **373 Figure Legend**

5
6 374 Figure 1. The study flow diagram, including participants recruitment, eligibility,
7
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9 375 screening, randomization, allocation concealment, and outcome assessments. EA,
10
11
12 376 electroacupuncture.

13
14 377 Figure 2. The difference between the acupuncture needle and placebo. (A) The
15
16
17 378 placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the
18
19
20 379 skin. The acupuncture needle (right) to be inserted into the skin through the adhesive
21
22
23 380 pads. (B) The tip of the placebo needle (left) is blunt.

24
25 381 Figure 3. Location of acupoints for the electroacupuncture and sham
26
27
28 382 electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach
29
30 383 36; SP9, Spleen 9.



43 Figure 1. Study flow diagram, including participants recruitment, eligibility, screening, randomization,
44 allocation concealment, and outcome assessments. EA, electroacupuncture.

45 107x122mm (300 x 300 DPI)

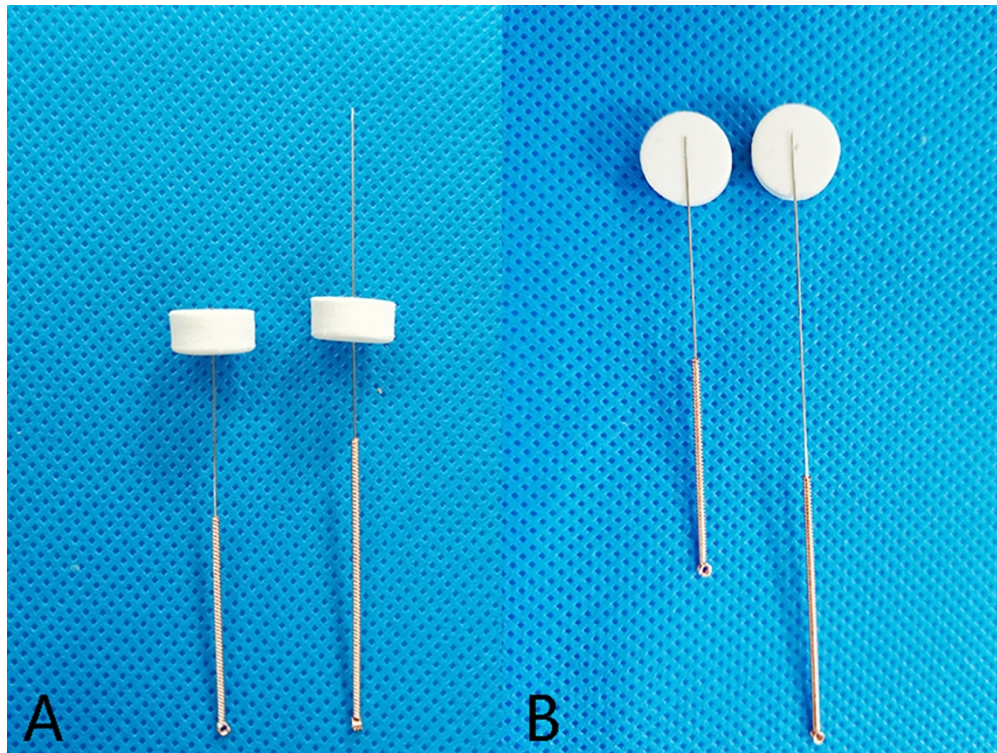


Figure 2. The difference between acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

119x90mm (300 x 300 DPI)

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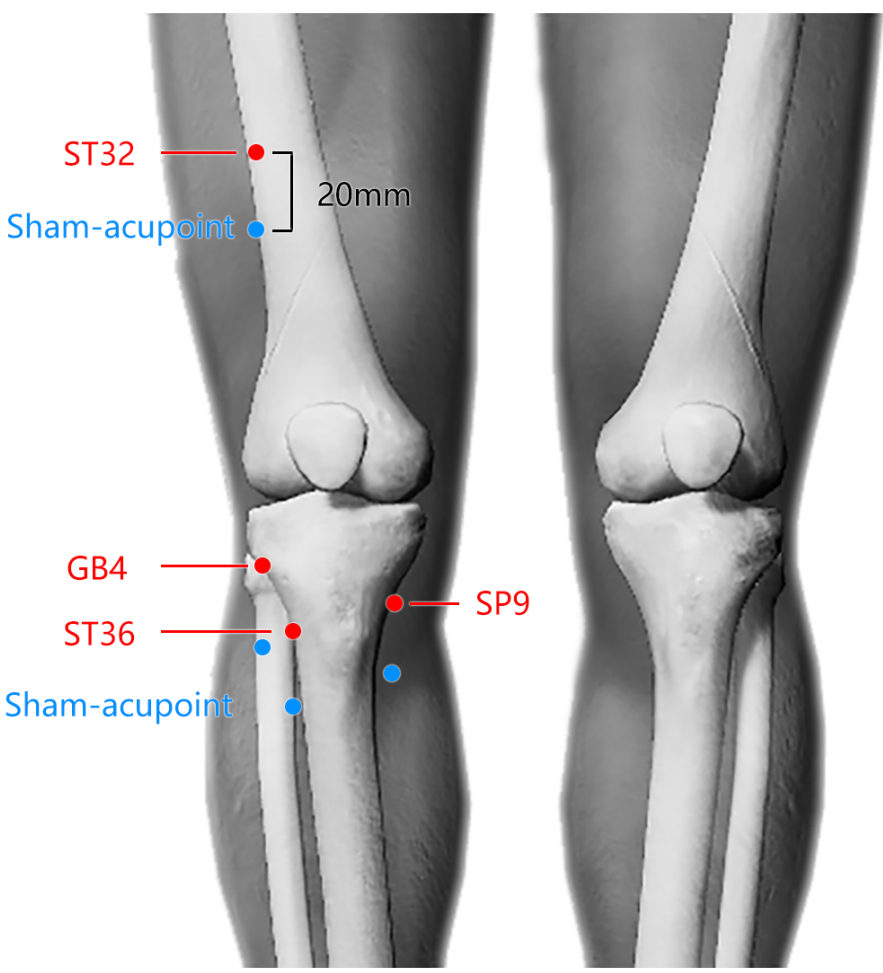


Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

94x90mm (300 x 300 DPI)

Supplemental file

1. Hospital for Special Surgery Knee-Rating Scale¹

Hospital for Special Surgery Knee-Rating Scale (HSS)

Criteria	Points
Pain (30 points)	
No pain at any time	30
No pain on walking	15
Mild pain on walking	10
Moderate pain on waling	5
Severe pain on walking	0
No pain at rest	15
Mild pain at rest	10
Moderate pain at rest	5
Severe pain at rest	0
Function (22 points)	
Walking and standing unlimited	12
Walking distance of 5-10 blocks and standing ability intermittent >1/2hr	10
Walking 1-5 blocks and standing up < 1/2hr	8
Walking less than 1 block	4
Cannot walk	0
Climbing stairs	5
Climbing stairs with support	2
Transfer activity	5
Transfer activity with support	2
Range of Motion (18 points)	
1 point for each 8 degrees (max 18 points)	18
Muscle Strength (10 points)	
Excellent: cannot break quadriceps power	10
Good: can break the quadriceps power	8
Fair: move through the arc of motion	4
Poor: cannot move through arc of motion	0
Flexion Deformity (10 points)	
No deformity	10
Less than 5 degrees	8
5-10 degrees	5
> 10 degrees	0
Instability (10 points)	
None	10

1		
2		
3	Mild: 0-5 degrees	8
4	Moderate: 5-15 degrees	5
5	Severe: > 15degrees	0
6		
7	Subtraction	
8	One cane	-1
9	One crutch	-2
10	Two crutches	-3
11	Extension lag of 5 degrees	-2
12	Extension lag of 10 degrees	-3
13	Extension lag of 15 degrees	-5
14	Each 5 degrees of varus	-1
15	Each 5 degrees of valgus	-1
16		
17		
18		
19		

20 Excellent ≥ 85

21 Good = 70-84

22 Fair = 60-69

23 Poor ≤ 60

26 2. Hamilton Anxiety Rating Scale (HAMA)²

30 **Hamilton Anxiety Rating Scale (HAMA)**

31 Below is a list of phrases that describe certain feeling that people have. Rate the
 32 patients by finding the answer which best describes the extent to which he/she has these
 33 conditions. Select one of the five responses for each of the fourteen questions.
 34
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36 0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

39 **1 Anxious mood**

40 Worries, anticipation of the worst, fearful anticipation,
 41 irritability.

42 0 1 2 3 4

43 **2 Tension**

44 Feelings of tension, fatigability, startle response, moved to
 45 tears easily, trembling, feelings of restlessness, inability to
 46 relax.

47 0 1 2 3 4

48 **3 Fears**

49 Of dark, of strangers, of being left alone, of animals, of
 50 traffic, of crowds.

51 0 1 2 3 4

52 **4 Insomnia**

53 Difficulty in falling asleep, broken sleep, unsatisfying sleep
 54 and fatigue on waking, dreams, nightmares, night terrors

55 0 1 2 3 4

56 **5 Intellectual**

57 Difficulty in concentration, poor memory.

58 0 1 2 3 4

6 Depressed mood

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

0 1 2 3 4

7 Somatic (muscular)

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

0 1 2 3 4

8 Somatic (sensory)

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

0 1 2 3 4

9 Cardiovascular symptoms

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

0 1 2 3 4

10 Respiratory symptoms

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

0 1 2 3 4

11 Gastrointestinal symptoms

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

0 1 2 3 4

12 Genitourinary symptoms

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

0 1 2 3 4

13 Autonomic symptoms

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

0 1 2 3 4

14 Behavior at interview

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

0 1 2 3 4

0 ~ 7: No anxiety

8~14: Possible anxiety

15~21: Mild anxiety

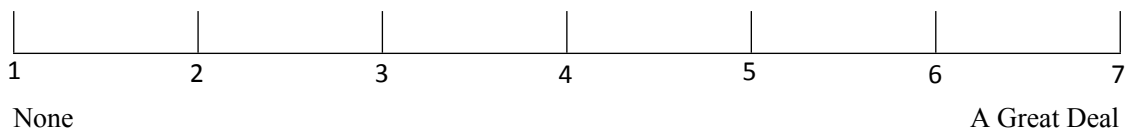
22~29: Obvious anxiety

>29: Severe anxiety

3. Functional Living Index Emesis (FLIE)³

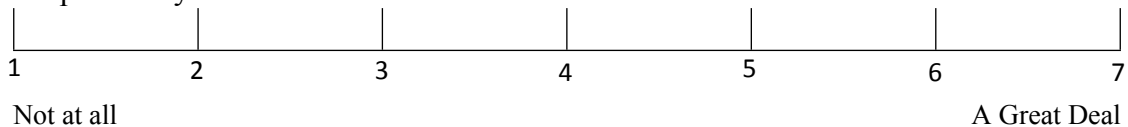
Functional Living Index Emesis (FLIE)

1. How much nausea have you had in the past 3 days?



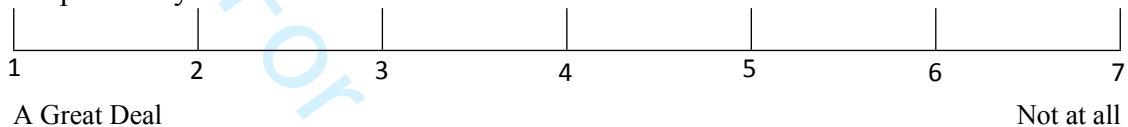
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2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?



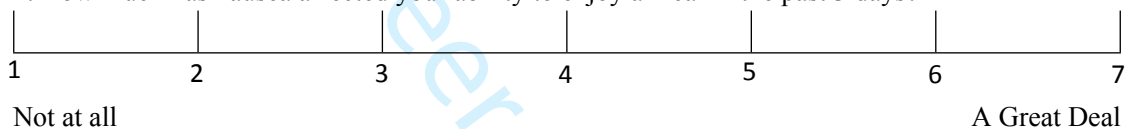
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3. Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?



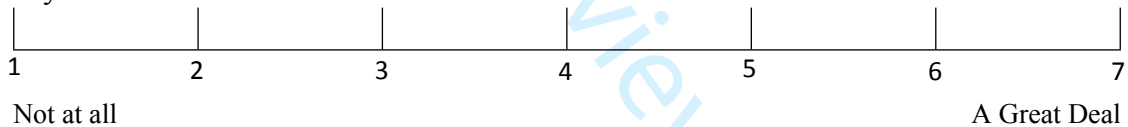
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4. How much has nausea affected your ability to enjoy a meal in the past 3 days?



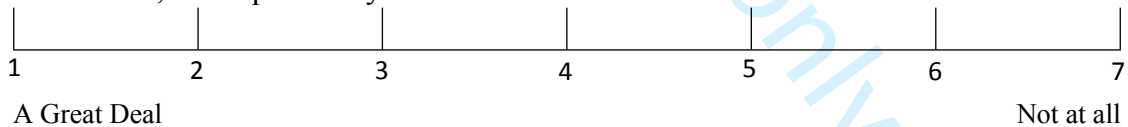
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5. How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?



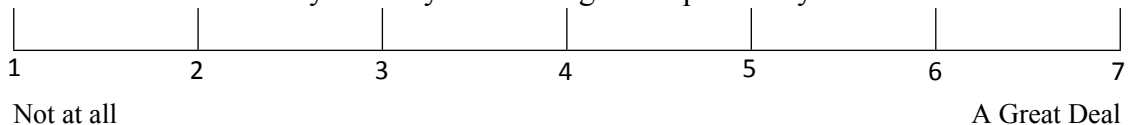
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6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?



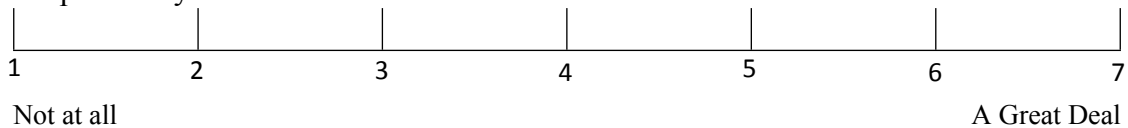
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7. Has nausea affected your daily functioning in the past 3 days?



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8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days.



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9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days.

1 2 3 4 5 6 7

Not at all A Great Deal

10. How much vomiting have you had in the past 3 days?

1 2 3 4 5 6 7

None A Great Deal

11. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?

1 2 3 4 5 6 7

A Great Deal Not at all

12. Has vomiting affected your ability to complete your usual household tasks during the past 3 days?

1 2 3 4 5 6 7

Not at all A Great Deal

13. How much has vomiting affected your ability to enjoy a meal in the past 3 days?

1 2 3 4 5 6 7

Not at all A Great Deal

14. How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?

1 2 3 4 5 6 7

Not at all A Great Deal

15. How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?

1 2 3 4 5 6 7

A Great Deal Not at all

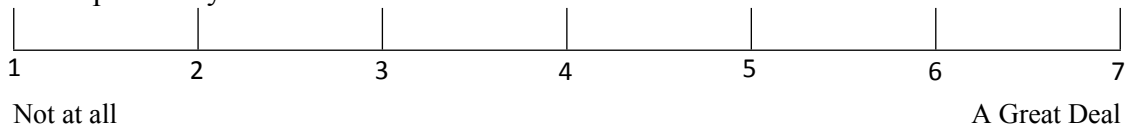
16. Has vomiting affected your daily functioning during the past 3 days?

1 2 3 4 5 6 7

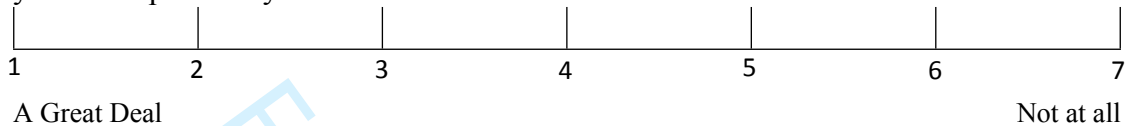
Not at all A Great Deal

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17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.



18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.



References:

- 1 Bach CM, Nogler M, Steingruber IE, *et al.* Scoring Systems in Total Knee Arthroplasty. 2002;:184–96.
- 2 HAMILTON M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50–5.<http://www.ncbi.nlm.nih.gov/pubmed/13638508>
- 3 Lindley CM, Hirsch JD, O’Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	13
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
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11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
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26				
27	Background and	#6b	Explanation for choice of comparators	4
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	3
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	3
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
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41				
42	Study setting	#9	Description of study settings (eg, community clinic,	5-6
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
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48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	7
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
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54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-8
55	description		replication, including how and when they will be	
56			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	9
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
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8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	9
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
11				
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13	Interventions:	#11d	Relevant concomitant care and interventions that are	9
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
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27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	17
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	6
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
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42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
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46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
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1	mechanism		envelopes), describing any steps to conceal the sequence	
2			until interventions are assigned	
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	6
5	implementation		participants, and who will assign participants to	
6			interventions	
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8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6-7
10			trial participants, care providers, outcome assessors, data	
11			analysts), and how	
12				
13				
14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	6-7
15	emergency		permissible, and procedure for revealing a participant's	
16	unblinding		allocated intervention during the trial	
17				
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19				
20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	11
21			and other trial data, including any related processes to	
22			promote data quality (eg, duplicate measurements, training	
23			of assessors) and a description of study instruments (eg,	
24			questionnaires, laboratory tests) along with their reliability	
25			and validity, if known. Reference to where data collection	
26			forms can be found, if not in the protocol	
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31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	11
32	retention		up, including list of any outcome data to be collected for	
33			participants who discontinue or deviate from intervention	
34			protocols	
35				
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38	Data management	#19	Plans for data entry, coding, security, and storage, including	11
39			any related processes to promote data quality (eg, double	
40			data entry; range checks for data values). Reference to	
41			where details of data management procedures can be	
42			found, if not in the protocol	
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46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
47			outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
49				
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
52	analyses		adjusted analyses)	
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
56	population and		adherence (eg, as randomised analysis), and any statistical	
57	missing data		methods to handle missing data (eg, multiple imputation)	
58				
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1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	n/a
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
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16	Harms	#22	Plans for collecting, assessing, reporting, and managing	11
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
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21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	11
22			and whether the process will be independent from	
23			investigators and the sponsor	
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27	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
28	approval		review board (REC / IRB) approval	
29				
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31	Protocol	#25	Plans for communicating important protocol modifications	12
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
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37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	12
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	12
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
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48	Confidentiality	#27	How personal information about potential and enrolled	12
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	2
56	interests		investigators for the overall trial and each study site	
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59	Data access	#29	Statement of who will have access to the final trial dataset,	12
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1			and disclosure of contractual agreements that limit such	
2			access for investigators	
3				
4	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	12
5	trial care		compensation to those who suffer harm from trial	
6			participation	
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9	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12
10	trial results		results to participants, healthcare professionals, the public,	
11			and other relevant groups (eg, via publication, reporting in	
12			results databases, or other data sharing arrangements),	
13			including any publication restrictions	
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17	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12
18	authorship		professional writers	
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21	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	12
22	reproducible		participant-level dataset, and statistical code	
23	research			
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27	Informed consent	#32	Model consent form and other related documentation given	n/a
28	materials		to participants and authorised surrogates	
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31	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
32			biological specimens for genetic or molecular analysis in the	
33			current trial and for future use in ancillary studies, if	
34			applicable	
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 38 BY-ND 3.0. This checklist was completed on 06. July 2018 using <http://www.goodreports.org/>, a tool
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BMJ Open

Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026084.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2019
Complete List of Authors:	Zhong, Sheng; Shanghai University of Traditional Chinese Medicine Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine Huang, Hai; Shanghai University of Traditional Chinese Medicine Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine Xie, Jun; Shanghai University of Traditional Chinese Medicine Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine Zhao, Ling; Shanghai University of Traditional Chinese Medicine Song, Xiu-ling; Shanghai University of Traditional Chinese Medicine Chen, Yue-lai; Shanghai University of Traditional Chinese Medicine Xiao, Lian-bo; Shanghai University of Traditional Chinese Medicine Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Research methods
Keywords:	electroacupuncture, postoperative pain, total knee arthroplasty, the study protocol

SCHOLARONE™
Manuscripts

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4 1 **Application of electroacupuncture for postoperative pain management after total**
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6 2 **knee arthroplasty: a study protocol for a single-blinded, randomised**
7
8 3 **placebo-controlled trial**

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11 4 Sheng Zhong, Hai Huang, Jun Xie, Ling Zhao, Xiu-ling Song, Yue-lai Chen, Lian-bo
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17 6 **Author Affiliations:**

18
19
20 7 Sheng Zhong, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
21
22 8 Medicine, Shanghai, China, drcyan@foxmail.com

23
24
25 9 Hai Huang, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
26
27 10 Medicine, Shanghai, China, haichuan880@163.com

28
29
30 11 Jun Xie, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
31
32 12 Medicine, Shanghai, China, leoxie199@126.com

33
34
35 13 Ling Zhao, PhD, Shanghai University of Traditional Chinese Medicine, Shanghai,
36
37 14 China, zhao099@hotmail.com

38
39
40 15 Xiu-ling Song, MD, Shanghai University of Traditional Chinese Medicine, Shanghai,
41
42 16 China, songxiuling2007@163.com

43
44
45 17 Yue-lai Chen, PhD, Shanghai University of Traditional Chinese Medicine, Shanghai,
46
47 18 China, chenyuelai@163.com

48
49
50 19 Lian-bo Xiao, MD, Guanghua Hospital, Shanghai University of Traditional Chinese
51
52 20 Medicine, Shanghai, China, 13701888178@163.com

53
54
55
56 21 **Corresponding Author:**

57
58
59 22 Lian-bo Xiao, PhD, Guanghua Hospital, Shanghai University of Traditional Chinese
60

1
2
3
4 23 Medicine, No. 540 Xinhua Road, Changning District, Shanghai (CN 200052), China,
5

6
7 24 13701888178@163.com, +8613701888178
8

9 25 Lian-bo Xiao and Yue-lai Chen contributed equally to this paper.
10
11

12 26

13 14 27 **Author Contributions**

15
16
17 28 SZ and LBX conceived the study while HH, JX, LZ, XLS designed the study.
18

19 29 The study protocol was drafted by SZ and LBX, and was revised by YLC. All authors
20

21 30 approved the final manuscript of this study protocol.
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23

24 31 **Word Count:**2190
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26 27 32 **Funding**

28
29 33 This work will be supported by Project of Shanghai University of Traditional
30

31 34 Chinese Medicine Grant (Y201812).
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34 35 **Conflicts of Interests**

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36 36 The authors declared that there are no potential conflicts of interest with respect
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38 37 to the research, authorship, and/or publication of this study.
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3 **Abstract:**
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5 40 Introduction: The purpose of this study is to assess the efficacy of electroacupuncture
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8 41 to relieve pain and promote functional rehabilitation after total knee surgery.
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10 42 Methods and analysis: We propose a single-blinded, randomised placebo-controlled
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13 43 trial to evaluate the efficacy of electroacupuncture. Patients with osteoarthritis (aged
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16 44 55 to 80 years) undergoing unilateral total knee arthroplasty will be included in the
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18 45 trial. They will be randomised to receive either electroacupuncture or
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21 46 sham-electroacupuncture. A total of 110 patients will receive electroacupuncture and
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23 47 sham-electroacupuncture for three days after TKA. Postoperative pain will be
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26 48 measured using VAS score, and the need for an additional dose of opioid and
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28
29 49 analgesics will be recorded as the primary outcome. Secondary outcomes include
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31 50 knee function and swelling, postoperative anxiety, postoperative nausea and vomiting
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33
34 51 among other complications.
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36 52 Ethics and dissemination: This study has been approved by the ethics committee, and
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39 53 subsequent modifications of the protocol will be reported and approved by it. Written
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41
42 54 inform content will be obtained from all of the participants or their authorized agents.
43

44 55 Trial registration number: ChiCTR1800016200
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46 56 Keywords: electroacupuncture, postoperative pain, total knee arthroplasty, study
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49 57 protocol
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54 **Article Summary**
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57 60 *Strengths and limitations of this study*
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60 61 1. The study is the first single-blinded, randomised placebo-controlled trial in China
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4 62 to assess the efficacy of electroacupuncture to relieve pain and promote functional
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7 63 rehabilitation after total knee surgery.

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9 64 2. The study will use an efficient sham-electroacupuncture method that makes it hard
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12 65 for patients with electroacupuncture treatment experience to distinguish between both
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15 66 treatments.

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17 67 3. The study is rigorously designed, which includes adequate sample size, proper
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20 68 randomization and allocation concealment, and prospective trial registration to reduce
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23 69 selection and confounding bias.

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25 70 4. There is still bias in the implementation of blind method due to the unblinded
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28 71 acupuncturists.

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31 32 73 **Introduction**

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35 74 Total knee arthroplasty (TKA) is the most frequently performed surgical
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38 75 procedure for end-stage osteoarthritis and rheumatoid arthritis. Moderate to severe
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41 76 postoperative pain is a major complaint in most patients. Acute and subacute
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44 77 postoperative pain is highly associated with persistent post-surgical pain (PPSP),
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47 78 especially when the acute pain is not treated with effective analgesia.¹ A recent study
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50 79 showed that 10%-34% and 7%-23% of patients reported severe pain after TKA and
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53 80 total hip arthroplasty (THA), respectively, which indicates that TKA patients are more
54
55
56 81 likely to develop PPSP.² Multimodal analgesia has been used for 20 years and it is
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59 82 considered to be the most effective strategy for PPSP. Abuse of analgesic drugs has
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62 83 increased exposure of the public to the side effects of non-steroidal anti-inflammatory

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4 84 drugs (NSAIDs) and opioids.^{3,4} Drug-free interventions to reduce pain or opioid
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6 85 consumption are more consistent with the principles of Enhanced Recovery After
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9 86 Surgery (ERAS).

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11 87 Clinical trials and systematic reviews have shown that the efficacy of
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14 88 electroacupuncture or acupuncture analgesia is controversial.⁵⁻⁸ Electrotherapy and
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17 89 acupuncture have been proved to be potentially beneficial for postoperative pain after
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20 90 TKA.⁹ Studies on the mechanism of electroacupuncture analgesia indicated that it
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23 91 activates many bioactive chemicals through peripheral, spinal, and supraspinal
24
25
26 92 mechanisms.¹⁰ The supraspinal mechanisms showed EA analgesia is highly associated
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28
29 93 with descending pain regulation of the periaqueductal grey (PAG) and the rostral
30
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32 94 ventromedial medulla (RVM).^{10,11} The PAG-RVM system is recognized as the central
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35 95 site of action of analgesic agents including opioids, cyclooxygenase inhibitors, and
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38 96 cannabinoids.^{12,13} We hypothesize that EA may exert an analgesic effect by activating
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41 97 the PAG-RVM system. Because the mechanism of electroacupuncture analgesia is not
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43
44 98 clear, there are also opinions that pain relief may be due to expectation or placebo
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47 99 effects.⁸ Besides, placebo analgesia is highly associated with both areas of the
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50 100 brain.¹⁴⁻¹⁶ Strict blinding and placebo-controlled is required to rule out the effects of
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52
53 101 the placebo effect on outcomes.

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55
56 102 The purpose of this study is to assess the efficacy of electroacupuncture on pain
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59 103 relief and promoting functional rehabilitation after total knee surgery. We will use a
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104 large sample size and a reliable blind method of electroacupuncture to ensure a
105 credible conclusion.

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4 1065
6 107 **Methods and analysis**7
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9 108 *Study Context*

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11 109 This study will be a single-blinded, randomised placebo-controlled trial
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14 110 performed at the inpatient ward of Shanghai University of Traditional Chinese
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17 111 Medicine Guanghai Hospital, Shanghai, China. The annual surgical number of total
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20 112 knee arthroplasty for osteoarthritis was about 600 in 2017. We planned to begin
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23 113 recruiting patients from June 2018 and patients preparing for unilateral TKA will be
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25
26 114 recruited. In this study, there will be 7 investigators, including a chief orthopaedic
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29 115 surgeon (LBX) with 20 years of clinical experience, two orthopaedic physicians (JX
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32 116 and SZ), two Chinese medicine acupuncturists (HH and YLC), and two outcome
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35 117 assessors (LZ, and XLS). Sheng Zhong (SZ) and Hai Huang (HH) will recruit patients
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38 118 who meet the inclusion criteria in the hospital and introduce the patient to the trial
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41 119 process, possible benefits and risks to obtain their informed consent. ERAS
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43
44 120 programme (Table 1) will be performed by trained nurses and physiotherapists at the
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46
47 121 inpatient ward. The ERAS programme is routinely applied, but electroacupuncture
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50 122 has been added to analgesia. The schedule and the study flow diagram is shown in
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53 123 Table 2 and Figure 1.

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56 124 *Sample size calculation*

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59 125 In a previous meta-analysis study in which pain relief was compared between EA
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126 groups and controls, the minimal mean difference of the two groups based on the
127 VAS score (on a scale of 0-10) was -1.14 (95% CI, -1.90 to -0.38), and the standard

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4 128 deviation was estimated to be 2.⁹ Considering a dropout rate of 10%, 110 patients
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6 129 are required to yield a power of 80% with a significance level of 0.05.¹⁷
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9 130 *Randomisation and allocation concealment*
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11 131 One hundred and ten patients will be divided into EA and Sham-EA groups with
12
13 132 a ratio of 1:1. An independent biostatistician will generate a random sequence using
14
15 133 the R (version 3.4.4). A sequence of numbers will be prepared and sealed in an
16
17 134 opaque envelope. Only the acupuncturist will be allowed to open the envelope to
18
19 135 obtain the grouping code.
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24 136 *Single-blinding*
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26
27 137 The acupuncturist will be blinded to the grouping information in advance, and the
28
29 138 treatment method according to the grouping information contained in envelopes. All
30
31 139 participants, orthopaedic surgeons, and relevant healthcare staff will be blinded to the
32
33 140 study. The outcome assessor will not be aware of the treatment that patients received
34
35 141 and will only instruct the patient to fill in the scales. The independent biostatistician
36
37 142 will also be blinded when performing the statistical analyses. To maximize the
38
39 143 blinding of patients, an effective sham electroacupuncture method will be applied
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41 144 with adhesive pads, a dull-tipped placebo needle, and a sham electrical stimulation
42
43 145 device. Details of the sham operation design are described in the following part.
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50 146 *Eligibility criteria*
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53 147 *Eligible*
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56 148 (1) Aged 55 to 80 years; (2) Meet the 1995 American College of Rheumatology
57
58 149 (ACR) diagnostic criteria for osteoarthritis; (3) Undergoing unilateral total knee
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4 150 arthroplasty under general anaesthesia without surgical contraindications; (4)

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7 151 American Society of Anesthesiologists (ASA) Grade I or II.

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9 152 *Ineligible*

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11 153 (1) The area of acupuncture points has skin damage and cannot perform

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14 154 acupuncture; (2) Preoperative deep venous thrombosis or swelling of the lower

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17 155 extremities; (3) Severe arrhythmia, heart failure, chronic obstructive pulmonary

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20 156 disease, epilepsy, mental disease; (4) Received treatment of acupuncture in past 1

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22 157 month.

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25 158 *Study interventions*

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27 159 *EA group*

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30 160 Patients will receive early acupuncture analgesia once a day from 24 to 72 hours

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32 161 after surgery. The first session of acupuncture treatment will be performed at 24 hours

33
34 162 postoperatively. Firstly, the adhesive pads will be put on the acupoints of bilateral

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37 163 *Futu* (Stomach 32, ST32), *Zusanli* (Stomach 36, ST36), *Yanglingquan* (Gall Bladder

38
39 164 34, GB34), and *Yinlingquan* (Spleen 9, SP9). 1.5 *cun* acupuncture needles

40
41
42 165 (0.25×40mm, Huatuo Inc.) will be manually inserted into the skin through the

43
44 166 adhesive pads (Figure. 2). When *De-qi* sensation is achieved, subsequent electrical

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47 167 stimulation with a frequency of 2Hz, a continuous wave and tolerable intensity by the

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50 168 patient will be applied to the four acupoints (GB 34 to ST32 and ST36 to SP9) using a

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53 169 Hwato SDZ-V electrical stimulation device (Suzhou Medical Appliance Factory,

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55
56 170 Suzhou, China). Needles with electrical stimulation will be retained for 20 minutes in

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59 171 each session. The patients will receive a total of 3 treatments which were given once a

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4 172 day.

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6 173 *Sham-EA group*

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9 174 Similar to the EA group, three sessions of acupuncture will be provided at the
10
11 175 same time. An adhesive pad will be put on the sham-acupoint which is 20 mm distal
12
13
14 176 to the real acupoint (Figure. 3). The placebo needle has a blunt-tip and it will be
15
16
17 177 manually inserted into the adhesive pads but without skin penetration to provide
18
19 178 participant-blinding effects (Figure. 2). The sham electrical stimulation device will
20
21
22 179 have a connecting cord with a broken inner wire with no actual current output.
23
24
25 180 Needles will also be retained for 20 minutes in each session. The patients will receive
26
27 181 a total of 3 sham treatments which were given once a day. This Sham-EA method was
28
29
30 182 proved to be effective in a previous study.¹⁸

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32 183 *Postoperative analgesia*

33
34
35 184 All patients will receive the same analgesic procedure. Fentanyl
36
37 185 patient-controlled analgesia (PCA) will be used at a continuous infusion rate of 0.25
38
39 186 $\mu\text{g}/(\text{kg}\cdot\text{h})$ and a bolus of 0.15 $\mu\text{g}/\text{kg}$ with a 10-minute lockout time. Patients will be
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41
42 187 allowed to use Celebrex 200 mg per day. Besides, additional rescue doses of
43
44 188 analgesics will be provided upon demand for patients with a VAS score above 60.

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48 189 *Discontinuing criteria*

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51 190 (1) Acupuncture cannot be tolerated after surgery or patients that cannot be
52
53 191 implemented according to the protocol; (2) Severe physiological and pathological
54
55 192 changes were found during surgery and it is not appropriate to receive acupuncture
56
57
58 193 treatment, such as anaesthesia accidents, cardiac-cerebrovascular accidents, nerve or
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4 194 vascular injury during surgery; (3) Patients in which the trial arrangement cannot be
5
6 195 completed or the safety judgment is affected due to surgical factors after the test; (4)
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9 196 Severe adverse reactions, severe complications, such as deep vein thrombosis,
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11 197 pulmonary embolism and severe allergic reactions.
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17 199 *Outcome*

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19 200 *Primary outcome*

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21 201 *Pain*

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23
24 202 When the patients are discharged from the operating room, this will be recorded
25
26 203 as 0 hours. Patients will put a mark on a 100 mm visual analogue scale to assess the
27
28 204 pain of their knee (from no pain to very severe) at 6, 24, 48, and 72 hours after
29
30 205 surgery, then assessors record it. Additional PCA dose requirement will be evaluated
31
32 206 in this study to reflect the degree of pain. Patients will be trained to adjust the PCA to
33
34 207 obtain an additional dose of analgesia depending on the degree of pain. This will be
35
36 208 recorded 48 hours after surgery. Patients will be given an additional dose of analgesia
37
38 209 upon demand if the VAS score is above 60. The additional use of analgesics within 2
39
40 210 weeks after surgery will be recorded in the case report forms.
41
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44 211 *Secondary outcome*

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46 212 *Knee function and swelling*

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48 213 Knee function will be measured based on Hospital for Special Surgery
49
50 214 Knee-Rating Scale ¹⁹ (HSS scale) (Supplemental file) at one day before surgery and
51
52 215 three days after surgery. All patients will first be educated about the HSS scale by a
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4 216 trained researcher until they fully understand the questionnaire, then asked to
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6 217 complete the form according to their actual conditions. At 24 hours after surgery, the
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9 218 outcome assessor will remove the elastic bandage and measure the circumference of
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11
12 219 the knee at the superior patellar pole. A second measurement will be performed 72
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14
15 220 hours after surgery.

17 221 *Perioperative anxiety*

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20 222 Perioperative anxiety will be measured by the Hamilton Anxiety Scale
21
22 223 (HAMA)²⁰ (Supplemental file) at one day before surgery and three days after surgery.
23
24 224 HAMA has 14 levels to assess the severity of a patient's anxiety, and it divides
25
26
27 225 anxiety into physical (7~13) and spiritual (1~6 and 14).

30 226 *Postoperative nausea and vomiting (PONV)*

32
33 227 PONV will be measured according to vomiting symptoms scores in 4-time points,
34
35 228 including on the day of surgery and 1, 2, 3 days after surgery.²¹ Functional Living
36
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38 229 Index-Emesis (FLIE)²² (Supplemental file) is used to evaluate the effect of PONV on
39
40
41 230 the quality of life, and it will be measured 3 days after surgery.

43 231 *Postoperative complications and adverse events*

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46 232 All expected and unexpected adverse events will be measured during the
47
48 233 allocated intervention process and during the entire study period. Acupuncture-related
49
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51 234 adverse events are hematoma and syncope during acupuncture. Other postoperative
52
53
54 235 complications including incision infection, urinary retention, deep vein thrombosis,
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56
57 236 and postoperative persistent pain will be recorded 6 weeks after surgery. All serious
58
59 237 adverse events (SAEs) will be reported immediately to the sponsor to allow further
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4 238 investigations into their causes.
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7 239 *Data management*
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9 240 Data entry will be conducted by two independent trained research assistants using
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11 241 paper CRFs to record the research data after completion of final data collection. As
12
13
14 242 acupuncture has known minimal risks, a formal data monitoring committee will not
15
16
17 243 be required.^{8,23} Independent investigators of the hospital staff will monitor and audit
18
19
20 244 the data periodically.
21

22 245 *Statistical analysis*
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24 246 According to the intention to treat (ITT) principle, full analysis set (FAS) and
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26
27 247 per-protocol set (PPS) will be used for primary analysis. Safety set (SS) will not be
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30 248 required since acupuncture has minimal risks.^{8,23} Sensitivity analysis will be
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33 249 performed to determine the impact of incomplete records on results. Missing data will
34
35
36 250 not be imputed. Statistical analysis will be performed using R (version 3.4.4). The
37
38 251 difference between the two groups will be calculated and compared using the t-test if
39
40
41 252 the Shapiro-Wilk test showed that the data is normally distributed, otherwise the
42
43 253 Mann-Whitney U test will be used. A Pearson χ^2 or Fisher's exact test will be used to
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45
46 254 calculate the differences in the count data. Mixed effects models will be used to
47
48 255 analyze the trend of changes in VAS scores with two factors of groups and time.²⁴
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51 256 *Ethics and dissemination*
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53 257 This study has been approved by the ethics committee of Shanghai Guanghua
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56 258 Hospital of Integrated Chinese and Western Medicine (approval number AF13v2-2),
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59 259 and any modification of the protocol will be reported and approved by it. Written
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4 260 inform consent will be obtained from all participants or their authorized agents. All
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6 261 electroacupuncture treatments will be free and the research data will be strictly
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9 262 confidential. The result of the trial will be presented on the website of the Chinese
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11 263 Clinical Trial Registry and published in peer-reviewed journals.

14 264 *Patient and Public Involvement*

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17 265 Patient and public were not involved in the design of this study. The participants
18
19 266 will be informed of the result of this study during the follow-up visit. Besides, we will
20
21 267 enlist their help in disseminating the research findings.

24 268 **Discussion**

26
27 269 Drug-free interventions, especially EA, have been proven effective in pain relief
28
29 270 and promoting functional rehabilitation,^{25,26} and they will have good prospects for
30
31 271 relieving opioid abuse or overuse of NSAIDs. However, the effect and mechanism of
32
33 272 acupuncture analgesia are not clear, and the placebo effect is considered to play an
34
35 273 important role.⁸ This study has enough samples to obtain reliable results and we have
36
37 274 improved the implementation of blinding to adequately characterize the placebo effect.
38
39 275 We hope that the results of the study will provide new evidence for
40
41 276 electroacupuncture treatment of postoperative pain in TKA. Another question is to
42
43 277 determine if the statistical difference between the two groups is clinically relevant.
44
45 278 The minimal clinically important difference (MCID) is a measure that is used to
46
47 279 evaluate the clinical significance of an intervention. In the case of standardized
48
49 280 multimodal analgesia, the MCID for VAS of postoperative pain after TKA is -22.6
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51 281 (on a scale of 0-100), and the MCID can be also used to evaluate the difference of EA
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4 282 and sham.²⁷
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6 283 Multiple evidence-based ERAS strategies for TKA have been shown to reduce
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9 284 postoperative complications and improve prognosis and patient satisfaction.
10
11 285 Postoperative analgesia is an important part of ERAS. This study is based on add-on
12
13 286 design, electroacupuncture and sham are applied to two groups of patients who used
14
15 287 standard multimodal analgesia to evaluate the benefits of electroacupuncture on
16
17 288 postoperative pain in TKA. We recommend EA and more non-drug therapies as a
18
19 289 routine treatment in ERAS programme of TKA if the results indicate effectiveness
20
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22 290 over placebo.
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For peer review only

Table 1. Enhanced Recovery After Surgery Programme

Preoperative

- 1 Preoperative education
 - 2 Carbohydrate loading preoperatively and avoidance of prolonged starving
 - 3 Use of preoperative probiotics
 - 4 No mechanical bowel preparation
 - 5 No premedication
 - 6 Preemptive analgesia
-

Intraoperative

- 7 Maintenance of normothermia
 - 8 Goal-directed perioperative fluid administration
 - 9 Minimally invasive incision
 - 10 Avoidance of nasogastric tubes and deep vein catheterization
 - 11 Avoidance of bladder catheters, if necessary early removal of bladder catheters
 - 12 Use of tranexamic acid
 - 13 Periarticular local injection analgesia
-

Postoperative

- 14 Multimodal analgesia: PCA analgesia, NSAIDs; Avoidance of opioid analgesia
 - 15 Use of postoperative antiemetic and laxatives
 - 16 Enforced early mobilisation
 - 17 Enforced early postoperative oral feeding
-

PCA, patient controlled analgesia; NSAIDs, non-steroidal antiinflammatory drugs

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Table 2. The schedule of trial enrolment, interventions and assessments

	Enrolment		Intervention period		
	Pre-OP	6 hours	24 hours	48 hours	72 hours
Enrolment					
Informed consent	•				
Assessment of eligibility	•				
Randomisation	•				
Interventions					
EA		•	•	•	•
Sham-EA		•	•	•	•
Assessments					
VAS	•	•	•	•	•
Additional dose released by PCA				•	
HSS scale	•				•
HAMA score	•				•
PONV		•	•	•	•
COK			•		•
Additional use of analgesics	•				•
Postoperative complications and adverse events		•	•	•	•

OP, operation; EA, electroacupuncture; VAS, Visual Analogue Score; PCA, patient-controlled analgesia; HSS, hospital for special surgery; HAMA, Hamilton Anxiety Scale; PONV, post-operative nausea and vomiting; COK, circumference of knee

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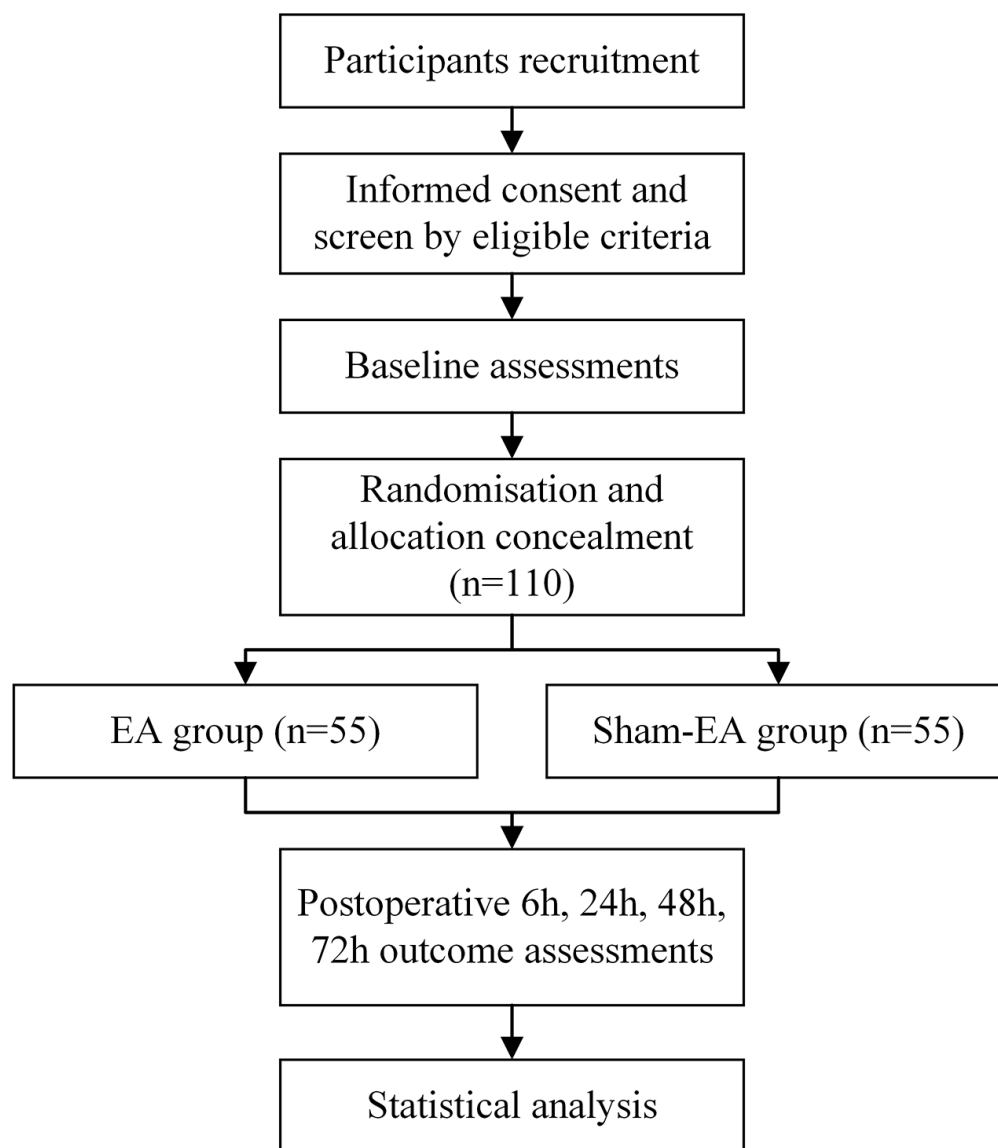
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379 **Figure Legend**

380 Figure 1. The study flow diagram, including participants recruitment, eligibility,
381 screening, randomization, allocation concealment, and outcome assessments. EA,
382 electroacupuncture.

383 Figure 2. The difference between the acupuncture needle and placebo. (A) The
384 placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the
385 skin. The acupuncture needle (right) to be inserted into the skin through the adhesive
386 pads. (B) The tip of the placebo needle (left) is blunt.

387 Figure 3. Location of acupoints for the electroacupuncture and sham
388 electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach
389 36; SP9, Spleen 9.



43 Figure 1. Study flow diagram, including participants recruitment, eligibility, screening, randomization,
44 allocation concealment, and outcome assessments. EA, electroacupuncture.

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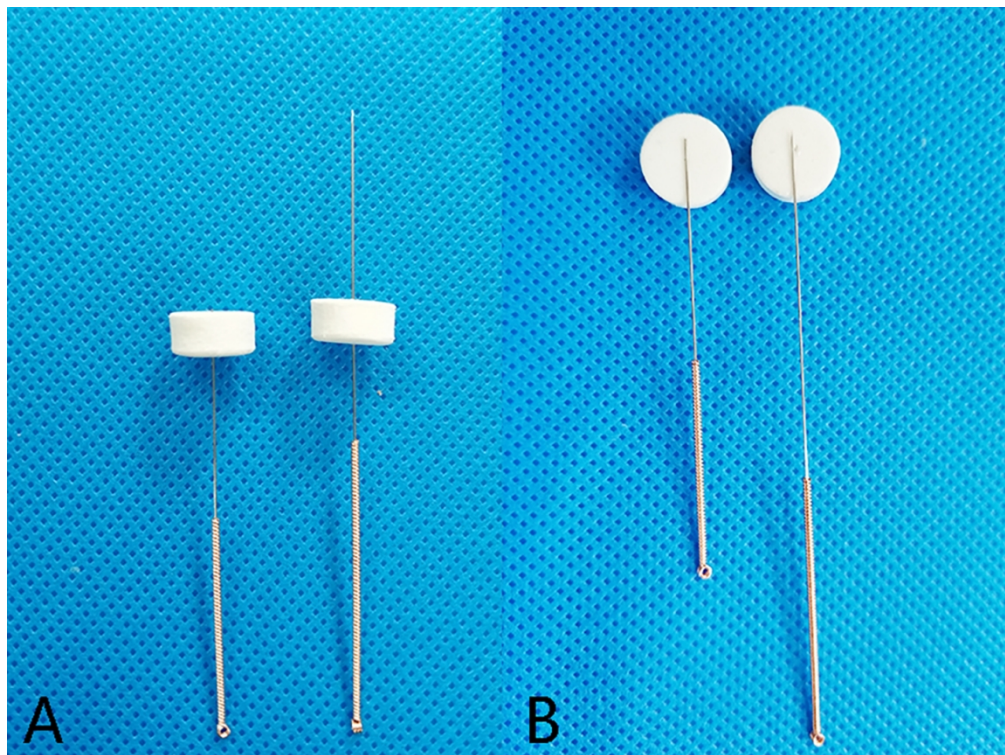


Figure 2. The difference between acupuncture needle and placebo. (A) The placebo needle (left) to be inserted into the adhesive pads and the tip can irritate the skin. The acupuncture needle (right) to be inserted into the skin through the adhesive pads. (B) The tip of the placebo needle (left) is blunt.

119x90mm (300 x 300 DPI)

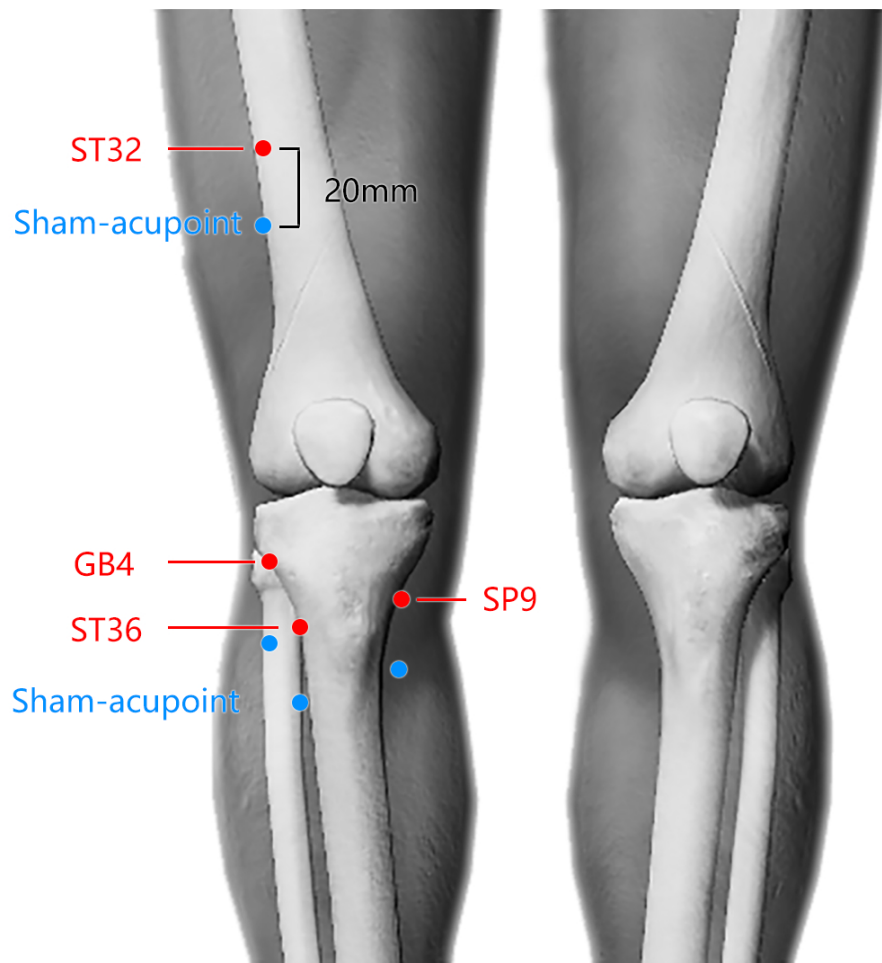


Figure 3. Location of acupoints for the electroacupuncture and sham electroacupuncture groups. ST32, Stomach 32; GB4, Gall Bladder 34; ST36, Stomach 36; SP9, Spleen 9.

94x90mm (300 x 300 DPI)

Supplemental file

1. Hospital for Special Surgery Knee-Rating Scale¹

Hospital for Special Surgery Knee-Rating Scale (HSS)

Criteria	Points
Pain (30 points)	
No pain at any time	30
No pain on walking	15
Mild pain on walking	10
Moderate pain on waling	5
Severe pain on walking	0
No pain at rest	15
Mild pain at rest	10
Moderate pain at rest	5
Severe pain at rest	0
Function (22 points)	
Walking and standing unlimited	12
Walking distance of 5-10 blocks and standing ability intermittent >1/2hr	10
Walking 1-5 blocks and standing up < 1/2hr	8
Walking less than 1 block	4
Cannot walk	0
Climbing stairs	5
Climbing stairs with support	2
Transfer activity	5
Transfer activity with support	2
Range of Motion (18 points)	
1 point for each 8 degrees (max 18 points)	18
Muscle Strength (10 points)	
Excellent: cannot break quadriceps power	10
Good: can break the quadriceps power	8
Fair: move through the arc of motion	4
Poor: cannot move through arc of motion	0
Flexion Deformity (10 points)	
No deformity	10
Less than 5 degrees	8
5-10 degrees	5
> 10 degrees	0
Instability (10 points)	
None	10

Mild: 0-5 degrees	8
Moderate: 5-15 degrees	5
Severe: > 15degrees	0
Subtraction	
One cane	-1
One crutch	-2
Two crutches	-3
Extension lag of 5 degrees	-2
Extension lag of 10 degrees	-3
Extension lag of 15 degrees	-5
Each 5 degrees of varus	-1
Each 5 degrees of valgus	-1

Excellent ≥ 85

Good = 70-84

Fair = 60-69

Poor ≤ 60

2. Hamilton Anxiety Rating Scale (HAMA)²

Hamilton Anxiety Rating Scale (HAMA)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 Anxious mood

Worries, anticipation of the worst, fearful anticipation, irritability.

0 1 2 3 4

2 Tension

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

0 1 2 3 4

3 Fears

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

0 1 2 3 4

4 Insomnia

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors

0 1 2 3 4

5 Intellectual

Difficulty in concentration, poor memory.

0 1 2 3 4

6 Depressed mood

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

0 1 2 3 4

7 Somatic (muscular)

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

0 1 2 3 4

8 Somatic (sensory)

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

0 1 2 3 4

9 Cardiovascular symptoms

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat

0 1 2 3 4

10 Respiratory symptoms

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

0 1 2 3 4

11 Gastrointestinal symptoms

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

0 1 2 3 4

12 Genitourinary symptoms

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence

0 1 2 3 4

13 Autonomic symptoms

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

0 1 2 3 4

14 Behavior at interview

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

0 1 2 3 4

0 ~ 7: No anxiety

8~14: Possible anxiety

15~21: Mild anxiety

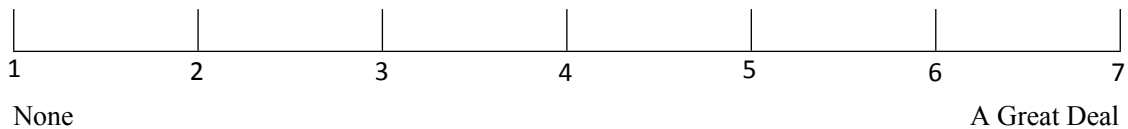
22~29: Obvious anxiety

>29: Severe anxiety

3. Functional Living Index Emesis (FLIE)³

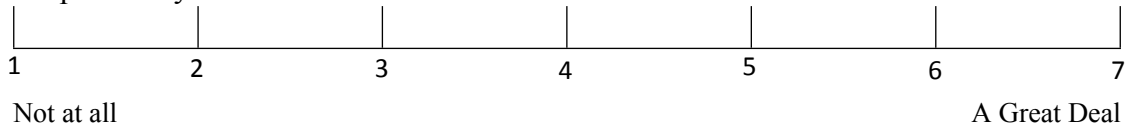
Functional Living Index Emesis (FLIE)

1. How much nausea have you had in the past 3 days?



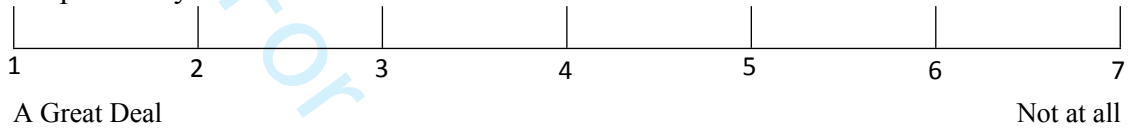
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2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?



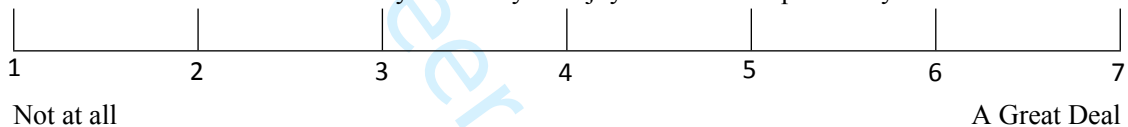
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3. Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?

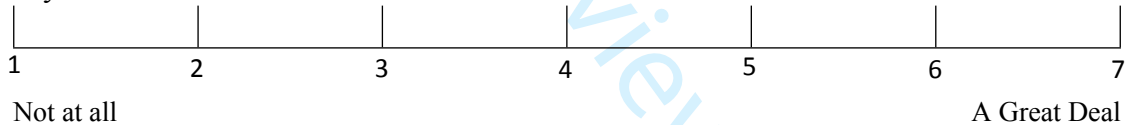


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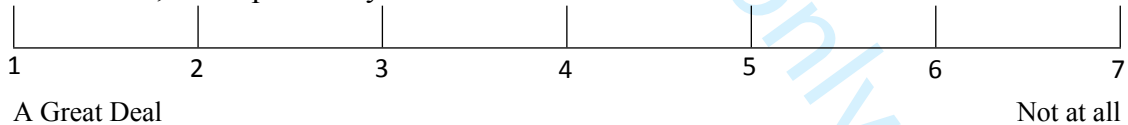
4. How much has nausea affected your ability to enjoy a meal in the past 3 days?



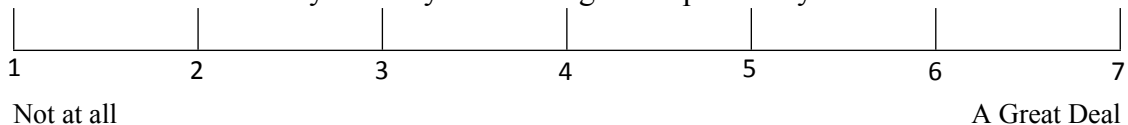
5. How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?



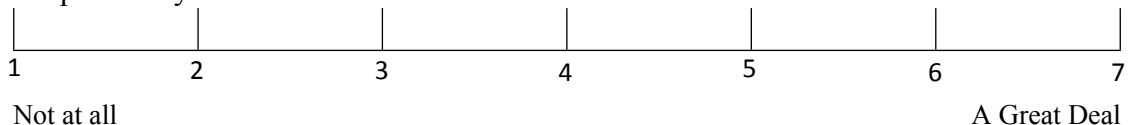
6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?



7. Has nausea affected your daily functioning in the past 3 days?



8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days.



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9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days.

1 2 3 4 5 6 7
Not at all A Great Deal

10. How much vomiting have you had in the past 3 days?

1 2 3 4 5 6 7
None A Great Deal

11. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?

1 2 3 4 5 6 7
A Great Deal Not at all

12. Has vomiting affected your ability to complete your usual household tasks during the past 3 days?

1 2 3 4 5 6 7
Not at all A Great Deal

13. How much has vomiting affected your ability to enjoy a meal in the past 3 days?

1 2 3 4 5 6 7
Not at all A Great Deal

14. How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?

1 2 3 4 5 6 7
Not at all A Great Deal

15. How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?

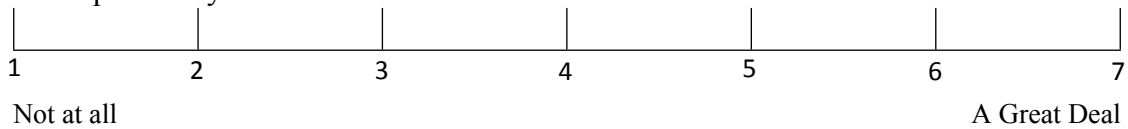
1 2 3 4 5 6 7
A Great Deal Not at all

16. Has vomiting affected your daily functioning during the past 3 days?

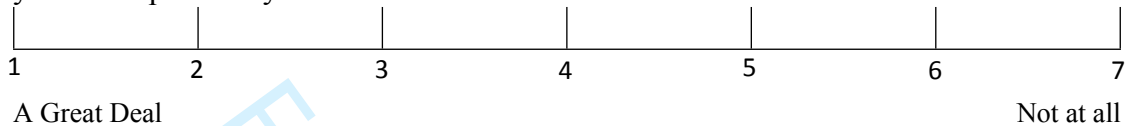
1 2 3 4 5 6 7
Not at all A Great Deal

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17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days.



18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days.



References:

- 1 Bach CM, Nogler M, Steingruber IE, *et al.* Scoring Systems in Total Knee Arthroplasty. 2002;:184–96.
- 2 HAMILTON M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50–5.<http://www.ncbi.nlm.nih.gov/pubmed/13638508>
- 3 Lindley CM, Hirsch JD, O’Neill C V., *et al.* Quality of life consequences of emesis. *Qual Life Res* 1992;**1**:331–40.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	13
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
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12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
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20	Background and	#6a	Description of research question and justification for	4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
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26				
27	Background and	#6b	Explanation for choice of comparators	4
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	3
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	3
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
40				
41				
42	Study setting	#9	Description of study settings (eg, community clinic,	5-6
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	7
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
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54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-8
55	description		replication, including how and when they will be	
56			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	9
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
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8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	9
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
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12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	9
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
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28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	17
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
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35	Sample size	#14	Estimated number of participants needed to achieve study	6
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
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42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
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46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
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1	mechanism		envelopes), describing any steps to conceal the sequence	
2			until interventions are assigned	
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	6
5	implementation		participants, and who will assign participants to	
6			interventions	
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6-7
10			trial participants, care providers, outcome assessors, data	
11			analysts), and how	
12				
13				
14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	6-7
15	emergency		permissible, and procedure for revealing a participant's	
16	unblinding		allocated intervention during the trial	
17				
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20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	11
21			and other trial data, including any related processes to	
22			promote data quality (eg, duplicate measurements, training	
23			of assessors) and a description of study instruments (eg,	
24			questionnaires, laboratory tests) along with their reliability	
25			and validity, if known. Reference to where data collection	
26			forms can be found, if not in the protocol	
27				
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31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	11
32	retention		up, including list of any outcome data to be collected for	
33			participants who discontinue or deviate from intervention	
34			protocols	
35				
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38	Data management	#19	Plans for data entry, coding, security, and storage, including	11
39			any related processes to promote data quality (eg, double	
40			data entry; range checks for data values). Reference to	
41			where details of data management procedures can be	
42			found, if not in the protocol	
43				
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46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
47			outcomes. Reference to where other details of the statistical	
48			analysis plan can be found, if not in the protocol	
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
52	analyses		adjusted analyses)	
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
56	population and		adherence (eg, as randomised analysis), and any statistical	
57	missing data		methods to handle missing data (eg, multiple imputation)	
58				
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1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	n/a
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	11
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
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21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	11
22			and whether the process will be independent from	
23			investigators and the sponsor	
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26				
27	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
28	approval		review board (REC / IRB) approval	
29				
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31	Protocol	#25	Plans for communicating important protocol modifications	12
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	12
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	12
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
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48	Confidentiality	#27	How personal information about potential and enrolled	12
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
52				
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55	Declaration of	#28	Financial and other competing interests for principal	2
56	interests		investigators for the overall trial and each study site	
57				
58				
59	Data access	#29	Statement of who will have access to the final trial dataset,	12
60				

1			and disclosure of contractual agreements that limit such	
2			access for investigators	
3				
4	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	12
5	trial care		compensation to those who suffer harm from trial	
6			participation	
7				
8				
9	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12
10	trial results		results to participants, healthcare professionals, the public,	
11			and other relevant groups (eg, via publication, reporting in	
12			results databases, or other data sharing arrangements),	
13			including any publication restrictions	
14				
15				
16				
17	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12
18	authorship		professional writers	
19				
20				
21	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	12
22	reproducible		participant-level dataset, and statistical code	
23	research			
24				
25				
26				
27	Informed consent	#32	Model consent form and other related documentation given	n/a
28	materials		to participants and authorised surrogates	
29				
30				
31	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
32			biological specimens for genetic or molecular analysis in the	
33			current trial and for future use in ancillary studies, if	
34			applicable	
35				
36				

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 39 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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