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Acupuncture for chronic neck pain with sensitized points: study protocol for a multicenter randomized controlled trial

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3 **Acupuncture for chronic neck pain with sensitized points: study protocol for a**
4 **multicenter randomized controlled trial**
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ABSTRACT

Introduction: Chronic neck pain is a challenging condition to treat in clinical practice, and has a considerable impact on quality of life and disability. This study aims to evaluate the efficacy and safety of needling at sensitized acupoints in providing pain relief, improvement of cervical vertebral function, and quality of life in patients with chronic neck pain.

Methods and analysis: This multicenter randomized controlled clinical trial will include 716 patients with chronic neck pain. Study participants will be randomly assigned in a 1:1:1:1 ratio to four treatment groups: the highly-sensitized acupoints group, low/non-sensitized acupoints group, sham acupuncture group, and waiting-list control group. The highly-sensitized acupoints group will receive acupuncture at five sensitized acupoints, while the low/non-sensitized acupoints group will receive acupuncture at five low/non-sensitized acupoints; the absolute value of the change in pressure pain threshold will be calculated at each of these five acupoints. The sham acupuncture group will receive shallow acupuncture at five non-acupoints. These three groups will receive 10 acupuncture sessions in 4 weeks: three times weekly for the first 2 weeks, and twice weekly for the subsequent 2 weeks. The waiting-list control group will not receive acupuncture treatment until the end of the 24-week follow-up period. The primary outcome will be the change in the visual analogue scale pain score from baseline to 4 weeks. Secondary outcomes will be the Northwick Park Neck Pain Questionnaire and McGill pain questionnaire, 12-item Short-Form health survey, Neck Disability Index, changes in the pressure pain threshold, range of cervical motion, Self-Rating Anxiety Scale, and Self-Rating Depression Scale at 0, 4, 8, 12, 16, 20, and 24 weeks.

Ethics and dissemination: Ethical approval of this study has been granted by local Institutional Review Board (ID: 2017KL-38). The outcomes of the trial will be disseminated through peer-reviewed publications.

Trial registration: ChiCTR1800016371.

Strengths and limitations of this study

- ▶ This study will be the first randomized controlled trial to evaluate the efficacy and safety of acupuncture at sensitized points in patients with chronic neck pain.
- ▶ To test the efficacy of acupuncture at sensitized acupoints, the trial will include three kinds of

control groups (low/non-sensitized acupoints acupuncture group, sham acupuncture group, and waiting-list control group), and strict quality control will be conducted, including adequate concealment of randomized group allocations.

► A limitation of this study is that acupuncture at the low/non-sensitized acupoints may play a role in the treatment of chronic neck pain, and the sham acupuncture may also be associated with treatment effects than other placebo; thus, the effect of acupuncture in the highly-sensitized acupoints group may be underestimated.

INTRODUCTION

Chronic neck pain can be caused by dysfunction of various structures in the neck, and can manifest as episodic pain and/or stiffness.(1, 2) The prevalence of neck pain in the adult general population reportedly varies from 30–50% worldwide.(3) Furthermore, neck pain-related diseases, such as cervical spondylosis, occur in 64.52% of subjects working in certain occupations in China.(4) Neck pain is the third most common chronic condition causing persistent pain in the US, and the fourth leading cause of disability worldwide.(5, 6) Chronic neck pain can lead to work absenteeism(7) or a heavy medical burden.(8) Several risk factors predispose to the development of chronic neck pain, including obesity, a sedentary lifestyle, previous neck pain, cervical disc degeneration, and poor general health. The current mainstay of treatment for chronic neck pain is non-steroidal anti-inflammatory drugs, but they are associated with many adverse reactions, such as gastrointestinal, cardiac, and renal toxicity.(9)

Although clinical trials have demonstrated that acupuncture can effectively relieve chronic neck pain,(10) the effect of acupuncture treatment is closely related to the selection of acupoints.(11) One study evaluating the effects of acupuncture on chronic neck pain showed that acupuncture at common distant acupoints is more effective than that at myofascial trigger points,(12) while another study found that acupuncture at local myofascial trigger points also has a good analgesic effect.(13) However, some studies have also reported that acupuncture does not relieve pain.(14, 15) Despite the increasing amount of randomized clinical trials (RCTs) investigating the effect of acupuncture, the quality of these RCTs needs to be improved, as many include inadequate sample sizes,(16) short follow-up,(17) an absence of sham acupuncture and non-treatment as control treatments,(18) no objective assessment method,(19) or a lack of individualized treatment based

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3 on each patient's condition.(20) Consequently, the efficacy of acupuncture for chronic neck pain
4 needs further evaluating due to the lack of objective clinical evidence.
5

6
7 The pressure pain threshold (PPT) is a semi-objective method used to quantify localized pain.(21,
8
9 22) Clinical studies have confirmed that the PPT at acupoints changes when patients are in a
10
11 diseased state.(23-25) The degree of change in the PPT may reflect the intensity of acupoint
12
13 sensitization, and may be related to the disease status.(26) Clinical studies have found that
14
15 performing acupuncture at sensitized points achieves a superior effect.(27, 28) However, no study
16
17 has yet focused on the efficacy of acupuncture at sensitized points for the treatment of chronic
18
19 neck pain. Therefore, we herein describe the protocol for a RCT that aims to evaluate the efficacy
20
21 of acupuncture at sensitized points (acupoints or tender points) in relieving neck pain and
22
23 improving cervical vertebral function and quality of life.
24

25 **METHODS AND ANALYSIS**

26 **Objective**

27
28 To assess the efficacy and safety of acupuncture at highly-sensitized acupoints in relieving pain
29
30 and improving the cervical vertebral function and quality of life in patients with chronic neck pain.
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33 **Trial design**

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35 This is a prospective, multicenter RCT in which patients will be allocated to four parallel
36
37 treatment groups using a 1:1:1:1 allocation ratio. The protocol was developed in accordance with
38
39 the Consolidated Standards of Reporting Trials guidelines(29) and the Standards for Reporting
40
41 Interventions in Clinical Trials of Acupuncture guidelines(30). The trial has been registered with
42
43 ChiCTR at Current Controlled Trials (ChiCTR1800016371). A flowchart of the trial design is
44
45 shown in Figure 1.
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47
48

49 **Inclusion criteria**

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51 The inclusion criteria will be: (1) males or females aged 18–75 years; (2) neck pain or limited
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53 cervical activity as the main complaint; (3) pain or discomfort visual analogue scale (VAS) score
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55 of ≥ 30 for at least 5 days within 1 week; (4) chronic neck pain for the last 3 months; (5) provision
56
57 of written informed consent for all procedures in this trial.
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Exclusion criteria

Patients meeting any one of the following criteria will be excluded: (1) history of neck fracture or surgery, or cervical congenital abnormality; (2) serious disease related to the heart, liver, kidney, or hematopoietic system; (3) difficulty in answering the questionnaires because of cognitive impairment; (4) dermatopathy and hemorrhagic diseases; (5) those who are pregnant, breastfeeding, or planning a pregnancy during the study period; (6) participation in other trials.

Recruitment strategies and randomization

We will enroll patients from the outpatient departments of Acupuncture and Moxibustion, and Orthopedics in four clinical centers in China: Chengdu University of Traditional Chinese Medicine, Shaanxi University of Traditional Chinese Medicine, Shanxi University of Traditional Chinese Medicine, and Guiyang College of Traditional Chinese Medicine. Recruitment strategies will include posting recruitment advertisements on social media (such as WeChat, which is similar to Facebook) and at community centers. Patients who consent to study participation will be examined by a hospital doctor who will make a diagnosis; an inspector will then perform a baseline evaluation. The inspector will apply for the grouping randomization after completing the PPT measurement.

Central randomization will be performed using stratified and permuted blocks. The inspectors will be registered in the randomization center (located in Brightech-Magnsoft Data Services Company), and will be trained to apply for randomization through the online website. This guarantees that randomization concealment is adequate.

Blinding

The inspector will be responsible for clinical reception, PPT measurement, and randomization. The acupuncture treatments will be performed by acupuncturists who have each held a practitioners license for more than 5 years. The efficacy of acupuncture will be evaluated by an assessor. Patients who receive acupuncture treatment will not be aware of their group assignment; however, the waiting-list control group cannot be blinded. The patients, inspectors, acupuncturists, assessors, and statisticians will not be permitted to have any communication with each other

regarding study information.

PPT measurement

The PPT is widely used in clinical practice as a semi-objective method with which to quantify localized pain.(21, 22) Individuals with chronic neck pain have altered pain sensitivity,(31-33) and so the PPT can be used to distinguish between patients with neck pain and healthy subjects.(34) In accordance with the results of literature data-mining and expert consensus on the treatment of chronic neck pain, we identified the 15 most frequently used acupoints (Table 1) and the five regions of the body with the most frequent occurrence of pain and the greatest degree of acupoint sensitization (Figure 2). The body was divided into five regions to standardize the treatment procedures and detection areas.

Inspectors will mark the 15 acupoints on each patient. The inspector will then palpate the detection area associated with each acupoint using the appropriate force (< 2,000 gf), and will identify the sensitized points that have pain/sourness/heaviness/fullness or nodules. Inspectors will use the FDIX Force Gauge (Force One™ FDIX, Wagner Instruments, USA) to make two measurements of the PPT at each of the 15 acupoints in the five regions. If there is a difference between the two PPT measurements of more than 500 gf at one acupoint, the acupoint will be measured for the third time. Progressive pressure will be applied at a rate of 100 gf/s at each acupoint. The PPTs will be summed to calculate the average. The absolute value of the change in the PPT in the included patients will then be calculated, and this will be compared with that of healthy subjects collected in the early stage (Appendix Table).

Table 1 Acupoints selected for use in the study

Acupoints	Location
Jianjing (GB-21)	On the shoulder, directly above the nipple, at the midpoint of the line connecting Dazhui(DU-14) with the acromial end of clavicle
Jianzhongshu(SI-15)	On the back, 2 cun lateral to the lower border of the spinous process of the 7 th cervical vertebra
Wangu(GB-12)	On the head, in the depression posterior and inferior to the mastoid process.
Fengchi(GB-20)	On the nape, below the occipital, on a level with Fengfu DU-16, in the depression between the upper portion of trapezius and the sternocleidomastoid

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3	Tianzhu(BL-10)	On the nape, 1.3 cun lateral to the posterior hairline, in the depression
4		of the posterior hairline lateral to the trapezius muscle
5	Dazhui(DU-14)	On the posterior median line, in the depression below the spinous
6		process of the 7 th cervical vertebra
7		
8	Dazhu(BL-11)	On the back, 1.5 cun lateral to the lower border of the spinous process
9		of the 1 st thoracic vertebra
10	Jianwaishu(SI-14)	On the back, 3 cun lateral to the lower border of the spinous process of
11		the first thoracic vertebra
12	Tianliao(SJ-15)	On the region of scapula, at the midpoint of the line connecting
13		Jianjing GB-21 with Quyuan SI-13, on the superior angle of the
14		scapula
15		
16	Jugu(LI-16)	In the upper portion of the shoulder, in the depression between the
17		acromial end of clavicle and the scapular spine
18	Tianzong(SI-11)	In the region of the scapula, in the depression of the center of the
19		subscapular fossa, on a level with the 4 th thoracic vertebra
20		
21	Shousanli(LI-10)	Flexing the elbow, on the dorsal radial side of the forearm, on the line
22		connecting Yangxi LI-5 with Quchi LI-11, 2cun below the transverse
23		cuticular crease
24		
25	Lieque(LU-7)	On the radial margin of the forearm, 1.5 cun above the transverse
26		crease of the wrist, between the branchioradial muscle and the long
27		abductor muscle tendon of thumb
28		
29	Zhongzhu(SJ-3)	On the dorsum of the hand, in the depression between the 4 th and 5 th
30		metacarpal bones, proximal to the 4 th metacarpalangeal joint
31	Houxi(SI-3)	On the ulna side of the palm, proximate to the fifth
32		metacarpophalangeal joint, at the end of transverse crease of
33		metacarpophalangeal joint, at the dorsoventral boundary
34		

Interventions

1) Highly-sensitized acupoints group

The acupuncturist will identify the five sensitized points/acupoints at which the absolute value of change in the PPT is the largest. Acupuncture will be performed at these five acupoints three times weekly for the first 2 weeks, and then two times weekly for the subsequent 2 weeks, giving a total of 10 sessions. Each of the five selected acupoints will be punctured using a stainless steel needle (0.25 × 40 mm), and the Deqi sensation (a sensation of distension or numbness, or a twitch response) will be achieved. Needle retention time will be 30 min. The PPT of the sensitized acupoints will be evaluated every 2 weeks, and the selection of acupuncture points will be adjusted as each patient's condition changes; this will ensure the implementation of individualized treatment.

2) Low/non-sensitized acupoints group

The acupuncturist will identify the five sensitized acupoints with the least change in the absolute value of the PPT, and acupuncture will be performed at these five acupoints. The puncture method and needles will be the same as for the highly-sensitized acupoints group.

3) Sham acupuncture group

Acupuncture will be performed at five non-acupoints. The protocol for choosing the non-acupoints was developed in our previous clinical trial(35) and another study(36) (Table 2 and Figure 3). Shallow acupuncture will be applied at the five non-acupoints, without attempting to yield the Deqi sensation.

Table 2 Details of the intervention in the sham acupuncture group

Non-acupoint	Location	Manipulation
Non-acupoint 1	In the middle of Binao(LI 14) and acromion	punctured perpendicularly 0.5–1 cun
Non-acupoint 2	At the medial arm on the anterior border of the insertion of the deltoid muscle at the junction of deltoid and biceps muscles	
Non-acupoint 3	Half way between the tip of the elbow and axillae	
Non-acupoint 4	Ulnar side, half way between the epicondylus medialis of the humerus and ulnar side of the wrist	
Non-acupoint 5	Edge of the tibia 1–2 cm lateral to the Zusanli (ST36) horizontally	

4) Waiting-list control group

No intervention will be performed in the waiting-list control group in the initial 24 weeks after randomization. The participants will be informed that they are scheduled to receive 10 free acupuncture treatments at the end of the 24-week follow-up period. If the participants experience severe neck pain during the initial 24 weeks, they will be permitted to take prescribed analgesic

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3 medications (such as non-steroidal anti-inflammatory drugs) or effective analgesic medications
4 that they are accustomed to taking, and the details will be recorded on the Case Report Form.
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8 **Outcome measurements**

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10 Follow-up examinations will be performed at 0, 4, 8, 12, 16, 20, and 24 weeks after randomization
11 in all four groups (Table 3).
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15 **Primary outcome**

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17 The primary outcome will be the change in the VAS score from baseline to 4 weeks. The VAS
18 score ranges from 0–100, with higher scores indicating a greater degree of pain.
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23 **Secondary outcomes**

24 **Pain**

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26 The intensity of neck pain will be measured using the Northwick Park Neck Pain Questionnaire
27 and the McGill Pain Questionnaire. The changes in the PPT during the treatment phase will be
28 evaluated. The times and doses of analgesic drugs taken during the study period, and the
29 disease-related treatment performed during the follow-up period will also be recorded.
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36 **Quality of life**

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38 Quality of life will be assessed using the Chinese version of the Medical Outcome Study
39 Short-form 12-Item Health Survey.
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43 **Neck function**

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45 The change in neck function will be evaluated using the Neck Disability Index and the cervical
46 range of motion. Recent research has shown that the Neck Disability Index has an excellent ability
47 to distinguish between patients with different levels of perceived dysfunction.(37)
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52 **Emotional disorders**

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54 Chronic pain is often accompanied by emotional disorders.(38, 39) Changes in mood will be
55 assessed using the Self-Rating Anxiety Scale and the Self-Rating Depression Scale.
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Table 3 Outcome measurements at each timepoint

Measurements	Baseline	Treatment phase			Follow-up phase				
	-4 weeks	0 week	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Measurements of pressure-pain threshold		×	×	×					
VAS	×	×		×	×	×	×	×	×
NPQ		×		×	×	×	×	×	×
MPQ		×		×	×	×	×	×	×
SF-12		×		×	×	×	×	×	×
NDI		×		×	×	×	×	×	×
CROM		×		×					
SAS		×		×	×	×	×	×	×
SDS		×		×	×	×	×	×	×
Adverse events		×	×	×	×	×	×	×	×

Data and Safety Monitoring Board

To ensure the integrity of the RCT and protect the rights and health of the participants, we will set up a Data and Safety Monitoring Board. The Data and Safety Monitoring Board is an independent advisory group that will maintain the scientific and ethical standards of the RCT, and will be responsible for data evaluation during the study period. The Data and Safety Monitoring Board will be developed in accordance with the Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards of the World Health Organization.

Safety and acupuncture-related adverse events

Acupuncture may cause several adverse events, including bleeding, hematoma, fainting, serious pain, and local infection.⁽⁴⁰⁾ Hence, we will record any acupuncture-related adverse events that occur during the treatment and follow-up phases, and record the potential reasons for these adverse events. The number and type of adverse events in each group will be calculated. Patients will receive appropriate intervention for any adverse events that occur. Serious adverse events will be immediately reported to the primary investigator, and the affected participants will be withdrawn from the study.

Sample size calculation

The sample size calculation was based on the superiority test. The primary outcome is the change in the VAS score from baseline to week 4. The clinical difference in the VAS score after acupuncture treatment is reportedly 6.3(16); therefore, we conservatively estimated that there would be a VAS score change of 5 between the highly-sensitized acupoints group and the low/non-sensitized acupoints group, 10 between the highly-sensitized acupoints group and the sham acupuncture group, and 20 between the highly-sensitized acupoints group and the waiting-list control group. Considering a two-sided significance level of 5% and power of 95%, 621 participants are required with a 1:1:1 group allocation rate, as calculated by Fisher's exact test in G*Power (version 3.1.5). To minimize attrition bias, we assumed a dropout rate of 15%, making it necessary to include at least 716 participants in total.

Statistical analysis

The included patients will be divided into the full analysis set (FAS), per protocol set (PPS), and safety set (SS). The FAS population will consist of all participants for whom the primary outcome is evaluable. The FAS population will be used as the primary population for all efficacy analyses. The PPS population will consist of all participants who undergo the planned interventions. The SS will consist of all randomized participants who received at least one acupuncture treatment during the study period. All data will be managed by the data coordinating center through a third party (the Brightech-Magnsoft Data Services Company).

A statistician blinded to the group allocations will conduct all analyses using the SAS version 9.4 software package (SAS Institute Inc., Cary, NC, USA). The intention-to-treat principle will be used to analyze the baseline characteristics data and outcome data. Measurement data will be expressed as the mean \pm SD, while enumeration data will be expressed as percentages. If an adjustment is needed for an incomparable baseline, covariance analysis will be performed. If the measurement data have normal distribution, the t-test will be used. If the measurement data have non-normal distribution, the Wilcoxon rank sum test will be used. A p value of less than 0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

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3 This RCT was designed in accordance with the principles of the Declaration of Helsinki. The trial
4 protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Chengdu
5 University of Traditional Chinese Medicine (permission number: 2017KL-38), and is registered on
6 the primary registry in the World Health Organization registry network (Chinese Clinical Trial
7 Registry: no. ChiCTR1800016371). Signed consent will be obtained from each patient after they
8 have been informed of the study procedures, possible risks, and their right to withdraw from the
9 trial.
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12 The concept of sensitized points comes from the theory of traditional Chinese medicine, which
13 purports a link between disease status and the condition of acupuncture points; when the body is
14 affected by diseases, particular points become sensitized(41). This study will be the first
15 multicenter RCT to evaluate the safety and effectiveness of acupuncture at sensitized points for
16 chronic neck pain. There is a need for non-pharmacological modalities that effectively relieve pain,
17 as there has been a sharp increase in the incidence of opioid abuse, misuse, and overdose in the
18 US.(42) The relief of physical pain is the most commonly reported reason for opioid misuse
19 (63.4%).(43) Acupuncture is a popular non-pharmacological pain-relieving modality that may
20 exert its analgesic properties via the release of endogenous opioids.(44) The results of this study
21 may provide further evidence for the effectiveness of acupuncture in relieving chronic neck pain,
22 and may thus lead to a reduction in the prescription of opioids.
23
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26 This study has some strength that warranted mention. The creation of a waiting-list control group
27 will enable the diagnostic component of the study to be maintained,(45) as this will rule out
28 self-healing of the disease, and control for the Hawthorne effect. The waiting-list control group
29 will receive the same acupuncture intervention after the 24-week follow-up period. This design
30 provides participants with a guarantee that they are going to receive acupuncture treatment,
31 overcoming the potential problem of control participants being disappointed.(46) In addition, the
32 blinding of the outcome evaluators will decrease potential bias.
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36 As this will be the first study to investigate the effectiveness of acupuncture at sensitized
37 acupoints for chronic neck pain, this RCT may have some limitations. The main problem is that
38 the acupuncture performed in the low/non-sensitized acupoints group may still produce a
39 treatment effect for chronic neck pain; hence, the effect of acupuncture in the highly-sensitized
40 acupoints group may be underestimated. Further study is needed to confirm the efficacy of
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3 acupuncture at sensitized acupoints. If the results show that acupuncture therapy at sensitized
4 acupoints is safe and effective in reducing chronic neck pain, this study provide evidence to
5 support the superior clinical efficacy of performing acupuncture at sensitized acupoints compared
6 with low/non-sensitized acupoints.
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10 11 12 **CONCLUSION**

13
14 This article describes the design and protocol of a study that aims to evaluate the effectiveness and
15 safety of acupuncture for chronic neck pain. The results will reveal whether sensitized acupoints
16 have specificity, and whether acupuncture at highly-sensitized acupoints is superior to acupuncture
17 at low/non-sensitized points or sham acupuncture at non-acupoints.
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21 22 23 **Trial status**

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25 This study is currently in the recruitment phase. The first patient was enrolled in June 2018, and
26 the study is expected to end in December 2019.
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30 31 32 **Acknowledgments**

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34 contributions to the design and statistical analysis plan of this trial. We thank the staff of Chengdu
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39 English text of a draft of this manuscript.
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46 47 48 **Authors' contributions**

49 MSS, GYG, JC, HZ, LZ, and FRL participated in the design of the trial, in creating the data
50 analysis plan, and in drafting the manuscript. XSM, MXY, XJL, and JRD collected the
51 information needed for the performance of this trial in each center. All of the authors discussed,
52 read, and revised the manuscript, and gave final approval for the publication of this study protocol.
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Competing interests

The authors declare that they have no competing interests.

Ethics approval

The study protocol has been approved by the institutional review board and ethics committee of the First Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (May 2018).

Provenance and peer review

Not commissioned; internally peer reviewed.

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20 **Figure 1** Flowchart of the trial design.

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24 **Figure 2** The test regions that will be used in the study. Regions 1 and 2 are each bordered by the
25 respective ipsilateral mastoid, sternal end of the clavicle, anterior axillary line, acromion, and C7
26 spinous process. Region 3 is the triangular region bordered by both sides of the mastoid and the
27 C7 spinous process. Regions 4 and 5 are each bordered by the respective ipsilateral C7 spinous
28 process, acromion, and axillary line; the two regions are divided by the posterior midline.

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32 **Figure 3** Locations of the five non-acupoints used in the study.

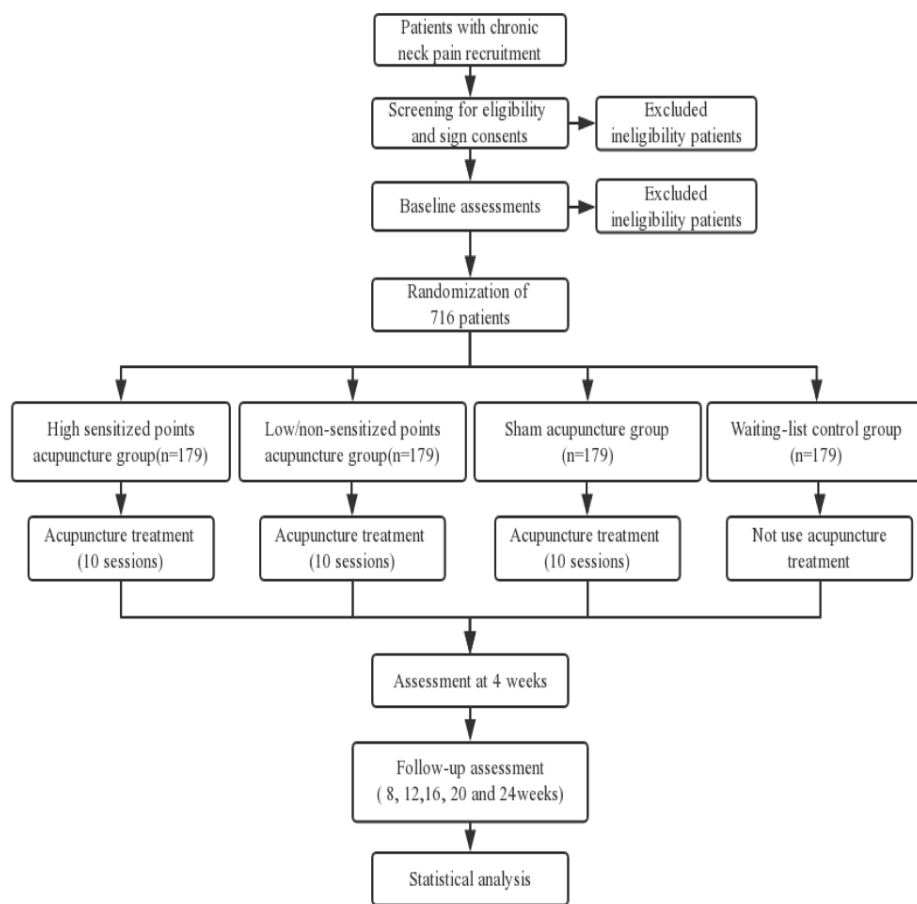


Figure 1 Flowchart of the trial design.

90x90mm (300 x 300 DPI)

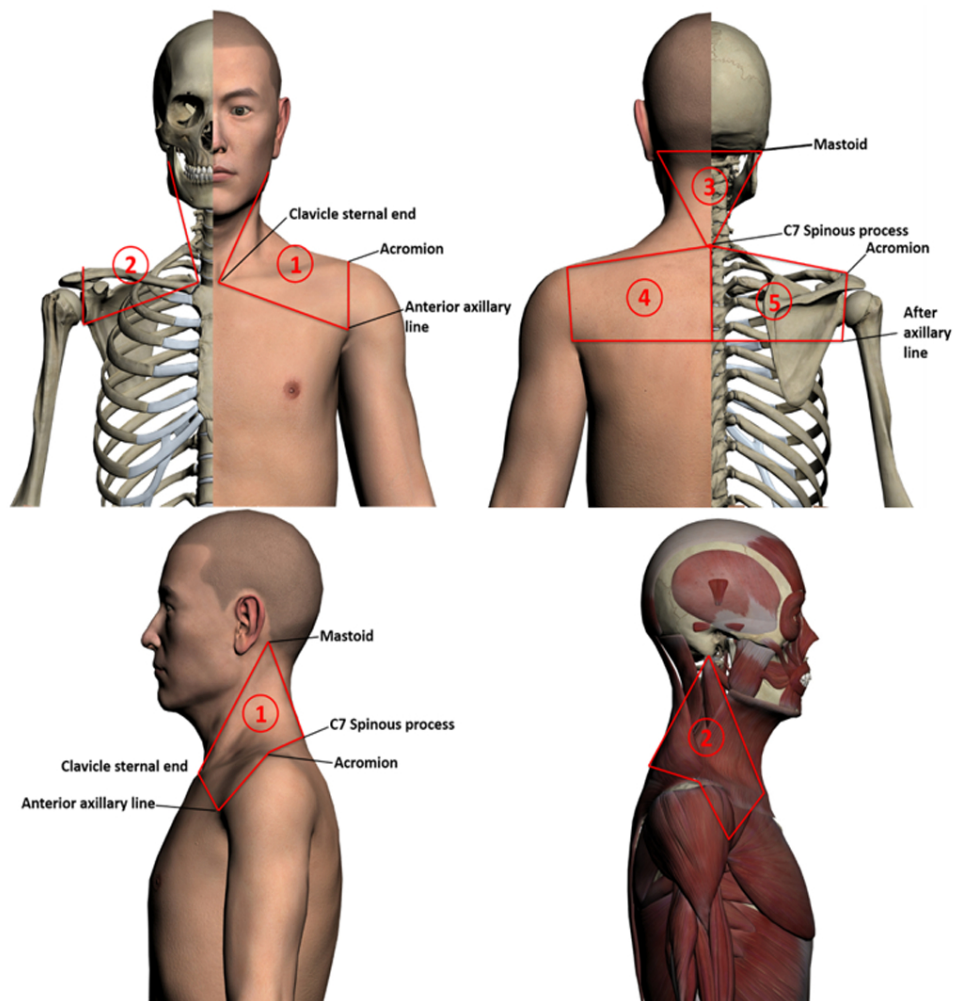


Figure 2 The test regions that will be used in the study. Regions 1 and 2 are each bordered by the respective ipsilateral mastoid, sternal end of the clavicle, anterior axillary line, acromion, and C7 spinous process. Region 3 is the triangular region bordered by both sides of the mastoid and the C7 spinous process. Regions 4 and 5 are each bordered by the respective ipsilateral C7 spinous process, acromion, and axillary line; the two regions are divided by the posterior midline.

90x90mm (300 x 300 DPI)

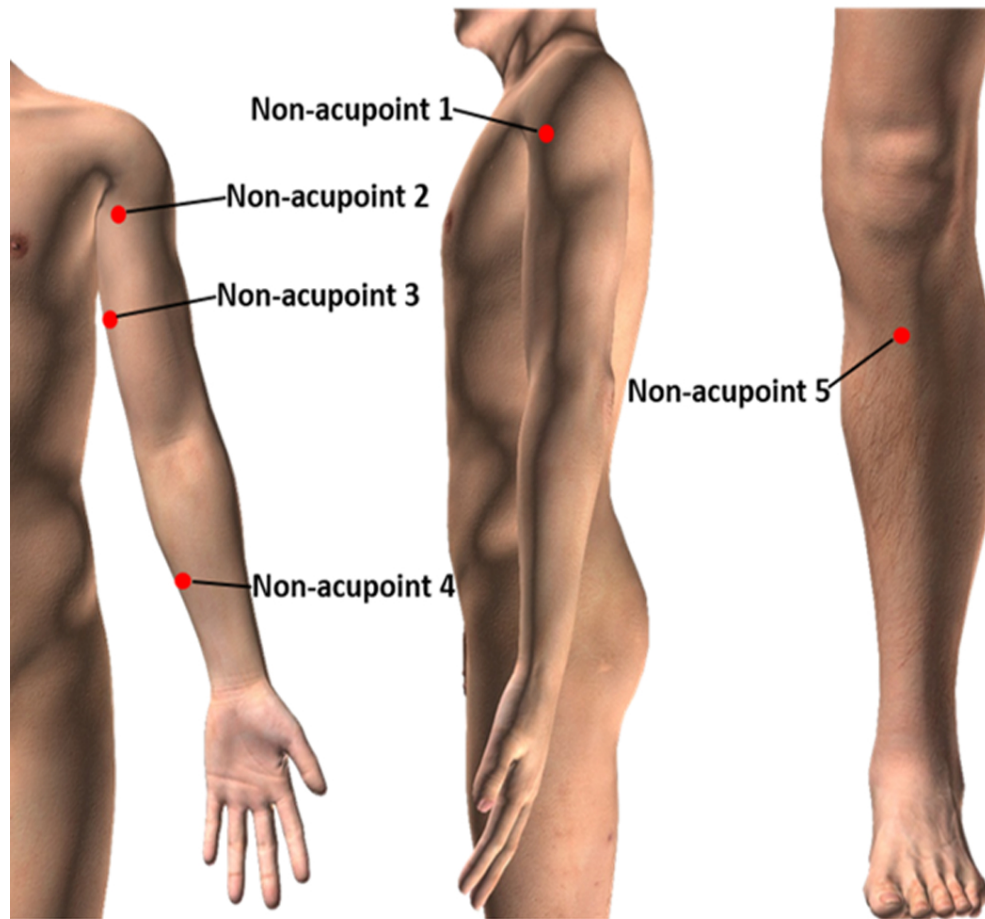


Figure 3 Locations of the five non-acupoints used in the study.

90x90mm (300 x 300 DPI)

Appendix Table

Regions	Acupoints	Pressure pain threshold of healthy subjects (gf)
Region 1	Jianjing (GB-21) L	2234
	Jianzhongshu(SI-15) L	2648
Region 2	Jianjing (GB-21) R	2222
	Jianzhongshu(SI-15) R	2650
Region 3	Wangu(GB-12) L	1616
	Fengchi(GB-20) L	1909
	Tianzhu(BL-10) L	2067
	Dazhui(DU-14)	2978
	Wangu(GB-12) R	1738
	Fengchi(GB-20) R	2037
	Tianzhu(BL-10) R	2083
Region 4	Dazhu(BL-11) L	2924
	Jianwaishu(SI-14) L	2856
	Tianliao(SJ-15) L	2788
	Jugu(LI-16) L	2611
	Tianzong(SI-11) L	2484
Region 5	Dazhu(BL-11) R	2932
	Jianwaishu(SI-14) R	2849
	Tianliao(SJ-15) R	3075
	Jugu(LI-16) R	2652
	Tianzong(SI-11) R	2478
Distant acupoints	Shousanli(LI-10) L	1645
	Lieque(LU-7) L	2003
	Zhongzhu(SJ-3) L	2011
	Houxi(SI-3) L	2326
	Shousanli(LI-10) R	1710
	Lieque(LU-7) R	2192
	Zhongzhu(SJ-3) R	2017
Houxi(SI-3) R	2419	

L:
left;
R:
right

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Acupuncture for chronic neck pain with sensitive points: study protocol for a multicenter randomized controlled trial

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4 **Acupuncture for chronic neck pain with sensitive points: study protocol for a**
5 **multicenter randomized controlled trial**
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ABSTRACT

Introduction: Chronic neck pain is a challenging condition to treat in clinical practice, and has a considerable impact on quality of life and disability. According to the theory of traditional Chinese medicine, acupoints and tender points may become sensitized when the body is in a diseased state; stimulation of such sensitive points may lead to disease improvement and improved clinical efficacy. This study aims to evaluate the efficacy and safety of needling at sensitive acupoints in providing pain relief, improvement of cervical vertebral function, and quality of life in patients with chronic neck pain.

Methods and analysis: This multicenter, randomized controlled, explanatory, and parallel clinical trial will include 716 patients with chronic neck pain. Study participants will be randomly assigned in a 1:1:1:1 ratio to four treatment groups: the highly-sensitive acupoints group, low/non-sensitive acupoints group, sham acupuncture group, and waiting-list control group. The primary outcome will be the change in the visual analogue scale score for neck pain from baseline to 4 weeks. Secondary outcomes will be the Northwick Park Neck Pain Questionnaire and McGill pain questionnaire, 12-item Short-Form health survey, Neck Disability Index, changes in the pressure pain threshold, range of cervical motion, Self-Rating Anxiety Scale, Self-Rating Depression Scale, and adverse events before treatment, post-treatment, and at 4, 8, 12, 16, and 20 weeks post-treatment. The intention-to-treat approach will be used in the statistical analysis. Group comparisons will be undertaken using χ^2 tests for categorical characteristics, and analysis of variance for continuous variables to analyze whether acupuncture in the highly-sensitive acupoints group achieves better treatment outcomes than in each of the other three groups.

Ethics and dissemination: Ethical approval of this study has been granted by the local Institutional Review Board (ID: 2017KL-038). The outcomes of the trial will be disseminated through peer-reviewed publications.

Trial registration: ChiCTR1800016371.

Strengths and limitations of this study

- ▶ This study will be the first randomized controlled trial to evaluate the efficacy and safety of acupuncture at sensitive points in patients with chronic neck pain.
- ▶ To test the efficacy of acupuncture at sensitive acupoints, the trial will include three kinds of

control groups (low/non-sensitive acupoints acupuncture group, sham acupuncture group, and waiting-list control group), and strict quality control will be conducted, including adequate concealment of randomized group allocations.

► A sham acupuncture group will be used to investigate the placebo effect of acupuncture.

► A limitation of this trial is that although there are several types of point sensitization, such as pain and heat, we will only be quantifying pain as an indicator of sensitization.

INTRODUCTION

Chronic neck pain can be caused by dysfunction of various structures in the neck, and can manifest as episodic pain and/or stiffness.[1 2] The prevalence of neck pain in the adult general population reportedly varies from 30–50% worldwide.[3] Furthermore, neck pain-related diseases, such as cervical spondylosis, occur in 65% of subjects working in certain occupations in China.[4] Neck pain is the third most common chronic condition causing persistent pain in the US, and the fourth leading cause of disability worldwide.[5 6] Chronic neck pain can lead to work absenteeism or a heavy medical burden.[7] The mean annual total costs accrued by patients with neck pain in the USA are \$8,512, which is 182% higher than the costs of the general population.[8] Several risk factors predispose to the development of chronic neck pain, including obesity, a sedentary lifestyle, previous neck pain, cervical disc degeneration, and poor general health. The current mainstay of treatment for chronic neck pain is non-steroidal anti-inflammatory drugs, but they are associated with many adverse reactions, such as gastrointestinal, cardiac, and renal toxicity.[9]

Although clinical trials have suggested that acupuncture can effectively relieve chronic neck pain,[10] the effect of acupuncture treatment is closely related to the selection of acupoints.[11] One study evaluating the effects of acupuncture on chronic neck pain showed that acupuncture at common distant acupoints is more effective than that at myofascial trigger points,[12] while another study found that acupuncture at local myofascial trigger points also has a good analgesic effect.[13] However, some studies have also reported that acupuncture does not relieve pain.[14-16] Despite the increasing amount of randomized clinical trials (RCTs) investigating the effect of acupuncture, the quality of these RCTs needs to be improved, as many include inadequate sample sizes,[17] short follow-up,[18] an absence of sham acupuncture and non-treatment as control treatments,[19] no objective assessment method,[20] or a lack of individualized treatment based on each patient's

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4 condition.[21] Consequently, the efficacy of acupuncture for chronic neck pain needs further
5
6 evaluating due to the lack of objective clinical evidence.

7
8 The pressure pain threshold (PPT) is a semi-objective method used to quantify localized pain.[22
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10 23] Clinical studies have confirmed that the sensitivity (PPT) at acupoints changes when patients
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12 are in a diseased state, such as shoulder pain,[24] knee osteoarthritis,[25] primary dysmenorrhea,
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14 [26] and premenstrual syndrome.[27] The degree of change in the PPT may objectively reflect the
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16 intensity of acupoint sensitization, and may be related to the disease status.[28] Clinical studies have
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18 found that performing acupuncture at sensitive points achieves a superior effect.[29 30] However,
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20 these studies did not quantify the sensitivity of the points, which undermines the validity of the
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22 results. Consequently, the improvement in clinical efficacy may not have been optimized. Clinical
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24 trials have recently investigated the efficacy of acupuncture at objectively evaluated sensitive
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26 points.[31] This will further reveal the relationship between objectively evaluated sensitive points
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28 and improved clinical efficacy. However, no study has yet focused on the efficacy of acupuncture
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30 at quantified sensitive points for the treatment of chronic neck pain. Therefore, we herein describe
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32 the protocol for an RCT that aims to evaluate the efficacy of acupuncture at sensitive points
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34 (acupoints or tender points) in relieving neck pain and improving cervical vertebral function and
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36 quality of life.

37 38 **METHODS AND ANALYSIS**

39 40 **Objective**

41
42 To assess the efficacy and safety of acupuncture at highly-sensitive acupoints in relieving pain and
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44 improving the cervical vertebral function and quality of life in patients with chronic neck pain.

45 46 47 48 **Trial design**

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50 This is a prospective, multicenter RCT in which patients will be allocated to four parallel treatment
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52 groups using a 1:1:1:1 allocation ratio. The protocol was developed in accordance with the
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54 Consolidated Standards of Reporting Trials guidelines[32] and the Standards for Reporting
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56 Interventions in Clinical Trials of Acupuncture guidelines.[33] The trial has been registered with
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58 ChiCTR at Current Controlled Trials (ChiCTR1800016371). A flowchart of the trial design is
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60 shown in Figure 1.

Inclusion criteria

The inclusion criteria will be: (1) males or females aged 18–75 years; (2) neck pain or limited cervical activity as the main complaint; (3) neck pain or discomfort visual analogue scale (VAS) score of ≥ 30 for at least 5 days within 1 week; (4) chronic neck pain for the last 3 months; (5) provision of written informed consent for all procedures in this trial.

Exclusion criteria

Patients meeting any one of the following criteria will be excluded: (1) history of neck fracture or surgery, or cervical congenital abnormality; (2) serious disease related to the heart, liver, kidney, or hematopoietic system; (3) difficulty in answering the questionnaires because of cognitive impairment; (4) dermatopathy and hemorrhagic diseases; (5) those who are pregnant, breastfeeding, or planning a pregnancy during the study period; (6) participation in other trials.

Recruitment strategies and randomization

We will enroll patients from the outpatient departments of Acupuncture and Moxibustion, and Orthopedics in four clinical centers in China: Chengdu University of Traditional Chinese Medicine, Shaanxi University of Traditional Chinese Medicine, Shanxi University of Traditional Chinese Medicine, and Guiyang College of Traditional Chinese Medicine. Recruitment strategies will include posting recruitment advertisements on social media (such as WeChat, which is similar to Facebook) and at community centers. Patients who consent to study participation will be examined by orthopedists who will make a diagnosis; a research assistant (RA) will then perform a baseline evaluation. The RA will apply for the grouping randomization after completing the PPT measurement.

Central randomization will be performed using stratified and permuted blocks. The RAs will be registered in the randomization center (located in Brightech-Magnsoft Data Services Company), and will be trained to apply for randomization through the online website. This guarantees that randomization concealment is adequate. Patients will be randomized in blocks of varying size within each site, stratified by sex and course of disease.

Blinding

The RA will be responsible for baseline evaluation, PPT measurement, and randomization. The acupuncture treatments will be performed by acupuncturists who have each held a practitioners license for more than 5 years. The efficacy of acupuncture will be evaluated by an assessor. Patients who receive acupuncture treatment will not be aware of their group assignment; however, the waiting-list control group cannot be blinded. The patients receiving acupuncture treatment during the trial period, RA who performs the baseline assessment, acupuncturists, assessors, and statisticians will all be blinded.

PPT measurement

The PPT is widely used in clinical practice as a semi-objective method with which to quantify localized pain.[22 23] Individuals with chronic neck pain have altered pain sensitivity,[34-36] and so the PPT can be used to distinguish between patients with neck pain and healthy subjects.[37] In accordance with the results of literature data-mining and expert consensus on the treatment of chronic neck pain, we identified the 15 most frequently used acupoints (Table 1) and the five regions of the body with the most frequent occurrence of pain and the greatest degree of acupoint sensitization (Figure 2). The body was divided into five regions to standardize the treatment procedures and detection areas.

RAs will mark the 15 acupoints on each patient. The RA will then palpate the detection area associated with each acupoint using the appropriate force (< 2,000 gf), and will identify the sensitive points that have pain/sourness/heaviness/fullness or nodules. RAs will use the FDIX Force Gauge (Force One™ FDIX, Wagner Instruments, USA) to make two measurements of the PPT at each of the 15 acupoints in the five regions. If there is a difference between the two PPT measurements of more than 500 gf at one acupoint, the acupoint will be measured for the third time. Progressive pressure will be applied at a rate of 100 gf/s at each acupoint. The PPTs will be summed to calculate the average. The absolute value of the change in the PPT in the included patients will then be calculated, and this will be compared with that of healthy subjects collected in the early stage (Appendix Table).

Table 1 Acupoints selected for use in the study

Acupoints	Location
Jianjing (GB-21)	On the shoulder, directly above the nipple, at the midpoint of the line connecting Dazhui(DU-14) with the acromial end of clavicle
Jianzhongshu(SI-15)	On the back, 2 cun lateral to the lower border of the spinous process of the 7 th cervical vertebra
Wangu(GB-12)	On the head, in the depression posterior and inferior to the mastoid process.
Fengchi(GB-20)	On the nape, below the occipital, on a level with Fengfu DU-16, in the depression between the upper portion of trapezius and the sternocleidomastoid
Tianzhu(BL-10)	On the nape, 1.3 cun lateral to the posterior hairline, in the depression of the posterior hairline lateral to the trapezius muscle
Dazhui(DU-14)	On the posterior median line, in the depression below the spinous process of the 7 th cervical vertebra
Dazhu(BL-11)	On the back, 1.5 cun lateral to the lower border of the spinous process of the 1 st thoracic vertebra
Jianwaishu(SI-14)	On the back, 3 cun lateral to the lower border of the spinous process of the first thoracic vertebra
Tianliao(SJ-15)	On the region of scapula, at the midpoint of the line connecting Jianjing GB-21 with Quyuan SI-13, on the superior angle of the scapula
Jugu(LI-16)	In the upper portion of the shoulder, in the depression between the acromial end of clavicle and the scapular spine
Tianzong(SI-11)	In the region of the scapula, in the depression of the center of the subscapular fossa, on a level with the 4 th thoracic vertebra
Shousanli(LI-10)	Flexing the elbow, on the dorsal radial side of the forearm, on the line connecting Yangxi LI-5 with Quchi LI-11, 2cun below the transverse cubital crease
Lieque(LU-7)	On the radial margin of the forearm, 1.5 cun above the transverse crease of the wrist, between the branchioradial muscle and the long abductor muscle tendon of thumb
Zhongzhu(SJ-3)	On the dorsum of the hand, in the depression between the 4 th and 5 th metacarpal bones, proximal to the 4 th metacarpalangeal joint
Houxi(SI-3)	On the ulna side of the palm, proximate to the fifth metacarpophalangeal joint, at the end of transverse crease of metacarpophalangeal joint, at the dorsoventral boundary

Interventions

1) Highly-sensitive acupoints group

The acupuncturist will identify the five sensitive points/acupoints at which the absolute value of change in the PPT is the largest. Acupuncture will be performed at these five acupoints three times weekly for the first 2 weeks, and then two times weekly for the subsequent 2 weeks, giving a total

of 10 sessions. Each of the five selected acupoints will be punctured using a stainless steel needle (0.25 × 40 mm), and the Deqi sensation (a sensation of distension or numbness, or a twitch response) will be achieved. Needle retention time will be 30 min. The PPT of the sensitive acupoints will be evaluated every 2 weeks, and the selection of acupuncture points will be adjusted as each patient's condition changes; this will ensure the implementation of individualized treatment.

2) Low/non-sensitive acupoints group

The acupuncturist will identify the five sensitive acupoints with the least change in the absolute value of the PPT, and acupuncture will be performed at these five acupoints. The puncture method and needles will be the same as for the highly-sensitive acupoints group.

3) Sham acupuncture group

Acupuncture will be performed at five non-acupoints. The protocol for choosing the non-acupoints was developed in our previous clinical trial[38] and another study[39] (Table 2 and Figure 3). Shallow acupuncture will be applied at the five non-acupoints, without attempting to yield the Deqi sensation.

Table 2 Details of the intervention in the sham acupuncture group

Non-acupoint	Location	Manipulation
Non-acupoint 1	In the middle of Binao(LI 14) and acromion	punctured perpendicularly 0.5–1 cun
Non-acupoint 2	At the medial arm on the anterior border of the insertion of the deltoid muscle at the junction of deltoid and biceps muscles	
Non-acupoint 3	Half way between the tip of the elbow and axillae	
Non-acupoint 4	Ulnar side, half way between the epicondylus medialis of the humerus and ulnar side of the wrist	
Non-acupoint 5	Edge of the tibia 1–2 cm lateral to the Zusanli (ST36) horizontally	

4) Waiting-list control group

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4 No intervention will be performed in the waiting-list control group in the initial 24 weeks after
5 randomization. The participants will be informed that they are scheduled to receive 10 free
6 acupuncture treatments at the end of the 24-week follow-up period.
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11 If any participants experience severe neck pain during the initial 24 weeks, they will be permitted
12 to take prescribed analgesic medications (such as non-steroidal anti-inflammatory drugs) or
13 effective analgesic medications that they are accustomed to taking, and the details will be recorded
14 on the Case Report Form. Sustained-release or prophylactic analgesics are not allowed.
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19 20 21 **Outcome measurements**

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23 Follow-up examinations will be performed at 0, 4, 8, 12, 16, 20, and 24 weeks after randomization
24 in all four groups (Table 3).
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29 **Primary outcome**

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31 The primary outcome will be the change in the VAS score for neck pain from baseline to 4 weeks.
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33 The VAS score ranges from 0–100, with higher scores indicating a greater degree of pain. The VAS
34 is considered a valid method with which to assess pain intensity in clinical trials.[40] The strengths
35 of the VAS are its ease of use, good reliability and validity, and metric measure that enables
36 parametric testing. However, its limitation is that it is difficult for some subjects to mentally
37 transform a subjective sensation into a mark on a straight line. Furthermore, previous research has
38 suggested that the validity of VAS estimates performed by patients with chronic pain may be
39 unsatisfactory.[41]
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48 **Secondary outcomes**

49 **Pain**

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51 We will also use the following indicators to comprehensively evaluate pain. The intensity of neck
52 pain will be measured using the Northwick Park Neck Pain Questionnaire and the McGill Pain
53 Questionnaire. The changes in the PPT during the treatment phase will be evaluated. The times and
54 doses of analgesic drugs taken during the study period, and the disease-related treatment performed
55 during the follow-up period will also be recorded.
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Quality of life

Quality of life will be assessed using the Chinese version of the Medical Outcome Study Short-form 12-Item Health Survey.

Neck function

The change in neck function will be evaluated using the Neck Disability Index and the cervical range of motion. Recent research has shown that the Neck Disability Index has an excellent ability to distinguish between patients with different levels of perceived dysfunction.[42]

Emotional disorders

Chronic pain is often accompanied by emotional disorders.[43 44] Changes in mood will be assessed using the Self-Rating Anxiety Scale and the Self-Rating Depression Scale.

Table 3 Outcome measurements at each timepoint

Measurements	Baseline	Treatment phase			Follow-up phase				
	-4 weeks	0 week	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Measurements of pressure-pain threshold		×	×	×					
VAS	×	×		×	×	×	×	×	×
NPQ		×		×	×	×	×	×	×
MPQ		×		×	×	×	×	×	×
SF-12		×		×	×	×	×	×	×
NDI		×		×	×	×	×	×	×
CROM		×		×					
SAS		×		×	×	×	×	×	×
SDS		×		×	×	×	×	×	×
Adverse events		×	×	×	×	×	×	×	×

Data and Safety Monitoring Board

To ensure the integrity of the RCT and protect the rights and health of the participants, we will set up a Data and Safety Monitoring Board. The Data and Safety Monitoring Board is an independent advisory group that will maintain the scientific and ethical standards of the RCT, and will be

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4 responsible for data evaluation during the study period. The Data and Safety Monitoring Board will
5
6 be developed in accordance with the Operational Guidelines for the Establishment and Functioning of
7
8 Data and Safety Monitoring Boards of the World Health Organization.
9

10 11 **Safety and acupuncture-related adverse events**

12
13 Acupuncture may cause several adverse events, including bleeding, hematoma, fainting, serious
14
15 pain, and local infection.[45] Hence, we will record any acupuncture-related adverse events that
16
17 occur during the treatment and follow-up phases, and record the potential reasons for these adverse
18
19 events. The number and type of adverse events in each group will be calculated. Patients will receive
20
21 appropriate intervention for any adverse events that occur. Serious adverse events will be
22
23 immediately reported to the primary investigator, and the affected participants will be withdrawn
24
25 from the study.
26
27
28

29 **Patients and public involvement**

30
31 Patients and the public are not involved in the design or conduct of the study or the outcome
32
33 measures, and no attempt will be made to assess the burden of the intervention on the patients
34
35 themselves.
36
37
38

39 **Sample size calculation**

40
41 The sample size calculation was based on the superiority test. The primary outcome is the change
42
43 in the VAS score from baseline to week 4. The clinical difference in the VAS score after acupuncture
44
45 treatment is reportedly 6.3;[17] therefore, we conservatively estimated that there would be a VAS
46
47 score change of 5 between the highly-sensitive acupoints group and the low/non-sensitive acupoints
48
49 group, 10 between the highly-sensitive acupoints group and the sham acupuncture group, and 20
50
51 between the highly-sensitive acupoints group and the waiting-list control group. Considering a two-
52
53 sided significance level of 5% and power of 95%, 621 participants are required with a 1:1:1:1 group
54
55 allocation rate, as calculated by Fisher's exact test in G*Power (version 3.1.5). To minimize attrition
56
57 bias, we assumed a dropout rate of 15%, making it necessary to include at least 716 participants in
58
59 total.
60

Statistical analysis

The included patients will be divided into the full analysis set (FAS), per protocol set (PPS), and safety set (SS). The FAS population will consist of all participants for whom the primary outcome is evaluable. The FAS population will be used as the primary population for all efficacy analyses. The PPS population will consist of all participants who undergo the planned interventions. The SS will consist of all randomized participants who received at least one acupuncture treatment during the study period. All data will be managed by the data coordinating center through a third party (the Brightech-Magnsoft Data Services Company).

A statistician blinded to the group allocations will conduct all analyses using the SAS version 9.4 software package (SAS Institute Inc., Cary, NC, USA). First, the basic information of the four groups will be described, including patient characteristics, medical characteristics, outcome variables, and adverse events. If an adjustment is needed for a baseline value that differs between groups, covariance analysis will be performed. Data will be presented as mean (SD) for continuous variables, and as frequency (percentage) for categorical variables. Group comparisons will then be undertaken using χ^2 tests for categorical characteristics, and analysis of variance for continuous variables. The primary analyses will examine whether acupuncture performed in the highly-sensitive acupoints group will achieve statistically better treatment outcomes (pain, quality of life, neck function, and emotional disorders) than acupuncture in the low/non-sensitive acupoints group, sham acupuncture group, and waiting-list control group. To accommodate the correlation between repeated measures from the same participant, generalized linear models with random effects will be fitted to assess the effect of intervention on outcome variables over time, while accounting for the effects of potential confounders (e.g., age, sex, analgesic medications, and other treatments). We will use the last value carried forward method to impute missing data for the primary and secondary outcomes. All analyses will use two-sided tests, and a p value of less than 0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

This RCT was designed in accordance with the principles of the Declaration of Helsinki. The trial protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (permission number: 2017KL-038), and is registered

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4 on the primary registry in the World Health Organization registry network (Chinese Clinical Trial
5 Registry: no. ChiCTR1800016371). Signed consent will be obtained from each patient after they
6 have been informed of the study procedures, possible risks, and their right to withdraw from the
7 trial.
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10
11 This study will be the first multicenter RCT to evaluate the safety and effectiveness of acupuncture
12 at sensitive points for chronic neck pain. The concept of sensitive points comes from the theory of
13 traditional Chinese medicine, which purports a link between disease status and the condition of
14 acupuncture points; when the body is affected by diseases, particular points become sensitive.[25]
15 The results of this study may provide further evidence for the effectiveness of acupuncture in
16 relieving chronic neck pain.
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23 This study has some strengths that warrant mention. In contrast with previous studies,[31] this trial
24 established a sham group to investigate the placebo effect of acupuncture. The creation of a waiting-
25 list control group will rule out self-healing of the disease, and control for the Hawthorne effect. The
26 waiting-list control group will receive the same acupuncture intervention after the 24-week follow-
27 up period. This design provides participants with a guarantee that they are going to receive
28 acupuncture treatment, overcoming the potential problem of control participants being
29 disappointed.[46] In addition, the blinding of the patients, operators, acupuncturists, assessors, and
30 statisticians will decrease potential bias.
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38 As this will be the first study to investigate the effectiveness of acupuncture at sensitive acupoints
39 for chronic neck pain, this RCT may have some limitations. There are several types of point
40 sensitization, such as pain and heat.[47 48] However, in this trial, we only quantified pain as the
41 indicator of sensitization, which might overlook the other forms of acupoint sensitization. Further
42 study is needed to confirm the improvement in clinical efficacy of acupuncture at different kinds of
43 sensitive acupoints. If the results show that acupuncture therapy at sensitive acupoints is safe and
44 effective in reducing chronic neck pain, this study will provide evidence to support the superior
45 clinical efficacy of performing acupuncture at sensitive acupoints compared with low/non-sensitive
46 acupoints.
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58 CONCLUSION

59 This article describes the design and protocol of a study that aims to evaluate the effectiveness and
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4 safety of acupuncture for chronic neck pain. The results will reveal whether sensitive acupoints have
5
6 specificity, and whether acupuncture at highly-sensitive acupoints is superior to acupuncture at
7
8 low/non-sensitive points or sham acupuncture at non-acupoints.
9

10 11 **Trial status**

12
13 This study is currently in the recruitment phase. The first patient was enrolled in June 2018, and the
14
15 study is expected to end in December 2019.
16

17 18 19 **Acknowledgments**

20
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22
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26
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28
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30
31 Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this
32
33 manuscript.
34
35

36 37 **Authors' contributions**

38
39 MSS, GYG, JC, DJC, HZ, LZ, and FRL participated in the design of the trial, in creating the data
40
41 analysis plan, and in drafting the manuscript. XSM, MXY, XJL, and JRD collected the information
42
43 needed for the performance of this trial in each center. All of the authors discussed, read, and revised
44
45 the manuscript, and gave final approval for the publication of this study protocol.
46
47

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50
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52
53 81590951, no. 81722050).
54

55 56 **Competing interests**

57
58 The authors declare that they have no competing interests.
59
60

Ethics approval

The study protocol has been approved by the institutional review board and ethics committee of the First Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (May 2018).

Provenance and peer review

Not commissioned; internally peer reviewed.

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17

18 **Figure 1** Flowchart of the trial design.
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20
21 **Figure 2** The test regions that will be used in the study. Regions 1 and 2 are each bordered by the
22 respective ipsilateral mastoid, sternal end of the clavicle, anterior axillary line, acromion, and C7
23 spinous process. Region 3 is the triangular region bordered by both sides of the mastoid and the C7
24 spinous process. Regions 4 and 5 are each bordered by the respective ipsilateral C7 spinous process,
25 acromion, and axillary line; the two regions are divided by the posterior midline.
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30 **Figure 3** Locations of the five non-acupoints used in the study.
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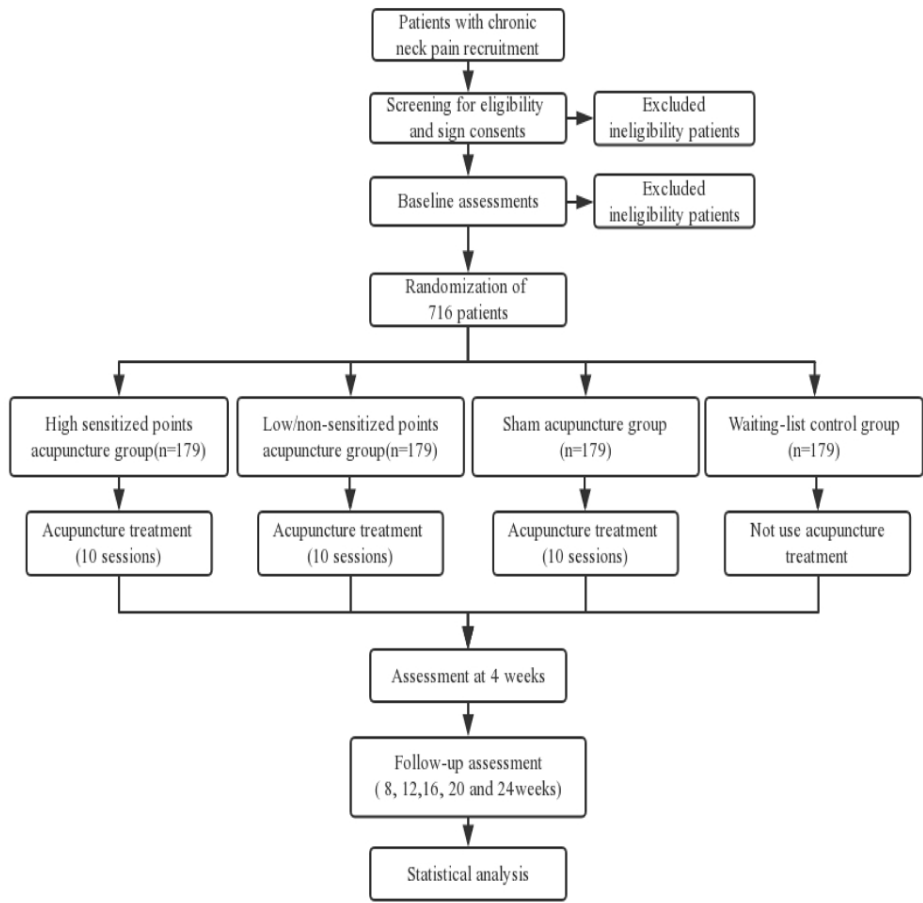


Figure 1 Flowchart of the trial design.

90x90mm (300 x 300 DPI)

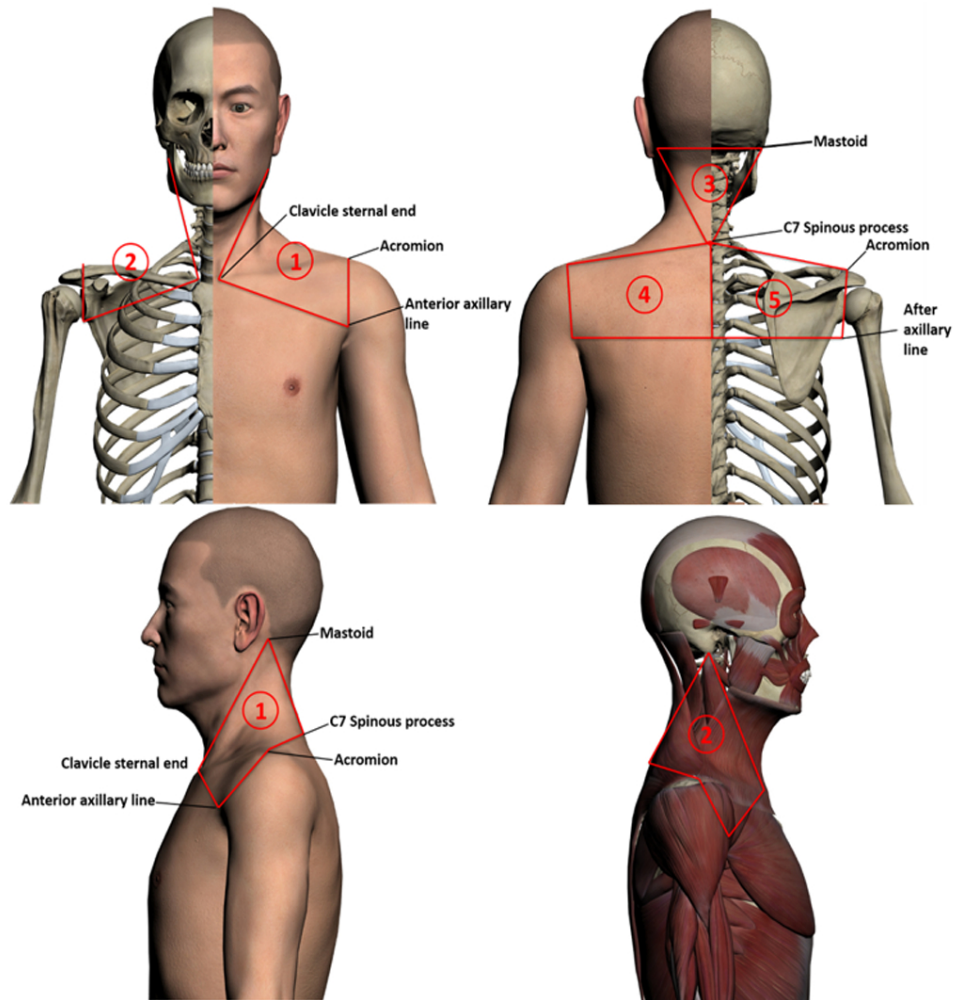


Figure 2 The test regions that will be used in the study. Regions 1 and 2 are each bordered by the respective ipsilateral mastoid, sternal end of the clavicle, anterior axillary line, acromion, and C7 spinous process. Region 3 is the triangular region bordered by both sides of the mastoid and the C7 spinous process. Regions 4 and 5 are each bordered by the respective ipsilateral C7 spinous process, acromion, and axillary line; the two regions are divided by the posterior midline.

90x90mm (300 x 300 DPI)

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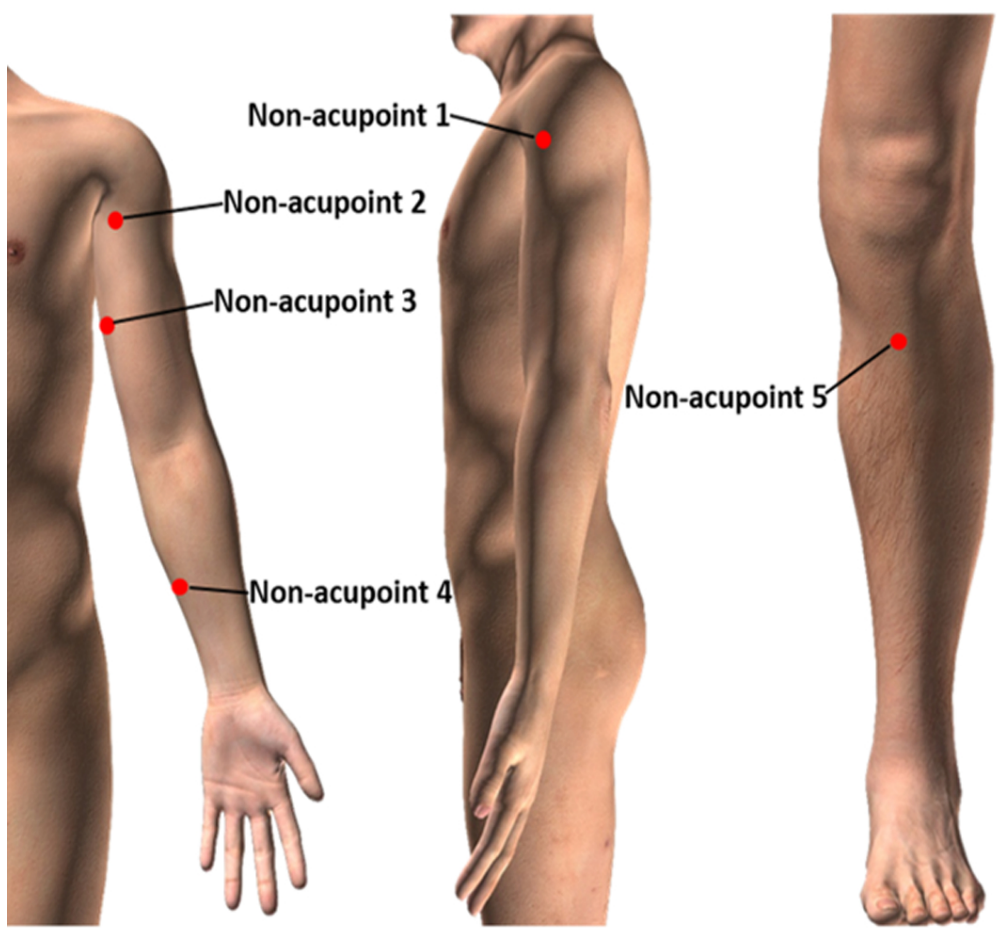


Figure 3 Locations of the five non-acupoints used in the study.

90x90mm (300 x 300 DPI)

Appendix Table

Regions	Acupoints	Pressure pain threshold of healthy subjects (gf)
Region 1	Jianjing (GB-21) L	2234
	Jianzhongshu(SI-15) L	2648
Region 2	Jianjing (GB-21) R	2222
	Jianzhongshu(SI-15) R	2650
Region 3	Wangu(GB-12) L	1616
	Fengchi(GB-20) L	1909
	Tianzhu(BL-10) L	2067
	Dazhui(DU-14)	2978
	Wangu(GB-12) R	1738
	Fengchi(GB-20) R	2037
	Tianzhu(BL-10) R	2083
Region 4	Dazhu(BL-11) L	2924
	Jianwaishu(SI-14) L	2856
	Tianliao(SJ-15) L	2788
	Jugu(LI-16) L	2611
	Tianzong(SI-11) L	2484
Region 5	Dazhu(BL-11) R	2932
	Jianwaishu(SI-14) R	2849
	Tianliao(SJ-15) R	3075
	Jugu(LI-16) R	2652
	Tianzong(SI-11) R	2478
Distant acupoints	Shousanli(LI-10) L	1645
	Lieque(LU-7) L	2003
	Zhongzhu(SJ-3) L	2011
	Houxi(SI-3) L	2326
	Shousanli(LI-10) R	1710
	Lieque(LU-7) R	2192
	Zhongzhu(SJ-3) R	2017
	Houxi(SI-3) R	2419

L: left; R: right