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Prospective comparison of acupuncture with sham acupuncture to determine impact on sedation and analgesia in mechanically ventilated critically ill patients (PASSION study): protocol for a randomized controlled trial

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Complete List of Authors:	Zhang, Yuzhuo; Guangzhou University of Chinese Medicine Yang, Guang; Guangzhou University of Chinese Medicine Wei, Jinyi; Guangzhou University of Chinese Medicine Chen, Fangliang; Guangzhou University of Chinese Medicine Zhang, Min-Zhou; Guangzhou University of Chinese Medicine; Guangdong Provincial Hospital of Chinese Medicine, Department of Critical Care Medicine Mao, Shuai; Guangzhou University of Chinese Medicine; Guangdong Provincial Hospital of Chinese Medicine, Department of Critical Care Medicine
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Manuscripts

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5 **Prospective comparison of acupuncture with sham acupuncture to**
6 **determine impact on sedation and analgesia in mechanically ventilated**
7 **critically ill patients (PASSION study): protocol for a randomized**
8 **controlled trial**
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15 Yuzhuo Zhang, Ph.D. ^{1*}

16
17
18
19 Guang Yang, M.D. ^{1,2*}

20
21
22
23 Jinyi Wei, M.D. ¹

24
25
26 Fangliang Chen, M.D. ¹

27
28
29
30 Minzhou Zhang, M.D. ^{1,2,4Δ}

31
32
33
34 Shuai Mao, M.D. ^{1,2,4Δ}

35
36
37 ¹ *Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou*
38 *510405, China*

39
40
41
42 ² *Department of Critical Care Medicine, Guangdong Provincial Hospital of Chinese*
43 *Medicine, Guangzhou 510120, China*

44
45
46
47 ³ *Guangdong Provincial Branch of National Clinical Research Centre for Chinese*
48 *Medicine Cardiology, Guangzhou 510120, China*

49
50
51
52
53
54
55 *The first two authors contribute equally to this article.

56
57
58 ΔCorrespondence to:

1
2
3
4 Prof. Shuai MAO
5

6 Department of Critical Care Medicine,
7

8
9 Guangdong Provincial Hospital of Chinese Medicine,
10

11 Guangzhou 510120, China
12

13
14 Phone: 86-20-81887233
15

16
17 Fax: 86-20-81867705
18

19 E-mail: maoshuai@gzucm.edu.cn
20

21
22 Or Prof. Minzhou Zhang minzhouzhang@gzucm.edu.cn
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ABSTRACT

Introduction Sedation and analgesia are recommended used in the intensive care unit (ICU) to enhance patient comfort and safety, facilitate mechanical ventilation, and reduce oxygen demands. However, the increasing evidence demonstrates that excessive sedation and analgesia might prolong mechanical ventilation and increase costs and mortality. Acupuncture, known to attenuate pain, anxiety, and agitation symptoms, might reduce the duration of mechanical ventilation and drug accumulation through avoiding excessively deep sedation and analgesia.

Methods and analysis Prospective, randomized controlled trial (RCT) of 180 adult medical/surgical ICU patients with mechanical ventilation needing sedation at 3 ICUs between December 2021 and December 2022. Patients would be treated with analgesia and sedation to achieve desired target sedation levels (Richmond Agitation Sedation Score of -2 to 1) from enrolment until extubation. Enrolled patients will be randomly assigned in a ratio of 1:1:1 to receive deep needle insertion with combined manual and alternating-mode electrical stimulation on acupoints (AC group), superficial needle insertion without manual stimulation and electrical stimulation on non-acupoints (SAC group), or no acupuncture intervention (NAC group).

The primary outcome is the duration of mechanical ventilation from randomization until patients were free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours. Secondary endpoints included the dose of

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2
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4 administered sedatives and analgesic at comparable sedation levels throughout the study
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6 period, ICU length of stay, hospital length of stay.
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10 **Ethics and dissemination** The trial was approved by the ethics committee at
11
12 Guangdong Provincial Hospital of Chinese Medicine. We will publish the study results.
13
14

15 **Trial Registration numbers: ChiCTR2100052650**
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18
19 **Keywords:**
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22 acupuncture; sedation; analgesia; critically ill patients; nonpharmacological therapy
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Strengths and limitations of this study

- ◆ Strengths include objective, methods to reduce bias and careful collection of safety data.
- ◆ The result would demonstrate nonpharmacological therapies could be used as adjuncts to sedatives and analgesics for critically ill patients.
- ◆ Limitations are the non-blinded interventions due to the nature of acupuncture.

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INTRODUCTION

Sedative and analgesic medications are routinely administered to mechanically ventilated critically ill patients to reduce pain, anxiety, and agitation, as well as to allow patients to tolerate invasive procedures in the intensive care unit (ICU).¹ Opiates are most commonly used as analgesics, while benzodiazepines, propofol, or dexmedetomidine are typically used to prevent or reduce anxiety and agitation.² However, overuse of these medications is associated with worsened clinical outcomes, such as prolonged time of mechanical ventilation and hospital length of stay, the increased risk of altered mental status, and even mortality.³ Thus, reducing the unnecessary dosage of sedative and analgesic medications and their side effects while providing desired sedation has always been a key objective when caring for critically ill patients.

As a therapeutic modality with fewer adverse effects, acupuncture has been used in China and other Asian countries for thousands of years to treat various conditions.⁴⁻⁶ Studies of acupuncture usually focused on its analgesic effect, such as relieving pain and partly reducing opioid-related side effects during or after surgical procedures.⁷⁻¹¹ Particularly, Centers for Medicare & Medicaid Services (CMS) of USA finalizes a decision to cover acupuncture for chronic low back pain for Medicare beneficiaries from January 2020. Moreover, acupuncture has been demonstrated to reduce sedative demands and improve patient experience during diagnostic endoscopic ultrasound.¹² However, there are few, if any, reports on the effect of acupuncture on reducing excessive sedation and analgesia, especially due to shortening duration of mechanical

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4 ventilation and drug accumulation. Furthermore, there is no evidence for an effect of
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6 “true” acupuncture over "sham" acupuncture (superficial needle insertion without
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8 manual stimulation at "non-points" or electrical stimulation) on clinical outcomes in
9
10 critically ill patients needing mechanical ventilation.
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15 Therefore, the PASSION study is designed to investigate the efficacy of acupuncture on
16
17 sedation and analgesia in mechanically ventilated critically ill patients. We are going to
18
19 test the hypothesis that acupuncture, as adjunctive therapy to sedation and analgesia
20
21 therapies, could reduce the duration of mechanical ventilation, the dose of administered
22
23 sedatives and analgesic, and subsequently improve other clinical outcomes for critically
24
25 ill patients when compared with sham acupuncture or non-acupuncture.
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30 **METHODS**

31 **Study Design Overview**

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34 This is a prospective, parallel-group, controlled trial that will recruit 180 patients with
35
36 a computer-generated allocation sequence and centralized randomization at tertiary and
37
38 regional ICUs in 3 hospital (Guangdong Provincial Hospital of Chinese Medicine,
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40 Charity Hospital of Guangzhou, University Hospital) in South China. Eligible patients
41
42 will be randomly assigned, in a ratio of 1:1:1, to receive deep needle insertion with
43
44 combined manual and alternating-mode electrical stimulation on acupoints (AC group,
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46 n =60), superficial needle insertion without manual or electrical stimulation on non-
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48 acupoints (SAC group, n =60) for 30 min/day, or no acupuncture intervention (NAC
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50 group, n =60) .
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4 Participants will be assessed the duration of mechanical ventilation, as well as the dose
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6 of administered sedatives and analgesic at comparable sedation levels, from
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8 randomization until patients were free of mechanical ventilation (including noninvasive)
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10 without reinstitution for the following 48 hours. They will be also assessed if
11
12 acupuncture could achieve better clinical outcomes than SAC or NAC treatment. The
13
14 design of the trial is summarized in Figure 1.
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20 **Ethical Requirements and Registration**

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23 This protocol and statistical analysis plan was approved by the institutional human
24
25 Clinical Research Ethical Committee at Guangdong Provincial Hospital of Chinese
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27 Medicine (Guangzhou, China) in October 2021 with permission number ZF2021-144-
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29 01. The PASSION study was registered on Nov 3, 2021 (ClinicalTrials.gov, number
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31 ChiCTR2100052650) and will be conducted following the Declaration of Helsinki from
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33 December 2021 to December 2022.
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40 Written informed consent will be provided before enrollment voluntarily. Considering
41
42 that patients will be sedated following ICU admission, complete adherence to patient
43
44 consent is deemed impossible. The investigational nature and details of the study,
45
46 together with the possible risks and all the benefits, will be informed to patients or their
47
48 authorized surrogates. Written informed consent will be subsequently obtained from
49
50 either of them. Patients for whom surrogate consent was obtained were asked again to
51
52 provide informed consent once determined to be competent. They can also withdraw
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54 from the study at any time they wish. Also, the investigator can decide to withdraw a
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4 subject from the study for urgent medical reasons. The researcher should complete the
5
6 case report form (CRF) and record the reason for dropping out.
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9 10 **Patients**

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13 Patients from medical and surgical ICU, aging from 18 to 80 years, for expected
14
15 mechanical ventilation longer than 24 hours, with agitation and/or discomfort after
16
17 recovering from drugs used to facilitate endotracheal intubation, requiring sedation and
18
19 agitation by continuous intravenous administration deemed by the ICU physician, are
20
21 eligible for participation as soon as they or their authorized surrogates are willing to
22
23 give informed consent (Table 1).
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27

28
29 Exclusion criteria include skin lesions near the acupuncture points; coagulopathy
30
31 (bleeding time >4 min, thrombocytes <50,000/ μ l), neurological disease (previous stroke,
32
33 cerebral palsy, etc.) that would confound the diagnosis of delirium, active seizures,
34
35 severe dementia, relevant psychiatric disorder, hypohepatia with Childs-Pugh class B
36
37 or C, second- or third-degree atrioventricular block, alcohol or drug abuse,
38
39 benzodiazepine dependency, a moribund state with the planned withdrawal of life
40
41 support, family or physician refusal, pregnancy or lactation, currently participated in
42
43 any other investigational therapeutic or device trial (Table 1).
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50 51 **ICU standard treatment**

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53
54 As is standard in each ICU of our study, mechanically ventilated critically ill patients
55
56 will be treated in a single treatment room. They will be taken care of by a trained ICU
57
58 physician responsible for all treatment decisions, including sedation analgesia
59
60

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4 management plans made in consultation with the bedside nurses. They will also receive
5
6 one-to-one nursing care to adjust the treatment based on a patient's response in time. A
7
8 team of medical officers will review patient care every day.
9
10

11 **Randomization and blinding**

12
13
14
15 Eligible patients will be stratified by participating sites to avoid patient-level
16
17 contamination from the systems-level organizational change in sedation practice and,
18
19 within each ICU, assigned to the AC, SAC, or NAC group in an equal ratio via
20
21 computer-generated randomization. In detail, an independent study coordinator will log
22
23 into the central randomization system using a password-protected account and enter
24
25 inclusion and exclusion criteria to ensure eligibility. After entering a patient's name and
26
27 identification card number, a randomization sequence will be generated in blocks of
28
29 varying sizes and stratified by the site under the control of the central computer system.
30
31 The random sequence will then be concealed in sealed envelopes and sent to an
32
33 acupuncturist from the assigned patient's site by the study coordinator.
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41
42 Allocation of participants will be known to the study coordinator and acupuncturists
43
44 who will not be involved in outcome assessment and be required to sign a confidentiality
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46 agreement about patient allocation. All patients will be treated in a single treatment
47
48 room. In both AC and SAC groups, patients, bedside nurses, and physicians will be
49
50 blinded to which acupuncture method the patients would receive. The data collectors
51
52 and the biostatisticians will be masked from the treatment assignment.
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58 **Acupuncture interventions and procedures**

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4 The acupuncture interventions will be developed by a consensus of acupuncture experts
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6 according to the Standards for Reporting of Controlled Trials in Acupuncture
7
8 (STRICTA).¹³ Patients will be assigned in a ratio of 1:1:1 to AC group (n=60), SAC
9
10 group (n=60), NAC group (n=60). Besides, each group shares the same basic Sedation
11
12 Analgesia Strategy
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16
17 For patients in the AC group, 8 disposable sterile acupuncture needles (filiform needles
18
19 made of stainless steel, Beijing Hanyi Medical Instruments, China) with a length of 40
20
21 mm and a diameter of 0.30 mm will be inserted into acupuncture points at Baihui
22
23 (DU20), Yintang (EX-HN3), and bilateral acupoints of Shenmen (HT7), Hegu (LI4),
24
25 Taichong (LR3) according to the theory of traditional Chinese medicine. The
26
27 localization of these points is measured with a unit of *cun*, a traditional Chinese unit of
28
29 length. One *cun* of a person is defined as the width of the thumb himself, whereas four
30
31 fingers are defined as 3 *cun*. The insertion will be followed by manual stimulation, a
32
33 lifting and thrusting technique combined with twirling and rotating the needle sheath to
34
35 produce a sensation of soreness, numbness, distention, or radiating. This sensation is
36
37 known as “*Deqi*” and is considered to be indicative of effective needling. Then,
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39 alternating-mode electrical stimulation will be given with the parameters: bursts
40
41 alternating at 2 Hz and 100 Hz every 3 s, with 10-15 mA intensity inducing no
42
43 discomfort and no muscle contraction.
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48 For patients in the SAC group, superficial needle insertion with a depth of 2 mm and no
49
50 manual stimulation will be performed for 30 min/day. The same sort of needles with the
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52 AC group will be placed 1 cm distant lateral the used acupoints that are not known as
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4 AC points. The electrical stimulator will likewise be connected but without electrical
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6 stimulation.
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10 Patients in the NAC group will receive no acupuncture-related intervention during the
11
12 trial. But they could receive a free 12-session daily acupuncture treatment after
13
14 completing the study at their convenience.
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18 Each Site will be required to have 2 licensed acupuncturists with more than 3 years of
19
20 experience and specialized training in the acupuncture protocols before starting the
21
22 study. The acupuncturists will be responsible for the whole acupuncture process but are
23
24 not further involved in this study.
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28 29 **Basic Sedation Analgesia Strategy** 30 31

32
33 In this study, diagnosis and therapeutic management of agitation and pain will be
34
35 prescribed by the physicians responsible for the clinical care of each patient according
36
37 to recommended guidelines¹⁴. An interruptive sedation strategy was used by bedside
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39 nurses, and sedation levels and pain intensity were assessed with the Richmond
40
41 Agitation Sedation Scale (RASS)^{15 16}, the Behavioral Pain Scale (BPS) ,or the Numeric
42
43 Rating Scale (NRS) ^{17 18} every 4 h in objective to adapt sedatives and analgesics to avoid
44
45 overuse. Authorized nurses will titrate infusions, including benzodiazepines, propofol,
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47 and dexmedetomidine for sedatives and opiates for analgesia, instead of bolus dosing to
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49 minimize potential adverse effects.
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56 The sedation analgesia strategy is designed to consider pain treatment before increasing
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58 sedatives to minimize the risk of oversedation. The pain will be assessed either by the
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4 BPS in patients unable to communicate or by the NRS, a 1-10 numeric rating scale, in
5
6 those sufficiently oriented and awake to communicate with the medical staff. Efficacy
7
8 of the study analgesics drug will be defined as the ability to achieve a score < 3 in both
9
10 of the pain scoring systems above, evaluated by the bedside nurse. Efficacy of the study
11
12 sedative drug will be defined as the ability to achieve a sedation score between -2 and
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14 1, set by the patient's medical team using the RASS, a highly reliable and well-validated
15
16 sedation scale for use within patients over time in the ICU.
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23 Each morning, a daily interruption of sedation (DIS) will be performed at the clinical
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25 medical team's discretion. Major opioid infusions needed for active pain will be
26
27 continued. Recommended criteria to interrupt sedation is used: no drug-induced
28
29 paralysis, no intracranial hypertension, no myocardial ischemia in the previous 24 h,
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31 primary disease healing in progress, hemodynamic stability, the partial pressure of
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33 arterial oxygen ≥ 60 mmHg, the fraction of inspired oxygen $\leq 50\%$, and positive end-
34
35 expiratory pressure ≤ 8 cmH₂O. The interruption of continuous sedation will be coupled
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37 with an assessment hourly for wakefulness, defined as the RASS score 1 to 4, and the
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39 ability to perform at least 3 of the following requests: eye-opening, tracking, hand
40
41 squeezing, and toe moving. With the criteria recommended, patients will be able to pass
42
43 the DIS if they can tolerate it for 4 h and awakening enough. Then, a spontaneous
44
45 breathing trial (SBT) will immediately be managed.¹⁹ If patients are insufficient for the
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47 DIS, sedatives will be restarted at half the previous dose and then titrated to achieve
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49 patient comfort. DIS will be performed the next morning again.
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Extubation Test

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4 Before extubation, patients will be managed with an SBT. During the SBT, without
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6 ventilatory support, patients will be allowed to breathe through a ventilatory circuit with
7
8 8cm H₂O PSV, 0 PEEP, and unchanged FiO₂ from the mechanical ventilation period
9
10 leading up to the SBT.²⁰ Criteria for a successful SBT were: respiratory rate between 8
11
12 and 35 breaths/min, arterial oxygen saturation > 88%, less than 20% change in mean
13
14 arterial pressure or heart rate, no signs of respiratory distress and acute cardiac
15
16 arrhythmia, no use of accessory muscles, no abdominal paradox, absence of sweating,
17
18 agitation or impaired vigilance status. Patients pass the SBT if they complete a 60 min
19
20 trial with the success criteria, and extubation will be implemented 6 h later. Patients who
21
22 fail the SBT will be ventilated immediately with the ventilator settings used before the
23
24 trial, and sedatives will be restarted at half the previous dose and then titrated to achieve
25
26 patient comfort. The SBT will be managed the next morning again. Extubation will be
27
28 implemented following standardized criteria, but the decision to extubate remains upon
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30 the authority of the attending physician in charge of the patient. Researchers did not
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32 participate in decisions to extubate patients.
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43 The clinical research team should make sure that the overall research protocol,
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45 especially the criteria for sedation and definition of successful SBT, is strictly followed
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47 by the bedside nurse and medical teams in charge of the patients. Related information
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49 will be reported on the Clinical Research Form.
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54 **Assessing Delirium**

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4 Delirium will be measured by the bedside nurses according to the Confusion
5
6 Assessment Method for the ICU (CAM-ICU) until out of ICU or hospital discharge.²¹

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9 Patients will be considered in this state if they have a RASS score ≥ -3 and a positive
10
11 CAM-ICU, defined as positive with the symptoms of feature 1, feature 2, and either
12
13 feature 3 or feature 4 as follows:

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16
17 Feature 1: acute onset of mental status change or fluctuation of mental status

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21 Feature 2: inattention

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24 Feature 3: disorganized thinking

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26
27 Feature 4: altered level of consciousness

28 29 30 **Adverse Event Monitoring**

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33
34 Adverse events will also be defined a priori and prospectively monitored. Adverse
35
36 events associated with acupuncture include bleeding, hematoma, and local infection.

37
38
39 Adverse events related to sedation and analgesia include inadequate pain and sedation
40
41 management (either pain score > 4 and RASS > 1 for 2 consecutive hours or pain and
42
43 agitation assumed present if receiving neuromuscular blockade), clinically significant
44
45 iatrogenic withdrawal. Adverse events associated with mechanical ventilation include
46
47 accidental removal of medical devices, extubation failure (reintubation within 24 hours),
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49 pressure ulcers, catheter-associated bloodstream infections, ventilator-associated
50
51 pneumonia. Every day, study personnel will monitor and assess the seriousness of all
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53 adverse events and document all details to determine whether or not any of the events
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55 would be related to acupuncture interventions or the study procedure. A report of all
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4 serious, unexpected, and study-related adverse events will be presented to an
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6 independent data and safety monitoring board and the institutional review board within
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9 7 days of occurrence.
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11 **Outcomes and Data Collection**

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15 The primary outcome is the duration of mechanical ventilation, defined as the time from
16
17 randomization to successful extubation without reinstitution for the following 48 hours.
18

19
20 The secondary outcomes will include the dose of administered sedatives and opiate
21
22 (absolute value as well as indexed value [total drug in mg/kg ÷ total number of hours
23
24 from the start of infusion to its ultimate discontinuation]) at comparable clinically
25
26 individualized target sedation goals throughout the study period, the duration of ICU
27
28 length of stay, and hospital length of stay. Additional outcomes include the prevalence
29
30 and days of delirium in ICU, mortality in ICU, and within 28 days after randomization.
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37 The day of extubation was considered as the day of death for patients who died while
38
39 still intubated. Censoring for ICU or hospital length analyses occurred at the time of
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41 death or study withdrawal. The number of ventilator free days at 28 days is defined as
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43 days alive and not using mechanical ventilation between days 1 and 28. For the 28-day
44
45 mortality analyses, patients were censored at the time of the last contact alive or at 28
46
47 days from enrollment, whichever was first.
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53 Baseline demographic data will be collected from the patients' record by the medical
54
55 team, including the reason for ICU admission, Acute Physiology and Chronic Health
56
57 Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure
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59 Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure
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4 Assessment (SOFA) scores, hematological and blood chemistry data, and clinical data
5
6 (detailed information of sedative and analgesic medications administered to the patients
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8 before randomization, cardiac safety profile including electrocardiograms and serum
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10 troponins, and liver function profile including serum bilirubin and glutamate pyruvate
11
12 transaminase, etc.). Vital signs such as blood pressure, heart rate, heart rhythm,
13
14 temperature, and oxygen saturations will be recorded and collected by the bedside
15
16 nurses, as well as scores of RASS, BPS, NRS, and CAM-ICU. Moreover, adverse events
17
18 data will also be collected from patients' records.
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25 **Patient and public involvement statement**

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28 There was no patient or public involvement in the design, conduct, reporting or
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30 dissemination plans of this research.
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33 **Statistical Analysis**

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37 Statistical power was estimated using the reduction in duration of mechanical
38
39 ventilation as the primary outcome. According to Carrasco and colleagues, the mean
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41 (\pm standard deviation) time for current sedation was 54.7 ± 12.3 hours.²² We calculated
42
43 that a sample size of 48 patients in each group would provide a power of 90% to detect
44
45 a 15% relative reduction in intubation time at a two-sided significance level of 0.05.
46
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48 With a dropout rate of 20%, the estimated sample size will be 60 patients per group.
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51 Thus a total of 180 patients will be enrolled for the study.
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56 The per-protocol set (PPS), including patients who completed the study without having
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58 major protocol violations, is used for the evaluation of clinical outcomes. While the full
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4 analysis set (FAS), determined according to the intention-to-treat population (ITT) who
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6 underwent randomization except for those who are excluded after randomization, is not
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8 only used for evaluation of clinical outcomes but also baseline characteristics to measure
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10 the balance of the three groups before intervention. Missing data will be replaced
11
12 according to the principle of multiple imputation. Continuous data will be presented as
13
14 median and interquartile range, while categorical data as number and proportions.
15
16 Normal distribution will be checked by the Kolmogorov test. For continuous variables,
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18 normal distributed data will be compared using one-way analysis of variance among
19
20 three groups, and independent Student's t-test between any of the two groups. While the
21
22 comparison of non-normally distributed parameters among three groups will be applied
23
24 by ANOVA (Kruska Wallis), and then Mann-Whitney U-test between any of the two
25
26 groups. Categorical data will be compared by using Fisher's exact test or the chi-square
27
28 test. Other factors that might affect the efficacy will be considered as co-variants for
29
30 covariance analysis or Cox proportional hazards regression model. $P \leq 0.05$ will be
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32 considered to indicate statistical significance. All analyses will be done with R statistical
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34 software, version 4.0.2.
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46 **DISCUSSION**

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49 This prospective trial is designed to provide evidence on the beneficial effect of
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51 acupuncture on reducing the duration of mechanical ventilation, avoiding excessive
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53 sedation and analgesia, as well as improving clinical outcomes in sedating mechanically
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55 ventilated ICU patients.
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4 General analgesia and sedation are necessary for mechanically ventilated critically ill
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6 patients. However, overuse of sedative and analgesic medications may cause varying
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8 degrees of side effects, like respiratory drive reduction.²³ These side effects are
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10 associated with worsened clinical outcomes, such as a prolonged time of mechanical
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12 ventilation and hospital length of stay, an increased risk of delirium, and even
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14 mortality.^{24 25} With many sophisticated attempts to mitigate this clinical problem, it has
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16 thus far been identified that optimizing analgesia and sedation strategy is able to prevent
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18 excessive sedation and analgesia and improve the clinical outcome by reducing the
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20 duration and dosage of sedative and analgesic medications.²⁶⁻²⁸ Thus, it become a key
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22 objective to formulate an intensive sedative and analgesic medications strategy when
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24 caring for critically ill patients.
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33 The rationale for evaluating the ability of acupuncture on this subject is based on
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35 research findings that acupuncture could manage pain relief and facilitate opioid
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37 tapering by increasing the μ -opioid receptor binding ability and the opioid peptides
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39 release.^{29 30} According to the meta-analysis of electroacupuncture on pain relief, the
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41 dosage of analgesics needed in AC group was lower than that in NAC group [MD=-
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43 6.33,95%CI (-7.20,-5.46), Z=14.24,P<0.00001] (Figure 2).³¹⁻³⁵ Meanwhile,
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45 acupuncture, without adverse effect, has been shown to exert sedation effects in various
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47 medical conditions. As it shown in meta-analysis, the bispectral index (BIS) values in
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49 AC group was also lower than that in NAC group [MD=-9.98,95%CI(-10.54,-
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51 9.42),Z=34.84,P<0.00001] (Figure 3).^{33 36-38} With these promising results, it is
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4 meaningful to assess acupuncture as a potential analgesia and sedation strategy in
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6 ameliorating the clinical outcomes in mechanically ventilated critically ill patients.
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10 RCT has been recognized as the gold standard for clinical trials since the late 20th
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12 century.³⁹ Another important designed technique to improve the quality of clinical trials
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14 is blinding. Over the past several decades, RCT and blinding have been used to avoid
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16 bias (selection bias, performance bias, and ascertainment bias) in clinical trials and
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18 improve the reliability of effects assessment. Sham acupuncture, aiming to blind the
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20 participants and control therapeutic components, is designed as a placebo control.
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22 However, this acupuncture technique is relatively difficult to fabricate because it should
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24 be both biologically inert and psychologically indistinguishable.⁴⁰ Even previous
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26 experience of acupuncture feeling might impact the present perception of verum and
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28 sham acupuncture intervention.
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36 In PASSION study, we utilize a rigorous set of methods to minimize bias, such as
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38 computer-generated central randomization, parallel control design, and statistical
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40 analysis according to the intent-to-treat principle. In control design, the superficial
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42 needle insertion without manual or electrical stimulation at non-point is applied to
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44 simulate deep skin penetration in the SAC group, which is used as the most predominant
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46 type of sham electropuncture method to ensure blinding according to the published
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48 literature.⁴¹ However, a few studies reported that superficial needle insertion at non-
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50 acupoints might not be physiologically inert since the locations of points are nearby true
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52 acupoints.^{42 43} Moreover, researchers found that even mechanical non-penetration can
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54 evoke slight acupressure effects and physiological activity.⁴⁴ Both of these factors will
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4 affect the effect assessment of acupuncture. Thus, the NA group, avoiding all
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6 therapeutic components, is designed to clarify if the sham acupuncture could be
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8 regarded as physiologically inert, as well as compared with the results of the AC group.
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12 A potential limitation of this trial is blinding. Given the nature of acupuncture, the
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14 patients and members of the medical team in the NA group are impossible to be blinded
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16 throughout the entire duration of this trial. However, adequate measures will be taken
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18 to put other people in a masked state. We will formulate a set of isolation and secrecy
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20 strategies for the study coordinator and acupuncturists to achieve satisfactory blinding
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22 levels in treatment administration. Thus, in both AC and SAC groups, patients and their
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24 medical team members will be blinded to the patients' acupuncture method. The data
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26 collectors and the biostatisticians will also be masked of the treatment assignment.
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33 The PASSION study is designed to demonstrate the efficacy of acupuncture on sedation
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35 and analgesia in mechanically ventilated critically ill patients. We expect the finding
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37 would provide evidence-based recommendations for acupuncture use for sedation and
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39 analgesia in critically ill patients with mechanical ventilation.
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49
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7
8 Guangdong Province of CM (20211187&20201142).
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11 **DISCLAIMER**

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14 The sponsors have had no role in the project development, in the collection of data, in
15
16 the preparation of this manuscript, nor the decision to publish. The researchers have
17
18 complete independence from the sources of funding in all aspects
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21 of this study.
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24 **PATIENT CONSENT FOR PUBLICATION**

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26
27 Consent obtained from parent(s)/guardian(s).
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29

30 **PROVENANCE AND PEER REVIEW**

31
32
33 Not commissioned; externally peer reviewed.
34
35

36 **ETHICS AND DISSEMINATION**

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38
39 The study was reviewed and approved by Ethics Committee of Guangdong Province
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41 Hospital of Chinese Medicine at Guangzhou University of Chinese Medicine (ZF2021-
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43 144-01) and performed in accordance with Guide for the Care and Use of Laboratory
44
45 Animals published by the US National Institutes of Health (publication No. 85-23,
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47 revised 1996).
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53 **COMPETING INTERESTS STATEMENT**

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56 All authors declare that they have no conflict of interest.
57
58

59 **AUTHORS' CONTRIBUTIONS**

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4 YZ & SM drafted this manuscript; GY, JW & FC made statistical analysis; MZZ made
5
6 a critical revision of the manuscript and contributed to the rationalization of the study.
7
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9 All authors read and approved the final manuscript.
10

11 **REFERENCE**

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Table 1. Inclusion and exclusion criteria

A. Inclusion criteria	B. Exclusion criteria
1. Aged 18 years or over and under 80 years;	1. Skin lesions near the acupuncture points;
2. Required mechanical ventilation >24 hours;	2. Coagulopathy (bleeding time >4 min, thrombocytes <50,000/ μ l);
3. Continuous intravenous administration of sedative and analgesic medications;	3. Hypohepatia with Childs-Pugh class B or C;
4. Willingness to provide informed consent prior to enrollment;	4. Second- or third-degree atrioventricular block;
5. Be able to comply with all follow-up evaluations (in investigator's opinion).	5. Severe dementia;
	6. Psychiatric disorder;
	7. Neurological disease;
	8. Active seizures;
	9. Alcohol or drug abuse;
	10. Benzodiazepine dependency;
	11. Moribund state with the planned withdrawal of life support;
	12. Family or physician refusal;

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4 13. Pregnancy or lactation;
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7 14. Currently participated in any other
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9 investigational therapeutic or device trial.
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Figure legend:

Figure 1. Trial design of PASSION study

Figure 2. Forest plot of AC group versus NAC group.

Figure 3. Forest plot of AC group versus NAC group.

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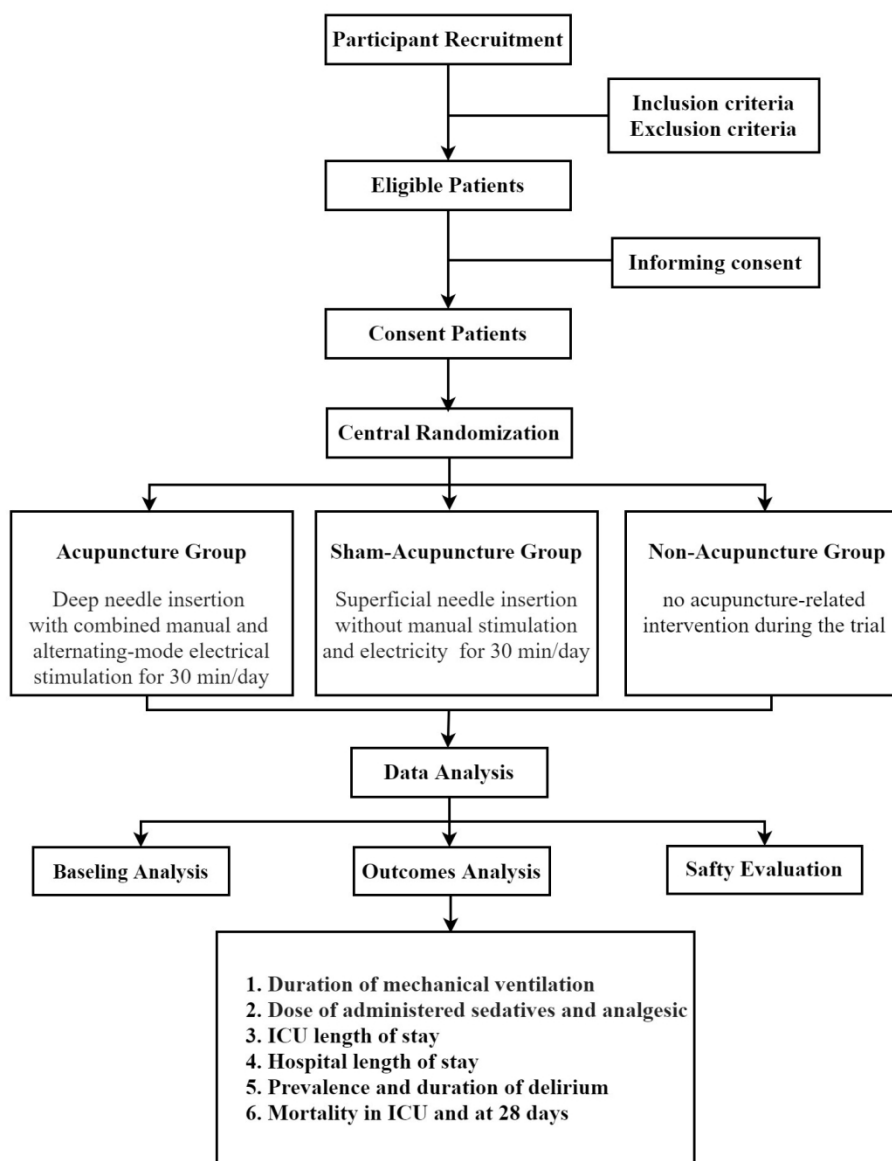


Figure 1

130x165mm (300 x 300 DPI)

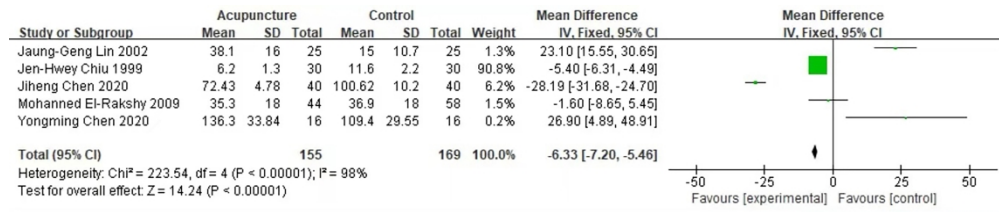


Figure 2

219x46mm (300 x 300 DPI)

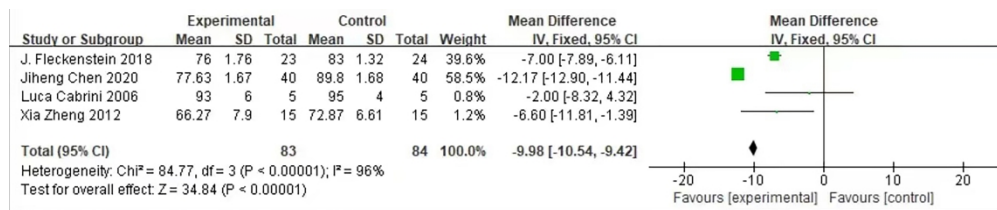


Figure 3

219x45mm (300 x 300 DPI)

BMJ Open

Prospective comparison of acupuncture with sham acupuncture to determine impact on sedation and analgesia in mechanically ventilated critically ill patients (PASSION study): protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059741.R1
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Complete List of Authors:	Zhang, Yuzhuo; Guangzhou University of Chinese Medicine Yang, Guang; Guangzhou University of Chinese Medicine Wei, Jinyi; Guangzhou University of Chinese Medicine Chen, Fangliang; Guangzhou University of Chinese Medicine Zhang, Min-Zhou; Guangzhou University of Chinese Medicine Mao, Shuai; Guangzhou University of Chinese Medicine; Guangdong Provincial Hospital of Chinese Medicine, Department of Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Complementary medicine
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Pain management < ANAESTHETICS

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5 1 **Prospective comparison of acupuncture with sham acupuncture to**
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7 2 **determine impact on sedation and analgesia in mechanically ventilated**
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9 3 **critically ill patients (PASSION study): Protocol for a randomized**
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11 4 **controlled trial**
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15 5 Yuzhuo Zhang, Ph.D. ^{1*}

16 6 Guang Yang, M.D. ^{1,2*}

17
18 7 Jinyi Wei, M.D. ¹

19
20 8 Fangliang Chen, M.D. ¹

21
22 9 Minzhou Zhang, M.D. ^{1,2,4Δ}

23
24
25
26 10 Shuai Mao, M.D. ^{1,2,4Δ}

27
28
29
30
31
32 11 *¹ Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou*
33 12 *510405, China*

34 13 *² Department of Critical Care Medicine, Guangdong Provincial Hospital of Chinese*
35 14 *Medicine, Guangzhou 510120, China*

36 15 *³ Guangdong Provincial Branch of National Clinical Research Centre for Chinese*
37 16 *Medicine Cardiology, Guangzhou 510120, China*

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43 18 *The first two authors contribute equally to this article.

44
45 19 ΔCorrespondence to:

46 20 Prof. Shuai MAO

47
48 21 Department of Critical Care Medicine,

49 22 Guangdong Provincial Hospital of Chinese Medicine,

50 23 Guangzhou 510120, China

51 24 Phone: 86-20-81887233

52 25 Fax: 86-20-81867705

53 26 E-mail: maoshuai@gzucm.edu.cn

54 27 Or Prof. Minzhou Zhang minzhouzhang@gzucm.edu.cn

ABSTRACT

Introduction Sedation and analgesia are recommended to be employed in the intensive care unit (ICU) to enhance patient comfort and safety, facilitate mechanical ventilation, and reduce oxygen demands. However, the increasing evidence demonstrates that excessive sedation and analgesia might prolong mechanical ventilation and increase costs and mortality. Acupuncture is known to be able to attenuate pain, anxiety, and agitation symptoms while avoiding excessive sedation and analgesia caused by drugs. Therefore, we present a protocol to investigate whether acupuncture, used for sedation and analgesia, can reduce the duration of mechanical ventilation, save medical resources, and reduce the mortality of critically ill patients receiving mechanical ventilation.

Methods and analysis Prospective, randomized controlled trial (RCT) is conducted on 180 adult medical/surgical ICU patients with mechanical ventilation needing sedation at 3 ICUs between 03 November 2021 and 16 August 2023. Patients will be treated with analgesia and sedation to achieve desired target sedation levels (Richmond Agitation Sedation Score of -2 to 1). Enrolled patients will be randomly assigned in a ratio of 1:1:1 to receive deep needle insertion with combined manual and alternating-mode electrical stimulation on acupoints (AC group), superficial needle insertion without manual stimulation and electrical stimulation on non-acupoints (SAC group), or no acupuncture intervention (NAC group).

The primary outcome is the duration of mechanical ventilation from randomization until patients are free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours. Secondary endpoints include the dose of administered sedatives and analgesic at comparable sedation levels throughout the study, ICU length of stay, hospital length of stay. Additional outcomes include the prevalence and days of delirium in ICU, mortality in ICU and within 28 days after randomization, and the number of ventilator free days in 28 days.

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Ethics and dissemination This trial was approved by the ethics committee at Guangdong Provincial Hospital of Chinese Medicine. We will publish the study results.

Trial Registration numbers: ChiCTR2100052650

Keywords:

acupuncture; sedation; analgesia; critically ill patients; nonpharmacological therapy

Word Count: 3805

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Strengths and limitations of this study

- This study is an RCT to investigate both the sedative and analgesic effects of acupuncture on critically ill patients needing mechanical ventilation in ICU.
- This study provides a sedative and analgesic strategy for mechanically ventilated critically ill patients with less side effects.
- The primary endpoint is the duration of mechanical ventilation from randomization until patients are free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours.
- Secondary endpoints include the dose of administered sedatives and analgesics at comparable sedation levels throughout the study, ICU length of stay, and hospital length of stay.
- Limitations are the non-blinded interventions due to the nature of acupuncture.

INTRODUCTION

Sedative and analgesic medications are routinely administered to mechanically ventilated critically ill patients to reduce pain, anxiety, and agitation, as well as to allow patients to tolerate invasive procedures in the intensive care unit (ICU).¹ Opiates are most commonly used analgesics, while benzodiazepines, propofol, or dexmedetomidine are typically used to prevent or reduce anxiety and agitation.² However, overuse of these medications is associated with worsened clinical outcomes, such as prolonged mechanical ventilation and hospital length of stay, increased risk of altered mental status, and even higher mortality.³ Thus, reducing the unnecessary dosage of sedative and analgesic medications, as well as their side effects while providing desired sedation has always been a key objective when caring for critically ill patients.

As a therapeutic modality with fewer adverse effects, acupuncture has been used in China and other Asian countries for thousands of years to treat various conditions.⁴⁻⁶ Studies of acupuncture usually focuses on its analgesic effect, such as relieving pain and partly reducing opioid-related side effects during or after surgical procedures.⁷⁻¹¹ Particularly, the Centers for Medicare & Medicaid Services (CMS) of the USA finalizes a decision to cover acupuncture for chronic low back pain for Medicare beneficiaries in January 2020. Moreover, some studies have investigated the use of acupuncture on reducing sedative and analgesic drug demands, and the duration of mechanical ventilation, while improving patients' experience during mechanical ventilation.¹²⁻¹⁵ However, there are still a few discrepant research findings on the sedative and analgesic effects of acupuncture.^{16 17} And studies investigating both the sedative and analgesic effects of acupuncture among all critically ill patients needing mechanical ventilation in ICU are limited.

Therefore, the PASSION study is designed to be an RCT which investigate the efficacy of acupuncture on sedation and analgesia in mechanically ventilated critically ill patients. We are going to test the hypothesis that acupuncture, as adjunctive therapy to

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4 100 sedation and analgesia therapies, could reduce the duration of mechanical ventilation,
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6 101 the dose of administered sedatives and analgesics, and subsequently improve other
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8 102 clinical outcomes for critically ill patients when compared with sham acupuncture or
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10 103 non-acupuncture.

11 12 13 104 **METHODS**

14 15 105 **Study Design Overview**

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18 106 This is a prospective, parallel-group, controlled trial will recruit 180 patients with a
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20 107 computer-generated allocation sequence and centralized randomization at tertiary and
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22 108 regional ICUs in 3 hospitals (Guangdong Provincial Hospital of Chinese Medicine,
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24 109 Charity Hospital of Guangzhou, University Hospital) in South China. Recruitment
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26 110 officially began on 03 November 2021, and the final follow-up of the last subject will
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28 111 not exceed 16 August 2023. Eligible patients will be randomly assigned, in a ratio of
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30 112 1:1:1, to receive deep needle insertion with combined manual and alternating-mode
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32 113 electrical stimulation on acupoints (AC group, n =60), superficial needle insertion
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34 114 without manual or electrical stimulation on non-acupoints (SAC group, n =60) for 30
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36 115 min/day, or no acupuncture intervention (NAC group, n =60), respectively.

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39 116 Participants will be assessed for the duration of mechanical ventilation, as well as the
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41 117 dose of administered sedatives and analgesics at comparable sedation levels, from
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43 118 randomization until patients are free of mechanical ventilation (including noninvasive)
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45 119 without reinstitution for the following 48 hours. They will be also assessed for whether
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47 120 acupuncture can achieve better clinical outcomes than SAC and NAC treatment. The
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49 121 design of the trial is summarized in Figure 1.

50 51 52 122 **Ethical Requirements and Registration**

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55 123 This protocol is approved by the Institutional Human Clinical Research Ethical
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57 124 Committee at Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China)
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59 125 in October 2021 with permission number ZF2021-144-01. The PASSION study was
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4 126 registered on Nov 3, 2021 (ClinicalTrials.gov, number ChiCTR2100052650) and will
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6 127 be conducted following the Declaration of Helsinki from 03 November 2021 to 16
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8 128 August 2023.

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11 129 Written informed consent will be provided before enrollment voluntarily. Considering
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13 130 that patients will be sedated following ICU admission, complete adherence to patient
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15 131 consent is deemed impossible. Patients or their authorized surrogates will be informed
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17 132 by the researchers of the investigational nature and details of the study, together with
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19 133 the possible risks and all the benefits. Written informed consent will be subsequently
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21 134 obtained from either of them. Patients from whom surrogate consent is obtained are
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23 135 asked again to provide informed consent once determined to be competent. They can
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25 136 also withdraw from the study at any time they wish. Also, the investigator can decide to
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27 137 withdraw a subject from the study for urgent medical reasons. The researcher should
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29 138 complete the case report form (CRF) and record the reason for dropping out.

30 31 32 139 **Patients**

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34 140 Patients from medical and surgical ICU, aging from 18 to 80 years, for expected
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36 141 mechanical ventilation longer than 24 hours, with agitation and/or discomfort after
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38 142 recovering from drugs used to facilitate endotracheal intubation, requiring sedation and
39
40 143 agitation by continuous intravenous administration deemed by the ICU physician, are
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42 144 eligible for participation as soon as they or their authorized surrogates are willing to
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44 145 give informed consent (Table 1).

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47 146 Exclusion criteria include skin lesions near the acupuncture points, coagulopathy
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49 147 (bleeding time >4 min, thrombocytes <50,000/ μ l), neurological disease (previous stroke,
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51 148 cerebral palsy, etc.) that would confound the diagnosis of delirium, active seizures,
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53 149 severe dementia, relevant psychiatric disorder, hypohepatia with Childs-Pugh class B
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55 150 or C, second- or third-degree atrioventricular block, alcohol or drug abuse,
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57 151 benzodiazepine dependency, a moribund state with the planned withdrawal of life
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4 152 support, family or physician refusal, pregnancy or lactation, currently participating in
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6 153 any other investigational therapeutic or device trial (Table 1).
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8 154 **ICU standard treatment**

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11 155 As a standard in each ICU of our study, mechanically ventilated critically ill patients
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13 156 will be treated in a single treatment room. They will be taken care of by a trained ICU
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15 157 physician responsible for all treatment decisions, including sedation analgesia
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17 158 management plans made in consultation with the bedside nurses. They will also receive
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19 159 one-to-one nursing care to adjust the treatment based on the patient's response in time.
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21 160 A team of medical officers will review patient care every day.
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24 161 **Randomization and blinding**

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27 162 Eligible patients will be stratified by participating sites to avoid patient-level
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29 163 contamination from the systems-level organizational change in sedation practice and,
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31 164 within each ICU, assigned to the AC, SAC, or NAC group in an equal ratio via
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33 165 computer-generated randomization. In detail, an independent study coordinator will log
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35 166 into the central randomization system using a password-protected account and enter
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37 167 inclusion and exclusion criteria to ensure eligibility. After entering a patient's name and
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39 168 identification card number, a randomization sequence will be generated in blocks of
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41 169 varying sizes and stratified by the site under the control of the central computer system.
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43 170 The random sequence will then be concealed in sealed envelopes and sent to an
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45 171 acupuncturist from the assigned patient's site by the study coordinator.
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48 172 Allocation of participants will be known to the study coordinator and acupuncturists
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50 173 who will not be involved in outcome assessment and be required to sign a confidentiality
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52 174 agreement about patient allocation. All patients will be treated in a single treatment
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54 175 room. In both AC and SAC groups, patients, bedside nurses, and physicians will be
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56 176 blinded to which acupuncture method the patients will receive. The data collectors and
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58 177 the biostatisticians will be masked from the treatment assignment.
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Acupuncture interventions and procedures

The acupuncture interventions will be developed by a consensus of acupuncture experts according to the Standards for Reporting of Controlled Trials in Acupuncture (STRICTA).¹⁸ Patients will be assigned in a ratio of 1:1:1 to AC group (n=60), SAC group (n=60), and NAC group (n=60). Besides, each group shares the same basic Sedation Analgesia Strategy.

For patients in the AC group, 8 disposable sterile acupuncture needles (filiform needles made of stainless steel, Beijing Hanyi Medical Instruments, China) with a length of 40 mm and a diameter of 0.30 mm will be inserted into acupuncture points at Baihui (DU20), Yintang (EX-HN3), and bilateral acupoints of Shenmen (HT7), Hegu (LI4), Taichong (LR3) according to the theory of traditional Chinese medicine. The localization of these points is measured with a unit of *cun*, a traditional Chinese unit of length. One *cun* of a person is defined as the width of the thumb himself, whereas four fingers are defined as 3 *cun*. The insertion will be followed by manual stimulation, a lifting and thrusting technique combined with twirling and rotating the needle sheath to produce a sensation of soreness, numbness, distention, or radiating. This sensation is known as “*Deqi*” and is considered to be indicative of effective needling. Then, alternating-mode electrical stimulation will be given with the parameters: bursts alternating at 2 Hz and 100 Hz every 3 s, with 10-15 mA intensity inducing no discomfort and no muscle contraction.

For patients in the SAC group, superficial needle insertion with a depth of 2 mm and no manual stimulation will be performed for 30 min/day. The same sort of needles with the AC group will be placed 1 cm distant lateral the used acupoints that are not known as AC points. The electrical stimulator will likewise be connected but without electrical stimulation. (Figure 2)

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4 203 Patients in the NAC group will receive no acupuncture-related intervention during the
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6 204 trial. But they can receive a free 12-session daily acupuncture treatment after completing
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8 205 the study at their convenience.
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11 206 Each site will be required to have 2 licensed acupuncturists with more than 3 years of
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13 207 experience and specialized training in the acupuncture protocols before starting the
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15 208 study. The acupuncturists will be responsible for the whole acupuncture process but are
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17 209 not further involved in this study.
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19 210 **Basic Sedation Analgesia Strategy**

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22 211 In this study, diagnosis and therapeutic management of agitation and pain will be
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24 212 prescribed by the physicians responsible for the clinical care of each patient according
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26 213 to recommended guidelines¹⁹. An interruptive sedation strategy will be adopted by
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28 214 bedside nurses, and sedation levels and pain intensity will be assessed with the
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30 215 Richmond Agitation Sedation Scale (RASS)^{20 21}, the Behavioral Pain Scale (BPS), or
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32 216 the Numeric Rating Scale (NRS)^{22 23} every 4 h in order to adapt sedatives and analgesics
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34 217 to avoid overuse. Authorized nurses will titrate infusions, including benzodiazepines,
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36 218 propofol, and dexmedetomidine for sedatives and opiates for analgesia, instead of bolus
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38 219 dosing to minimize potential adverse effects.
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41 220 The sedation analgesia strategy is designed to consider pain treatment before increasing
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43 221 sedatives to minimize the risk of oversedation. The pain will be assessed either by the
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45 222 BPS in patients unable to communicate or by the NRS, a 1-10 numeric rating scale, in
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47 223 those sufficiently oriented and awake to communicate with the medical staff. Efficacy
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49 224 of the study analgesics drug will be defined as the ability to achieve a score < 3 in both
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51 225 of the pain scoring systems above, evaluated by the bedside nurse. Efficacy of the
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53 226 sedative drug will be defined as the ability to achieve a sedation score between -2 and
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55 227 1, set by the patient's medical team using the RASS (a highly reliable and well-validated
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57 228 sedation scale for use within patients) over time in the ICU.
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4 229 Each morning, a daily interruption of sedation (DIS) will be performed at the clinical
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6 230 medical team's discretion. Major opioid infusions needed for active pain will be
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8 231 continued. Recommended criteria to interrupt sedation are used: no drug-induced
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10232 paralysis, no intracranial hypertension, no myocardial ischemia in the previous 24 h,
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12233 primary disease healing in progress, hemodynamic stability, the partial pressure of
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14234 arterial oxygen ≥ 60 mmHg, the fraction of inspired oxygen $\leq 50\%$, and positive end-
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16235 expiratory pressure ≤ 8 cmH₂O. The interruption of continuous sedation will be coupled
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18236 with an assessment hourly for wakefulness, defined as the RASS score 1 to 4, and the
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20237 ability to perform at least 3 of the following requests: eye-opening, tracking, hand
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22238 squeezing, and toe moving. With the criteria recommended, patients will be able to pass
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24239 the DIS if they can tolerate it for 4 h and keep awakening enough. Then, a spontaneous
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26240 breathing trial (SBT) will immediately be managed.²⁴ If patients are insufficient for the
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28241 DIS, sedatives will be restarted at half the previous dose and then titrated to achieve
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30242 patient comfort. DIS will be performed the next morning again.

31 32 33243 **Extubation Test**

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36244 Before extubation, patients will be managed with an SBT. During the SBT, without
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38245 ventilatory support, patients will be allowed to breathe through a ventilatory circuit with
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40246 8cm H₂O PSV, 0 PEEP, and unchanged FiO₂ from the mechanical ventilation period
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42247 leading up to the SBT.²⁵ The criteria for a successful SBT are respiratory rate between
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44248 8 and 35 breaths/min, arterial oxygen saturation $> 88\%$, less than 20% change in mean
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46249 arterial pressure or heart rate, no signs of respiratory distress and acute cardiac
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48250 arrhythmia, no use of accessory muscles, no abdominal paradox, absence of sweating,
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50251 agitation or impaired vigilance status. Patients will pass the SBT if they complete a 60
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52252 min trial meeting the criteria, and extubation will be implemented 6 h later. Patients who
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54253 fail the SBT will be ventilated immediately with the ventilator settings used before the
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56254 trial, and sedatives will be restarted at half the previous dose and then titrated to achieve
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58255 patient comfort. The SBT will be managed the next morning again. Extubation will be
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60256 implemented following standardized criteria, but the decision to extubate remains upon

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4 257 the authority of the attending physician in charge of the patient. Researchers will not
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6 258 participate in decisions to extubate patients.
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9 259 The clinical research team will make sure that the overall research protocol, especially
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11 260 the criteria for sedation and definition of successful SBT, is strictly followed by the
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13 261 bedside nurse and medical teams in charge of the patients. Related information will be
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15 262 reported on the clinical research form.
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17 263 **Assessing Delirium**

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20 264 Delirium will be measured by the bedside nurses according to the Confusion
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22 265 Assessment Method for the ICU (CAM-ICU) until out of ICU or hospital discharge.²⁶
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24 266 Patients will be considered in this state if they have a RASS score ≥ -3 and a positive
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26 267 CAM-ICU, defined as positive with the symptoms of feature 1, feature 2, and either
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28 268 feature 3 or feature 4 as follows:
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31 269 Feature 1: acute onset of mental status change or fluctuation of mental status
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34 270 Feature 2: inattention
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36 271 Feature 3: disorganized thinking
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39 272 Feature 4: altered level of consciousness
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41 273 **Adverse Event Monitoring**

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44 274 Adverse events will also be defined a priori and prospectively monitored. Adverse
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46 275 events associated with acupuncture include bleeding, hematoma, and local infection.
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48 276 Adverse events related to sedation and analgesia include inadequate pain and sedation
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51 277 management (either pain score > 4 and RASS > 1 for 2 consecutive hours or pain and
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53 278 agitation assumed present if receiving neuromuscular blockade), clinically significant
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55 279 iatrogenic withdrawal. Adverse events associated with mechanical ventilation include
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57 280 accidental removal of medical devices, extubation failure (reintubation within 24 hours),
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59 281 pressure ulcers, catheter-associated bloodstream infections, ventilator-associated
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4 282 pneumonia. Every day, research personnel will monitor and assess the seriousness of all
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6 283 adverse events and document all details to determine whether the events are related to
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8 284 acupuncture interventions or the study procedure, as well as developing further
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10 285 treatment strategies including whether it is necessary to uncover blindness. A report of
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12 286 all serious, unexpected, and study-related adverse events will be presented to an
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14 287 independent data and safety monitoring board and the institutional review board within
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16 288 7 days of occurrence.

17 18 19 289 **Outcomes and Data Collection**

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21 290 The primary outcome is the duration of mechanical ventilation, defined as the time from
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23 291 randomization to successful extubation without reinstitution for the following 48 hours.

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25 292 The secondary outcomes will include the dose of administered sedatives and opiate
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27 293 (absolute value as well as indexed value [total drug in mg/kg ÷ total number of hours
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29 294 from the start of infusion to its ultimate discontinuation]) at comparable clinically
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31 295 individualized target sedation goals throughout the study, the duration of ICU length of
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33 296 stay, and hospital length of stay. Additional outcomes include the prevalence and days
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35 297 of delirium in ICU, mortality in ICU and within 28 days after randomization, and the
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37 298 number of ventilator-free days in 28 days.

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40 299 The day of extubation is considered as the day of death for patients who died while still
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42 300 intubated. Censoring for ICU or hospital length analyses occurred at the time of death
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44 301 or study withdrawal. The number of ventilator-free days in 28 days is defined as days
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46 302 alive and not using mechanical ventilation between days 1 and 28. For the 28-day
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48 303 mortality analyses, patients are censored at the time of the last contact alive or at 28
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50 304 days from enrollment, whichever is first.

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53 305 Baseline demographic data will be collected from patients' records by the medical team,
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55 306 including the reason for ICU admission, Acute Physiology and Chronic Health
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57 307 Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure
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59 308 Assessment (SOFA) scores, hematological and blood chemistry data, and clinical data
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(detailed information of sedative and analgesic medications administered to the patients before randomization, cardiac safety profile including electrocardiograms and serum troponins, and liver function profile including serum bilirubin and glutamate pyruvate transaminase, etc.). Vital signs such as blood pressure, heart rate, heart rhythm, temperature, and oxygen saturations will be recorded and collected by the bedside nurses, as well as scores of RASS, BPS, NRS, and CAM-ICU. Moreover, adverse events data will also be collected from patients' records. All of data mentioned above will be entered using the double entry method.

Patient and public involvement statement

There is no patient or public involvement in the design, conduct, reporting or dissemination plans of this research.

Statistical Analysis

Statistical power is estimated using the reduction in duration of mechanical ventilation as the primary outcome. According to Carrasco and colleagues, the mean (\pm standard deviation) time for current sedation is 54.7 ± 12.3 hours.²⁷ We calculate that a sample size of 48 patients in each group will provide a power of 90% to detect a 15% relative reduction in intubation time at a two-sided significance level of 0.05. With a dropout rate of 20%, the estimated sample size will be 60 patients per group. Thus, a total of 180 patients will be enrolled in the study.

The per-protocol set (PPS), including patients who complete the study without having major protocol violations, is used for the evaluation of clinical outcomes. While the full analysis set (FAS), determined according to the intention-to-treat population (ITT) who undergo randomization except for those who are excluded after randomization, is not only used for evaluation of clinical outcomes but also baseline characteristics to measure the balance of the three groups before intervention. Missing data will be replaced according to the principle of multiple imputation. Continuous data will be presented as median and interquartile range, while categorical data as numbers and proportion.

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4 336 Normal distribution will be checked by the Kolmogorov test. For continuous variables,
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6 337 normal distributed data will be compared using one-way analysis of variance among
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8 338 three groups, and independent Student's t-test between any of the two groups. While the
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10339 comparison of non-normally distributed parameters among three groups will be applied
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12340 by ANOVA (Kruska Wallis), and then the Mann-Whitney U-test between any of the
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14341 two groups. Categorical data will be compared by using Fisher's exact test or the chi-
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16342 square test. Other factors that may affect the efficacy will be considered as co-variants
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18343 for covariance analysis or Cox proportional hazards regression model. $P \leq 0.05$ will be
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20344 considered to indicate statistical significance. All analyses will be done with R statistical
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22345 software, version 4.0.2.

23 24 25346 **DISCUSSION**

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28347 This prospective trial is designed to provide evidence on the beneficial effect of
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30348 acupuncture on reducing the duration of mechanical ventilation, avoiding excessive
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32349 sedation and analgesia, as well as improving clinical outcomes in sedating mechanically
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34350 ventilated ICU patients.

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36351 General analgesia and sedation are necessary for mechanically ventilated critically ill
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38352 patients. However, overuse of sedative and analgesic medications may cause varying
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40353 degrees of side effects, like respiratory drive reduction.²⁸ These side effects are
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42354 associated with worsened clinical outcomes, such as prolonged mechanical ventilation
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44355 and hospital length of stay, increased risk of delirium, and even higher mortality.^{29 30}
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46356 With many sophisticated attempts to mitigate this clinical problem, it has thus far been
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48357 identified that optimizing analgesia and sedation strategy is able to prevent excessive
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50358 sedation and analgesia and improve the clinical outcome by reducing the duration and
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52359 dosage of sedative and analgesic medications.³¹⁻³³ Thus, it become a key objective to
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54360 formulate an intensive sedative and analgesic medications strategy when caring for
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56361 critically ill patients.

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4 362 The rationale for evaluating the ability of acupuncture on this subject is based on
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6 363 research findings that acupuncture can manage pain relief and facilitate opioid tapering
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8 364 by increasing the μ -opioid receptor binding ability and the release of the opioid
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10 365 peptide.^{34 35} According to the meta-analysis of acupuncture on pain relief, visual analog
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12 366 scale (VAS) pain scores in the AC group is lower than that in the NAC group [MD=-
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14 367 11.13, 95%CI(-13.59,-8.68), Z=8.9, P < 0.00001], Figure 3A.³⁶⁻⁵⁰ However, there is a
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17 368 substantial heterogeneity of results in these trials ($I^2 = 70\%$). As shown in Figure 3B,
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19 369 heterogeneity decreases ($I^2 = 14\%$) when the studies by Xian Wang and Zheng Lihong
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21 370 are excluded, and the AC group consistently shows a greater pain relief compared to
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23 371 NAC group [MD=-10.92, 95%CI(-12.93,-8.91), Z=10.66, P < 0.00001]. Meanwhile,
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25 372 acupuncture, without adverse effects, has been shown to exert sedation effects in various
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27 373 medical conditions. As it shown in the meta-analysis, with a high heterogeneity($I^2 =$
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29 374 95%), the bispectral index (BIS) value in the AC group is also lower than that in the
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31 375 NAC group [MD=-5.82,95%CI (-9.36, -2.27), Z=3.22, P=0.001], Figure 4A.⁵¹⁻⁵⁶ As
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33 376 shown in Figure 4B, heterogeneity decreases ($I^2 = 0\%$) when the studies by J.
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35 377 Fleckenstein and Jiheng Chen are excluded, and the AC group consistently shows a
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37 378 better sedative effect compared to NAC group [MD=-3.18,95%CI(-5.53,-0.84),Z=2.66,
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40 379 P < 0.008]. In addition, previous studies have shown that Yintang (EX-HN3) and
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42 380 Shenmen (HT7) have good sedative effects, Hegu (LI4) and Taichong (LR3) have
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44 381 analgesic advantages, while Baihui (DU20) appears both sedative and analgesic
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46 382 effects.^{54 57-60} With these promising results, it is meaningful to assess acupuncture as a
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48 383 potential analgesia and sedation strategy in ameliorating the clinical outcomes in
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50 384 mechanically ventilated critically ill patients.

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53 385 RCT has been recognized as the gold standard for clinical trials since the late 20th
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55 386 century.⁶¹ Another important designed technique to improve the quality of clinical trials
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57 387 is blinding. Over the past several decades, RCT and blinding have been used to avoid
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59 388 bias (selection bias, performance bias, and ascertainment bias) in clinical trials and
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4 389 improve the reliability of effects assessment. Sham acupuncture, aiming to blind the
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6 390 participants and control therapeutic components, is designed as a placebo control.
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8 391 However, this acupuncture technique is relatively difficult to fabricate because it should
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10392 be both biologically inert and psychologically indistinguishable.⁶² Even previous
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12393 experience of acupuncture feeling might impact the present perception of verum and
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14394 sham acupuncture intervention.

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17395 In PASSION study, we utilize a rigorous set of methods to minimize bias, such as
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19396 computer-generated central randomization, parallel control design, and statistical
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21397 analysis according to the intent-to-treat principle. In control design, the superficial
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23398 needle insertion without manual or electrical stimulation at the non-point is applied to
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25399 simulate deep skin penetration in the SAC group, which is used as the most predominant
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27400 type of sham electropuncture method to ensure blinding according to the published
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29401 literature.⁶³ However, a few studies reported that superficial needle insertion at non-
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31402 acupoints might not be physiologically inert since the locations of points are nearby true
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33403 acupoints.^{64 65} Moreover, researchers found that even mechanical non-penetration can
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35404 evoke slight acupressure effects and physiological activity.⁶⁶ Both of these factors will
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37405 affect the effect assessment of acupuncture. Thus, the NA group, avoiding all
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39406 therapeutic components, is designed to clarify whether the sham acupuncture can be
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41407 regarded as physiologically inert, as well as compared with the results of the AC group.

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44408 A potential limitation of this trial is blinding. Given the nature of acupuncture, the
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46409 patients and members of the medical team in the NA group are impossible to be blinded
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48410 throughout the entire duration of this trial. However, adequate measures will be taken
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50411 to put the patients and medical team members of the other two groups in a masked state.
51
52412 For example, we will formulate a set of isolation and secrecy strategies for the study
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54413 coordinator and acupuncturists to achieve satisfactory blinding levels in treatment
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56414 administration. Thus, in both AC and SAC groups, patients and their medical team
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58415 members will be blinded to the patients' acupuncture method. The data collectors and
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60416 the biostatisticians will also be masked from the treatment assignment.

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4 417 The PASSION study is designed to demonstrate the efficacy of acupuncture on sedation
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6 418 and analgesia in mechanically ventilated critically ill patients. We expect the finding
7
8 419 can provide evidence-based recommendations for acupuncture use for sedation and
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10 420 analgesia in critically ill patients with mechanical ventilation.
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50
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57 443 revised 1996).
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59 60 444 **COMPETING INTERESTS STATEMENT**

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AUTHORS' CONTRIBUTIONS

YZ & SM drafted this manuscript; GY, JW & FC made statistical analysis; MZZ made a critical revision of the manuscript and contributed to the rationalization of the study.

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acupuncture in the real world: a preliminary network meta-analysis of studies of acupuncture for hot

flashes in menopausal women. *Acupuncture in Medicine* 2020;38(1):37-44. doi: 10.1136/acupmed-

2018-011671

Table 1. Inclusion and exclusion criteria

A. Inclusion criteria	B. Exclusion criteria
1. Aged 18 years or over and under 80 years;	1. Skin lesions near the acupuncture points;
2. Required mechanical ventilation >24 hours;	2. Coagulopathy (bleeding time >4 min, thrombocytes <50,000/ μ l);
3. Continuous intravenous administration of sedative and analgesic medications;	3. Hypohepatia with Childs-Pugh class B or C;
4. Willingness to provide informed consent prior to enrollment;	4. Second- or third-degree atrioventricular block;
5. Be able to comply with all follow-up evaluations (in investigator's opinion).	5. Severe dementia;
	6. Psychiatric disorder;
	7. Neurological disease;
	8. Active seizures;
	9. Alcohol or drug abuse;
	10. Benzodiazepine dependency;
	11. Moribund state with the planned withdrawal of life support;
	12. Family or physician refusal;
	13. Pregnancy or lactation;
	14. Currently participated in any other investigational therapeutic or device trial.

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652 Figure legend:

653 Figure 1. Trial design of PASSION study

654 Figure 2. Illustration of the sham points

655 Figure 3. Forest plot of AC group versus NAC group.

656 Figure 4. Forest plot of AC group versus NAC group.

For peer review only

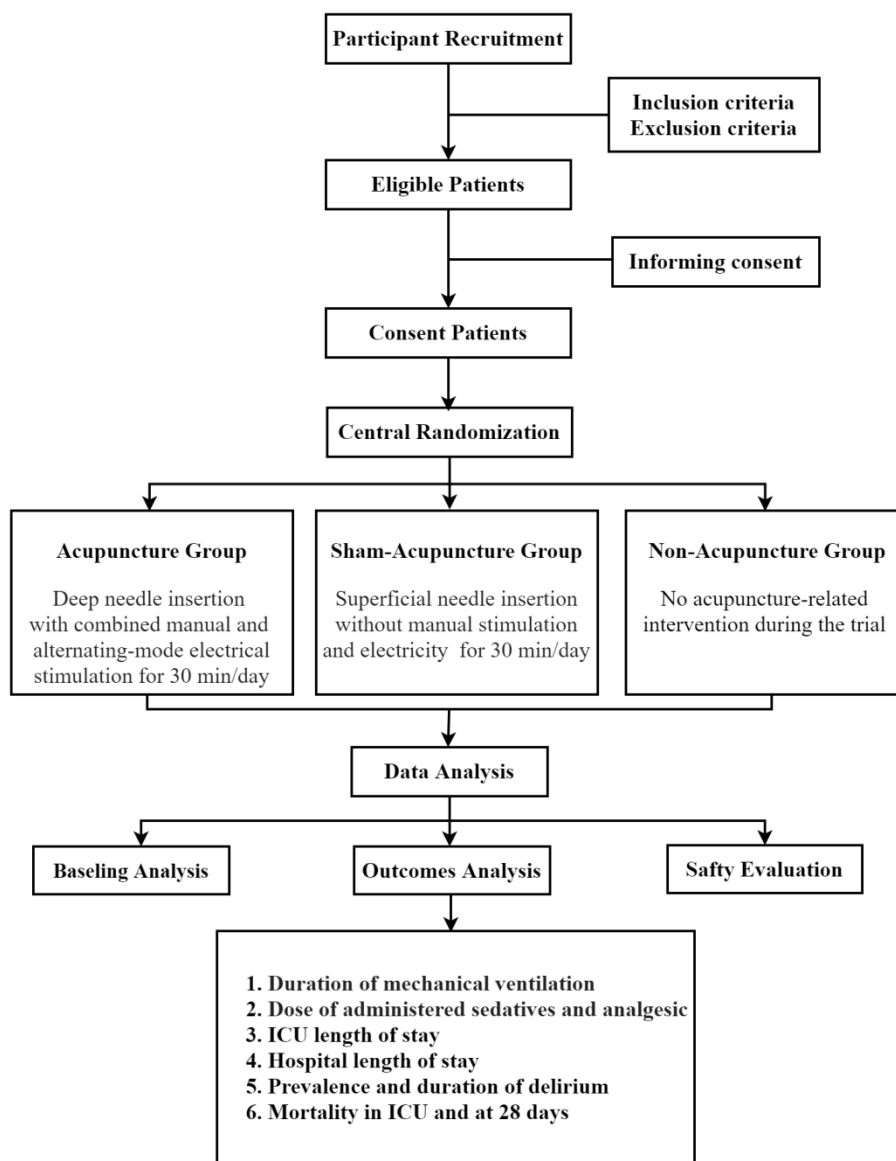


Figure1

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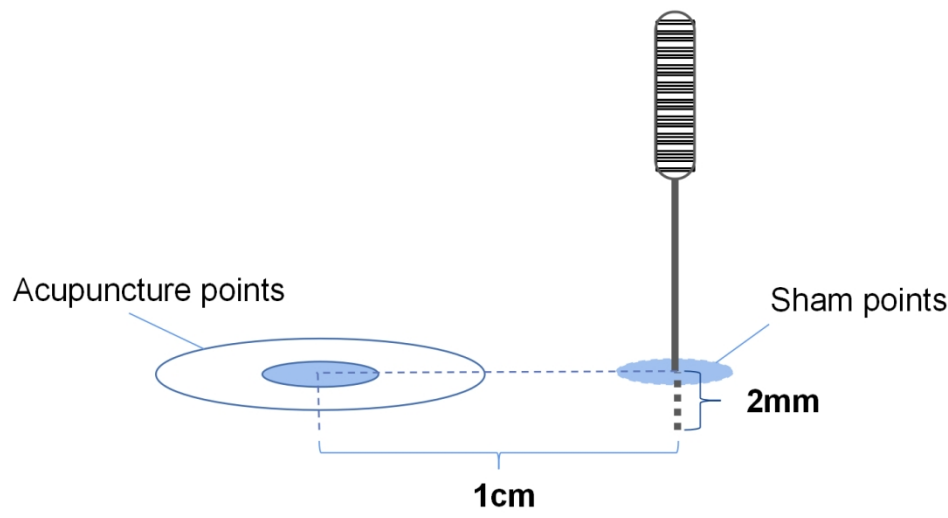


Figure2

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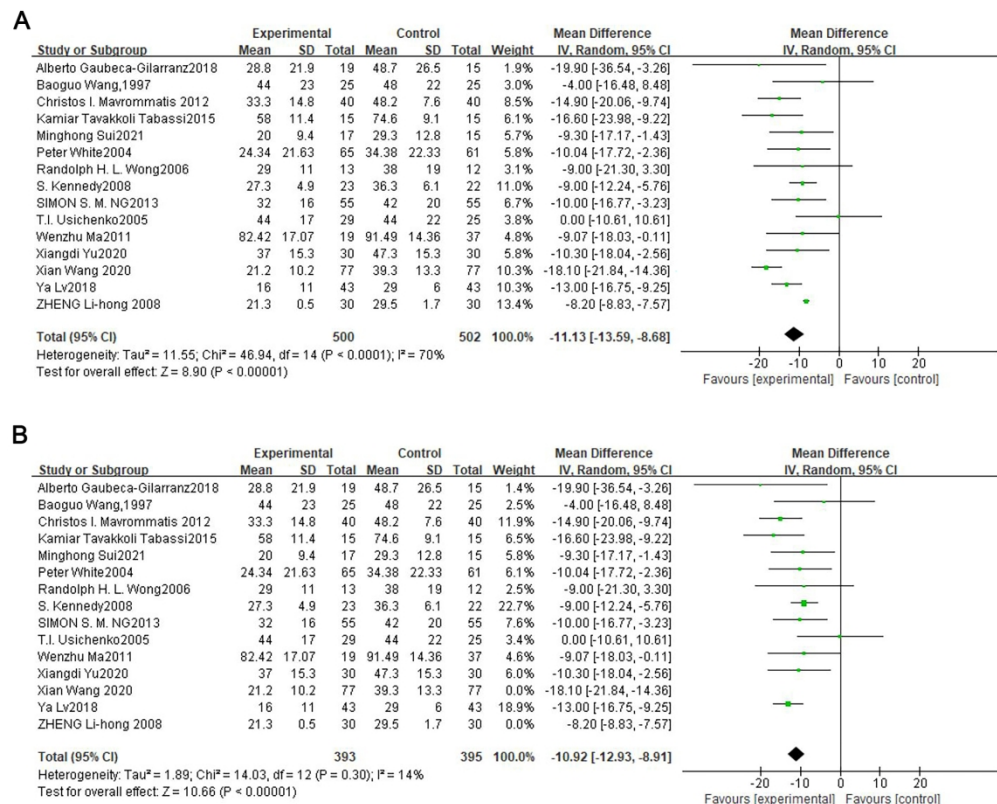


Figure3

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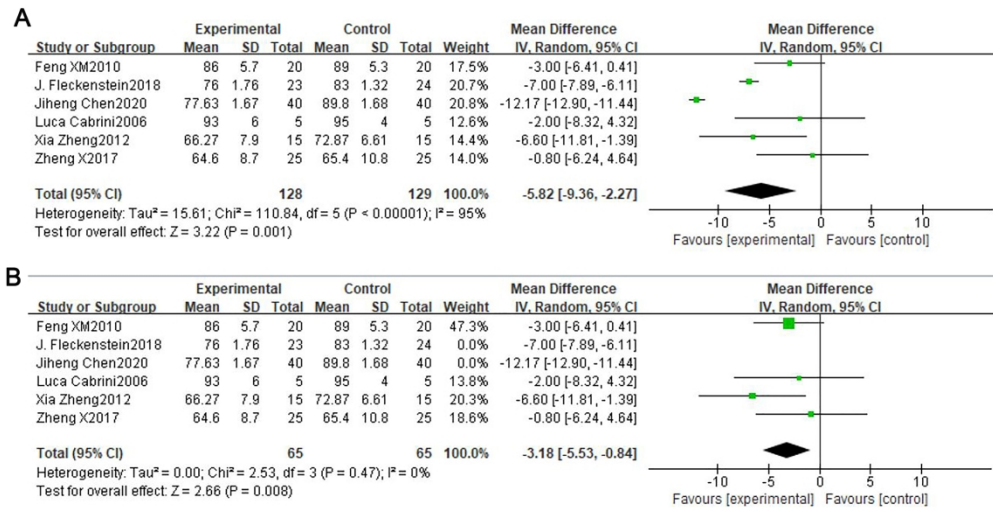


Figure 4

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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, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line 1-4.
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3, line 58; Page 7, line 130.
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	Page 18, line 427-434.

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	Page 1;
2	responsibilities:			Page 18-
3	contributorship			19, line
4				444-449.
5				
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7				
8	Roles and	#5b	Name and contact information for the trial sponsor	Page 18,
9	responsibilities:			line 427-
10	sponsor contact			434.
11	information			
12				
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14				
15	Roles and	#5c	Role of study sponsor and funders, if any, in study	Page 18,
16	responsibilities:		design; collection, management, analysis, and	line 435-
17	sponsor and funder		interpretation of data; writing of the report; and the	438.
18			decision to submit the report for publication, including	
19			whether they will have ultimate authority over any of	
20			these activities	
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25	Roles and	#5d	Composition, roles, and responsibilities of the	Page 13,
26	responsibilities:		coordinating centre, steering committee, endpoint	line 290-
27	committees		adjudication committee, data management team, and	292.
28			other individuals or groups overseeing the trial, if	
29			applicable (see Item 21a for data monitoring committee)	
30				
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33	Introduction			
34				
35				
36	Background and	#6a	Description of research question and justification for	Page 5,
37	rationale		undertaking the trial, including summary of relevant	line 77-
38			studies (published and unpublished) examining benefits	100.
39			and harms for each intervention	
40				
41				
42				
43	Background and	#6b	Explanation for choice of comparators	Page 6,
44	rationale: choice of			line 106-
45	comparators			107.
46				
47				
48	Objectives	#7	Specific objectives or hypotheses	Page 6,
49				line 103-
50				107.
51				
52				
53	Trial design	#8	Description of trial design including type of trial (eg,	Page 5-6,
54			parallel group, crossover, factorial, single group),	line 101-
55			allocation ratio, and framework (eg, superiority,	103.
56			equivalence, non-inferiority, exploratory)	
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1 **Methods:**

2 **Participants,**

3 **interventions, and**

4 **outcomes**

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8	Study setting	#9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6, line 112-113.
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10			
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14	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7-8, line 144-157.
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20			Page 8, line 159-164;
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24			
25			Page 10, line 210-213;
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33	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-10, line 188-213;
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40	Interventions: modifications	#11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 13, line 286-290;
41			
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48	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 8, line 207-209.
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56	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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1	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 13, line 294-302;
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12	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 9, line 183-187.
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20	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 14, line 325-331;
21				
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28	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 14, line 330-331.
29				
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35	Methods:			
36	Assignment of interventions (for controlled trials)			
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42	Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8, line 166-175.
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53	Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 8, line 166-175.
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1	Allocation:	#16c	Who will generate the allocation sequence, who will	Page 8,
2	implementation		enrol participants, and who will assign participants to	line 169-
3			interventions	175.
4				
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6	Blinding (masking)	#17a	Who will be blinded after assignment to interventions	Page 8,
7			(eg, trial participants, care providers, outcome	line 179-
8			assessors, data analysts), and how	181.
9				
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	Page 13,
15	emergency unblinding		permissible, and procedure for revealing a participant's	line 286-
16			allocated intervention during the trial	290.
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22	Methods: Data			
23	collection,			
24	management, and			
25	analysis			
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28	Data collection plan	#18a	Plans for assessment and collection of outcome,	Page 13-
29			baseline, and other trial data, including any related	14,
30			processes to promote data quality (eg, duplicate	line 309-
31			measurements, training of assessors) and a description	320.
32			of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known.	
34			Reference to where data collection forms can be found,	
35			if not in the protocol	
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41	Data collection plan:	#18b	Plans to promote participant retention and complete	Page 10,
42	retention		follow-up, including list of any outcome data to be	line 207-
43			collected for participants who discontinue or deviate from	209.
44			intervention protocols	
45				
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49	Data management	#19	Plans for data entry, coding, security, and storage,	Page 14,
50			including any related processes to promote data quality	line 320
51			(eg, double data entry; range checks for data values).	
52			Reference to where details of data management	
53			procedures can be found, if not in the protocol	
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56				
57	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	Page 14-
58			outcomes. Reference to where other details of the	15, line
59				
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1		statistical analysis plan can be found, if not in the	332-349.
2		protocol	
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4			
5	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	Page14,
6	analyses	adjusted analyses)	line 337-
7			338.
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11			
12	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	Page14,
13	population and	adherence (eg, as randomised analysis), and any	line 337-
14	missing data	statistical methods to handle missing data (eg, multiple	338.
15		imputation)	
16			
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19	Methods: Monitoring		
20			
21	Data monitoring:	#21a Composition of data monitoring committee (DMC);	Page13,
22	formal committee	summary of its role and reporting structure; statement of	line 290-
23		whether it is independent from the sponsor and	292.
24		competing interests; and reference to where further	
25		details about its charter can be found, if not in the	
26		protocol. Alternatively, an explanation of why a DMC is	
27		not needed	
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33	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
34	interim analysis	guidelines, including who will have access to these	
35		interim results and make the final decision to terminate	
36		the trial	
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40	Harms	#22 Plans for collecting, assessing, reporting, and managing	Page12,
41		solicited and spontaneously reported adverse events	line 286-
42		and other unintended effects of trial interventions or trial	292.
43		conduct	
44			
45			
46	Auditing	#23 Frequency and procedures for auditing trial conduct, if	n/a
47		any, and whether the process will be independent from	
48		investigators and the sponsor	
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52	Ethics and		
53	dissemination		
54			
55	Research ethics	#24 Plans for seeking research ethics committee /	Page 6-7,
56	approval	institutional review board (REC / IRB) approval	line127-
57			129.
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1	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
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9	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7, line135-137.
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14	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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20	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page13-14, line 309-320.
21				
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27	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
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31	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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36	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
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41	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
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49	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
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53	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
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Appendices

1	Informed consent	#32	Model consent form and other related documentation	n/a
2	materials		given to participants and authorised surrogates	
3				
4				
5	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
6			biological specimens for genetic or molecular analysis in	
7			the current trial and for future use in ancillary studies, if	
8			applicable	
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12 Commons Attribution License CC-BY-NC. This checklist can be completed online using
13 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with
14 [Penelope.ai](#)
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BMJ Open

Prospective comparison of acupuncture with sham acupuncture to determine impact on sedation and analgesia in mechanically ventilated critically ill patients (PASSION study): protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059741.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Aug-2022
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Complementary medicine
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Pain management < ANAESTHETICS

SCHOLARONE™
Manuscripts

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5 1 **Prospective comparison of acupuncture with sham acupuncture to**
6
7 2 **determine impact on sedation and analgesia in mechanically ventilated**
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9 3 **critically ill patients (PASSION study): Protocol for a randomized**
10
11 4 **controlled trial**

15 5 Yuzhuo Zhang, Ph.D. ^{1*}

18 6 Guang Yang, M.D. ^{1,2*}

20 7 Jinyi Wei, M.D. ¹

23 8 Fangliang Chen, M.D. ¹

26 9 Minzhou Zhang, M.D. ^{1,2,3Δ}

29 10 Shuai Mao, M.D. ^{1,2,3Δ}

32 11 *¹ Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou*
34 12 *510405, China*

36 13 *² Department of Critical Care Medicine, Guangdong Provincial Hospital of Chinese*
37 14 *Medicine, Guangzhou 510120, China*

39 15 *³ Guangdong Provincial Branch of National Clinical Research Centre for Chinese*
40 16 *Medicine Cardiology, Guangzhou 510120, China*

44 18 *The first two authors contribute equally to this article.

46 19 ΔCorrespondence to:

48 20 Prof. Shuai MAO

50 21 Department of Critical Care Medicine,

51 22 Guangdong Provincial Hospital of Chinese Medicine,

53 23 Guangzhou 510120, China

54 24 Phone: 86-20-81887233

56 25 Fax: 86-20-81867705

57 26 E-mail: maoshuai@gzucm.edu.cn

59 27 Or Prof. Minzhou Zhang minzhouzhang@gzucm.edu.cn

ABSTRACT

Introduction Sedation and analgesia are recommended to be employed in the intensive care unit (ICU) to enhance patient comfort and safety, facilitate mechanical ventilation, and reduce oxygen demands. However, the increasing evidence demonstrates that excessive sedation and analgesia might prolong mechanical ventilation and increase costs and mortality. Acupuncture is known to be able to attenuate pain, anxiety, and agitation symptoms while avoiding excessive sedation and analgesia caused by drugs. Therefore, we present a protocol to investigate whether acupuncture, used for sedation and analgesia, can reduce the duration of mechanical ventilation, save medical resources, and reduce the mortality of critically ill patients receiving mechanical ventilation.

Methods and analysis Prospective, randomized controlled trial (RCT) is conducted on 180 adult medical/surgical ICU patients with mechanical ventilation needing sedation at 3 ICUs between 03 November 2021 and 16 August 2023. Patients will be treated with analgesia and sedation to achieve desired target sedation levels (Richmond Agitation Sedation Score of -2 to 1). Enrolled patients will be randomly assigned in a ratio of 1:1:1 to receive deep needle insertion with combined manual and alternating-mode electrical stimulation on acupoints (AC group), superficial needle insertion without manual stimulation and electrical stimulation on non-acupoints (SAC group), or no acupuncture intervention (NAC group).

The primary outcome is the duration of mechanical ventilation from randomization until patients are free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours. Secondary endpoints include the dose of administered sedatives and analgesic at comparable sedation levels throughout the study, ICU length of stay, hospital length of stay. Additional outcomes include the prevalence and days of delirium in ICU, mortality in ICU and within 28 days after randomization, and the number of ventilator free days in 28 days.

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Ethics and dissemination This trial was approved by the ethics committee at Guangdong Provincial Hospital of Chinese Medicine. We will publish the study results.

Trial Registration numbers: ChiCTR2100052650

Keywords:

acupuncture; sedation; analgesia; critically ill patients; nonpharmacological therapy

Word Count: 3815

For peer review only

Strengths and limitations of this study

- This study is an RCT to investigate both the sedative and analgesic effects of acupuncture on critically ill patients needing mechanical ventilation in ICU.
- This study provides a sedative and analgesic strategy for mechanically ventilated critically ill patients with less side effects.
- The primary endpoint is the duration of mechanical ventilation from randomization until patients are free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours.
- Secondary endpoints include the dose of administered sedatives and analgesics at comparable sedation levels throughout the study, ICU length of stay, and hospital length of stay.
- Limitations are the non-blinded interventions due to the nature of acupuncture.

INTRODUCTION

Sedative and analgesic medications are routinely administered to mechanically ventilated critically ill patients to reduce pain, anxiety, and agitation, as well as to allow patients to tolerate invasive procedures in the intensive care unit (ICU).¹ Opiates are most commonly used analgesics, while benzodiazepines, propofol, or dexmedetomidine are typically used to prevent or reduce anxiety and agitation.² However, overuse of these medications is associated with worsened clinical outcomes, such as prolonged mechanical ventilation and hospital length of stay, increased risk of altered mental status, and even higher mortality.³ Thus, reducing the unnecessary dosage of sedative and analgesic medications, as well as their side effects while providing desired sedation has always been a key objective when caring for critically ill patients.

As a therapeutic modality with fewer adverse effects, acupuncture has been used in China and other Asian countries for thousands of years to treat various conditions.⁴⁻⁶ Studies of acupuncture usually focuses on its analgesic effect, such as relieving pain and partly reducing opioid-related side effects during or after surgical procedures.⁷⁻¹¹ Particularly, the Centers for Medicare & Medicaid Services (CMS) of the USA finalizes a decision to cover acupuncture for chronic low back pain for Medicare beneficiaries in January 2020. Moreover, some studies have investigated the use of acupuncture on reducing sedative and analgesic drug demands, and the duration of mechanical ventilation, while improving patients' experience during mechanical ventilation.¹²⁻¹⁵ However, there are still a few discrepant research findings on the sedative and analgesic effects of acupuncture.^{16 17} And studies investigating both the sedative and analgesic effects of acupuncture among all critically ill patients needing mechanical ventilation in ICU are limited.

Therefore, the PASSION study is designed to be an RCT which investigate the efficacy of acupuncture on sedation and analgesia in mechanically ventilated critically ill patients. We are going to test the hypothesis that acupuncture, as adjunctive therapy to

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4 100 sedation and analgesia therapies, could reduce the duration of mechanical ventilation,
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6 101 the dose of administered sedatives and analgesics, and subsequently improve other
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8 102 clinical outcomes for critically ill patients when compared with sham acupuncture or
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10 103 non-acupuncture.

11 12 13 104 **METHODS**

14 15 105 **Study Design Overview**

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18 106 This is a prospective, parallel-group, controlled trial will recruit 180 patients with a
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20 107 computer-generated allocation sequence and centralized randomization at tertiary and
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22 108 regional ICUs in 3 hospitals (Guangdong Provincial Hospital of Chinese Medicine,
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24 109 Charity Hospital of Guangzhou, University Hospital) in South China. Recruitment
25
26 110 officially began on 03 November 2021, and the final follow-up of the last subject will
27
28 111 not exceed 16 August 2023. Eligible patients will be randomly assigned, in a ratio of
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30 112 1:1:1, to receive deep needle insertion with combined manual and alternating-mode
31
32 113 electrical stimulation on acupoints (AC group, n =60), superficial needle insertion
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34 114 without manual or electrical stimulation on non-acupoints (SAC group, n =60) for 30
35
36 115 min/day, or no acupuncture intervention (NAC group, n =60), respectively.

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39 116 Participants will be assessed for the duration of mechanical ventilation, as well as the
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41 117 dose of administered sedatives and analgesics at comparable sedation levels, from
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43 118 randomization until patients are free of mechanical ventilation (including noninvasive)
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45 119 without reinstitution for the following 48 hours. They will be also assessed for whether
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47 120 acupuncture can achieve better clinical outcomes than SAC and NAC treatment. The
48
49 121 design of the trial is summarized in Figure 1.

50 51 52 122 **Ethical Requirements and Registration**

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54
55 123 This protocol is approved by the Institutional Human Clinical Research Ethical
56
57 124 Committee at Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China)
58
59 125 in October 2021 with permission number ZF2021-144-01. The PASSION study was
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registered on Nov 3, 2021 (ClinicalTrials.gov, number ChiCTR2100052650) and will be conducted following the Declaration of Helsinki from 03 November 2021 to 16 August 2023.

Written informed consent will be provided before enrollment voluntarily. Considering that patients will be sedated following ICU admission, complete adherence to patient consent is deemed impossible. Patients or their authorized surrogates will be informed by the researchers of the investigational nature and details of the study, together with the possible risks and all the benefits. Written informed consent will be subsequently obtained from either of them. Patients from whom surrogate consent is obtained are asked again to provide informed consent once determined to be competent. They can also withdraw from the study at any time they wish. Also, the investigator can decide to withdraw a subject from the study for urgent medical reasons. The researcher should complete the case report form (CRF) and record the reason for dropping out.

Patients

Patients from medical and surgical ICU, aging from 18 to 80 years, for expected mechanical ventilation longer than 24 hours, with agitation and/or discomfort after recovering from drugs used to facilitate endotracheal intubation, requiring sedation and agitation by continuous intravenous administration deemed by the ICU physician, are eligible for participation as soon as they or their authorized surrogates are willing to give informed consent (Table 1).

Table 1. Inclusion and exclusion criteria

A. Inclusion criteria	B. Exclusion criteria
1. Aged 18 years or over and under 80 years;	1. Skin lesions near the acupuncture points;
2. Required mechanical ventilation >24 hours;	2. Coagulopathy (bleeding time >4 min, thrombocytes <50,000/ μ l);
3. Continuous intravenous administration of sedative and analgesic medications;	3. Hypohepatia with Childs-Pugh class B or C;

4. Willingness to provide informed consent prior to enrollment;	4. Second- or third-degree atrioventricular block;
5. Be able to comply with all follow-up evaluations (in investigator's opinion).	5. Severe dementia;
	6. Psychiatric disorder;
	7. Neurological disease;
	8. Active seizures;
	9. Alcohol or drug abuse;
	10. Benzodiazepine dependency;
	11. Moribund state with the planned withdrawal of life support;
	12. Family or physician refusal;
	13. Pregnancy or lactation;
	14. Currently participated in any other investigational therapeutic or device trial.

Exclusion criteria include skin lesions near the acupuncture points, coagulopathy (bleeding time >4 min, thrombocytes <50,000/ μ l), neurological disease (previous stroke, cerebral palsy, etc.) that would confound the diagnosis of delirium, active seizures, severe dementia, relevant psychiatric disorder, hypohepatia with Childs-Pugh class B or C, second- or third-degree atrioventricular block, alcohol or drug abuse, benzodiazepine dependency, a moribund state with the planned withdrawal of life support, family or physician refusal, pregnancy or lactation, currently participating in any other investigational therapeutic or device trial (Table 1).

ICU standard treatment

As a standard in each ICU of our study, mechanically ventilated critically ill patients will be treated in a single treatment room. They will be taken care of by a trained ICU physician responsible for all treatment decisions, including sedation analgesia management plans made in consultation with the bedside nurses. They will also receive one-to-one nursing care to adjust the treatment based on the patient's response in time. A team of medical officers will review patient care every day.

Randomization and blinding

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4 163 Eligible patients will be stratified by participating sites to avoid patient-level
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6 164 contamination from the systems-level organizational change in sedation practice and,
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8 165 within each ICU, assigned to the AC, SAC, or NAC group in an equal ratio via
9
10 166 computer-generated randomization. In detail, an independent study coordinator will log
11
12 167 into the central randomization system using a password-protected account and enter
13
14 168 inclusion and exclusion criteria to ensure eligibility. After entering a patient's name and
15
16 169 identification card number, a randomization sequence will be generated in blocks of
17
18 170 varying sizes and stratified by the site under the control of the central computer system.
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20 171 The random sequence will then be concealed in sealed envelopes and sent to an
21
22 172 acupuncturist from the assigned patient's site by the study coordinator.

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25 173 Allocation of participants will be known to the study coordinator and acupuncturists
26
27 174 who will not be involved in outcome assessment and be required to sign a confidentiality
28
29 175 agreement about patient allocation. All patients will be treated in a single treatment
30
31 176 room. In both AC and SAC groups, patients, bedside nurses, and physicians will be
32
33 177 blinded to which acupuncture method the patients will receive. The data collectors and
34
35 178 the biostatisticians will be masked from the treatment assignment.

37 38 179 **Acupuncture interventions and procedures**

39
40 180 The acupuncture interventions will be developed by a consensus of acupuncture experts
41
42 181 according to the Standards for Reporting of Controlled Trials in Acupuncture
43
44 182 (STRICTA).¹⁸ Patients will be assigned in a ratio of 1:1:1 to AC group (n=60), SAC
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46 183 group (n=60), and NAC group (n=60). Besides, each group shares the same basic
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48 184 Sedation Analgesia Strategy.

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51 185 For patients in the AC group, 8 disposable sterile acupuncture needles (filiform needles
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53 186 made of stainless steel, Beijing Hanyi Medical Instruments, China) with a length of 40
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55 187 mm and a diameter of 0.30 mm will be inserted into acupuncture points at Baihui
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57 188 (DU20), Yintang (EX-HN3), and bilateral acupoints of Shenmen (HT7), Hegu (LI4),
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59 189 Taichong (LR3) according to the theory of traditional Chinese medicine. The
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4 190 localization of these points is measured with a unit of *cun*, a traditional Chinese unit of
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6 191 length. One *cun* of a person is defined as the width of the thumb himself, whereas four
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8 192 fingers are defined as 3 *cun*. The insertion will be followed by manual stimulation, a
9
10 193 lifting and thrusting technique combined with twirling and rotating the needle sheath to
11
12 194 produce a sensation of soreness, numbness, distention, or radiating. This sensation is
13
14 195 known as “*Deqi*” and is considered to be indicative of effective needling. Then,
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16 196 alternating-mode electrical stimulation will be given with the parameters: bursts
17
18 197 alternating at 2 Hz and 100 Hz every 3 s, with 10-15 mA intensity inducing no
19
20 198 discomfort and no muscle contraction.

21
22
23 199 For patients in the SAC group, superficial needle insertion with a depth of 2 mm and no
24
25 200 manual stimulation will be performed for 30 min/day. The same sort of needles with the
26
27 201 AC group will be placed 1 cm distant lateral the used acupoints that are not known as
28
29 202 AC points. The electrical stimulator will likewise be connected but without electrical
30
31 203 stimulation. (Figure 2)

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34 204 Patients in the NAC group will receive no acupuncture-related intervention during the
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36 205 trial. But they can receive a free 12-session daily acupuncture treatment after completing
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38 206 the study at their convenience.

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40 207 Each site will be required to have 2 licensed acupuncturists with more than 3 years of
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42 208 experience and specialized training in the acupuncture protocols before starting the
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44 209 study. The acupuncturists will be responsible for the whole acupuncture process but are
45
46 210 not further involved in this study.

49 211 **Basic Sedation Analgesia Strategy**

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51
52 212 In this study, diagnosis and therapeutic management of agitation and pain will be
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54 213 prescribed by the physicians responsible for the clinical care of each patient according
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56 214 to recommended guidelines¹⁹. An interruptive sedation strategy will be adopted by
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58 215 bedside nurses, and sedation levels and pain intensity will be assessed with the
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60 216 Richmond Agitation Sedation Scale (RASS)^{20 21}, the Behavioral Pain Scale (BPS), or

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4 217 the Numeric Rating Scale (NRS) ^{22 23} every 4 h in order to adapt sedatives and analgesics
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6 218 to avoid overuse. Authorized nurses will titrate infusions, including benzodiazepines,
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8 219 propofol, and dexmedetomidine for sedatives and opiates for analgesia, instead of bolus
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10 220 dosing to minimize potential adverse effects.

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13 221 The sedation analgesia strategy is designed to consider pain treatment before increasing
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15 222 sedatives to minimize the risk of oversedation. The pain will be assessed either by the
16
17 223 BPS in patients unable to communicate or by the NRS, a 1-10 numeric rating scale, in
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19 224 those sufficiently oriented and awake to communicate with the medical staff. Efficacy
20
21 225 of the study analgesics drug will be defined as the ability to achieve a score < 3 in both
22
23 226 of the pain scoring systems above, evaluated by the bedside nurse. Efficacy of the
24
25 227 sedative drug will be defined as the ability to achieve a sedation score between -2 and
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27 228 1, set by the patient's medical team using the RASS (a highly reliable and well-validated
28
29 229 sedation scale for use within patients) over time in the ICU.

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31
32 230 Each morning, a daily interruption of sedation (DIS) will be performed at the clinical
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34 231 medical team's discretion. Major opioid infusions needed for active pain will be
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36 232 continued. Recommended criteria to interrupt sedation are used: no drug-induced
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38 233 paralysis, no intracranial hypertension, no myocardial ischemia in the previous 24 h,
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40 234 primary disease healing in progress, hemodynamic stability, the partial pressure of
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42 235 arterial oxygen ≥ 60 mmHg, the fraction of inspired oxygen $\leq 50\%$, and positive end-
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44 236 expiratory pressure ≤ 8 cmH₂O. The interruption of continuous sedation will be coupled
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46 237 with an assessment hourly for wakefulness, defined as the RASS score 1 to 4, and the
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48 238 ability to perform at least 3 of the following requests: eye-opening, tracking, hand
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50 239 squeezing, and toe moving. With the criteria recommended, patients will be able to pass
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52 240 the DIS if they can tolerate it for 4 h and keep awakening enough. Then, a spontaneous
53
54 241 breathing trial (SBT) will immediately be managed. ²⁴ If patients are insufficient for the
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56 242 DIS, sedatives will be restarted at half the previous dose and then titrated to achieve
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58 243 patient comfort. DIS will be performed the next morning again.

Extubation Test

Before extubation, patients will be managed with an SBT. During the SBT, without ventilatory support, patients will be allowed to breathe through a ventilatory circuit with 8cm H₂O PSV, 0 PEEP, and unchanged FiO₂ from the mechanical ventilation period leading up to the SBT.²⁵ The criteria for a successful SBT are respiratory rate between 8 and 35 breaths/min, arterial oxygen saturation > 88%, less than 20% change in mean arterial pressure or heart rate, no signs of respiratory distress and acute cardiac arrhythmia, no use of accessory muscles, no abdominal paradox, absence of sweating, agitation or impaired vigilance status. Patients will pass the SBT if they complete a 60 min trial meeting the criteria, and extubation will be implemented 6 h later. Patients who fail the SBT will be ventilated immediately with the ventilator settings used before the trial, and sedatives will be restarted at half the previous dose and then titrated to achieve patient comfort. The SBT will be managed the next morning again. Extubation will be implemented following standardized criteria, but the decision to extubate remains upon the authority of the attending physician in charge of the patient. Researchers will not participate in decisions to extubate patients.

The clinical research team will make sure that the overall research protocol, especially the criteria for sedation and definition of successful SBT, is strictly followed by the bedside nurse and medical teams in charge of the patients. Related information will be reported on the clinical research form.

Assessing Delirium

Delirium will be measured by the bedside nurses according to the Confusion Assessment Method for the ICU (CAM-ICU) until out of ICU or hospital discharge.²⁶ Patients will be considered in this state if they have a RASS score ≥ -3 and a positive CAM-ICU, defined as positive with the symptoms of feature 1, feature 2, and either feature 3 or feature 4 as follows:

Feature 1: acute onset of mental status change or fluctuation of mental status

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4 271 Feature 2: inattention

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6 272 Feature 3: disorganized thinking

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9 273 Feature 4: altered level of consciousness

10 11 12 274 **Adverse Event Monitoring**

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15 275 Adverse events will also be defined a priori and prospectively monitored. Adverse
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17 276 events associated with acupuncture include bleeding, hematoma, and local infection.
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19 277 Adverse events related to sedation and analgesia include inadequate pain and sedation
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21 278 management (either pain score > 4 and RASS > 1 for 2 consecutive hours or pain and
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23 279 agitation assumed present if receiving neuromuscular blockade), clinically significant
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25 280 iatrogenic withdrawal. Adverse events associated with mechanical ventilation include
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27 281 accidental removal of medical devices, extubation failure (reintubation within 24 hours),
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29 282 pressure ulcers, catheter-associated bloodstream infections, ventilator-associated
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31 283 pneumonia. Every day, research personnel will monitor and assess the seriousness of all
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33 284 adverse events and document all details to determine whether the events are related to
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35 285 acupuncture interventions or the study procedure, as well as developing further
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37 286 treatment strategies including whether it is necessary to uncover blindness. A report of
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39 287 all serious, unexpected, and study-related adverse events will be presented to an
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41 288 independent data and safety monitoring board and the institutional review board within
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43 289 7 days of occurrence.

44 45 46 47 290 **Outcomes and Data Collection**

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49 291 The primary outcome is the duration of mechanical ventilation, defined as the time from
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51 292 randomization to successful extubation without reinstitution for the following 48 hours.
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53 293 The secondary outcomes will include the dose of administered sedatives and opiate
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55 294 (absolute value as well as indexed value [total drug in mg/kg \div total number of hours
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57 295 from the start of infusion to its ultimate discontinuation]) at comparable clinically
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59 296 individualized target sedation goals throughout the study, the duration of ICU length of
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1
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4 297 stay, and hospital length of stay. Additional outcomes include the prevalence and days
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6 298 of delirium in ICU, mortality in ICU and within 28 days after randomization, and the
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8 299 number of ventilator-free days in 28 days.

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11 300 The day of extubation is considered as the day of death for patients who died while still
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13 301 intubated. Censoring for ICU or hospital length analyses occurred at the time of death
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15 302 or study withdrawal. The number of ventilator-free days in 28 days is defined as days
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17 303 alive and not using mechanical ventilation between days 1 and 28. For the 28-day
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19 304 mortality analyses, patients are censored at the time of the last contact alive or at 28
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21 305 days from enrollment, whichever is first.

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23 306 Baseline demographic data will be collected from patients' records by the medical team,
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25 307 including the reason for ICU admission, Acute Physiology and Chronic Health
26
27 308 Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure
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29 309 Assessment (SOFA) scores, hematological and blood chemistry data, and clinical data
30
31 310 (detailed information of sedative and analgesic medications administered to the patients
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33 311 before randomization, cardiac safety profile including electrocardiograms and serum
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35 312 troponins, and liver function profile including serum bilirubin and glutamate pyruvate
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37 313 transaminase, etc.). Vital signs such as blood pressure, heart rate, heart rhythm,
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39 314 temperature, and oxygen saturations will be recorded and collected by the bedside
40
41 315 nurses, as well as scores of RASS, BPS, NRS, and CAM-ICU. Moreover, adverse events
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43 316 data will also be collected from patients' records. All of data mentioned above will be
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45 317 entered using the double entry method.

46 47 48 318 **Patient and public involvement statement**

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51 319 There is no patient or public involvement in the design, conduct, reporting or
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53 320 dissemination plans of this research.

54 55 321 **Statistical Analysis**

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4 322 Statistical power is estimated using the reduction in duration of mechanical ventilation
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6 323 as the primary outcome. According to Carrasco and colleagues, the mean (\pm standard
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8 324 deviation) time for current sedation is 54.7 ± 12.3 hours.²⁷ We calculate that a sample
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10325 size of 48 patients in each group will provide a power of 90% to detect a 15% relative
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12326 reduction in intubation time at a two-sided significance level of 0.05. With a dropout
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14327 rate of 20%, the estimated sample size will be 60 patients per group. Thus, a total of 180
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16328 patients will be enrolled in the study.

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19329 The per-protocol set (PPS), including patients who complete the study without having
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21330 major protocol violations, is used for the evaluation of clinical outcomes. While the full
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23331 analysis set (FAS), determined according to the intention-to-treat population (ITT) who
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25332 undergo randomization except for those who are excluded after randomization, is not
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27333 only used for evaluation of clinical outcomes but also baseline characteristics to measure
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29334 the balance of the three groups before intervention. Missing data will be replaced by
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31335 Markov Chain Monte Carlo (MCMC) method with 5-10 iterations according to the
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33336 principle of multiple imputation. Continuous data will be presented as median and
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35337 interquartile range, while categorical data as numbers and proportion. Normal
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37338 distribution will be checked by the Kolmogorov test. For continuous variables, normal
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39339 distributed data will be compared using one-way analysis of variance among three
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41340 groups, and independent Student's t-test between any of the two groups. While the
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43341 comparison of non-normally distributed parameters among three groups will be applied
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45342 by ANOVA (Kruska Wallis), and then the Mann-Whitney U-test between any of the
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47343 two groups. Categorical data will be compared by using Fisher's exact test or the chi-
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49344 square test. Other factors that may affect the efficacy will be considered as co-variants
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51345 for covariance analysis or Cox proportional hazards regression model. $P \leq 0.05$ will be
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53346 considered to indicate statistical significance. All analyses will be done with R statistical
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55347 software, version 4.0.2.

58348 **DISCUSSION**

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4 349 This prospective trial is designed to provide evidence on the beneficial effect of
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6 350 acupuncture on reducing the duration of mechanical ventilation, avoiding excessive
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8 351 sedation and analgesia, as well as improving clinical outcomes in sedating mechanically
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10352 ventilated ICU patients.

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13353 General analgesia and sedation are necessary for mechanically ventilated critically ill
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15354 patients. However, overuse of sedative and analgesic medications may cause varying
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17355 degrees of side effects, like respiratory drive reduction.²⁸ These side effects are
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19356 associated with worsened clinical outcomes, such as prolonged mechanical ventilation
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21357 and hospital length of stay, increased risk of delirium, and even higher mortality.²⁹⁻³⁰
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23358 With many sophisticated attempts to mitigate this clinical problem, it has thus far been
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25359 identified that optimizing analgesia and sedation strategy is able to prevent excessive
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27360 sedation and analgesia and improve the clinical outcome by reducing the duration and
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29361 dosage of sedative and analgesic medications.³¹⁻³³ Thus, it become a key objective to
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31362 formulate an intensive sedative and analgesic medications strategy when caring for
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33363 critically ill patients.

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36364 The rationale for evaluating the ability of acupuncture on this subject is based on
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38365 research findings that acupuncture can manage pain relief and facilitate opioid tapering
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40366 by increasing the μ -opioid receptor binding ability and the release of the opioid
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42367 peptide.³⁴⁻³⁵ According to the meta-analysis of acupuncture on pain relief, visual analog
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44368 scale (VAS) pain scores in the AC group is lower than that in the NAC group [MD=-
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46369 11.13, 95%CI(-13.59,-8.68), Z=8.9, P < 0.00001], Figure 3A.³⁶⁻⁵⁰ However, there is a
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48
49370 substantial heterogeneity of results in these trials ($I^2 = 70\%$). As shown in Figure 3B,
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51371 heterogeneity decreases ($I^2 = 14\%$) when the studies by Xian Wang and Zheng Lihong
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53372 are excluded, and the AC group consistently shows a greater pain relief compared to
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55373 NAC group [MD=-10.92, 95%CI(-12.93,-8.91), Z=10.66, P < 0.00001]. Meanwhile,
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57374 acupuncture, without adverse effects, has been shown to exert sedation effects in various
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59375 medical conditions. As it shown in the meta-analysis, with a high heterogeneity($I^2 =$
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4 376 95%), the bispectral index (BIS) value in the AC group is also lower than that in the
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6 377 NAC group [MD=-5.82,95%CI (-9.36, -2.27), Z=3.22, P=0.001], Figure 4A.⁵¹⁻⁵⁶ As
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8 378 shown in Figure 4B, heterogeneity decreases ($I^2 = 0\%$) when the studies by J.
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10379 Fleckenstein and Jiheng Chen are excluded, and the AC group consistently shows a
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12380 better sedative effect compared to NAC group [MD=-3.18,95%CI(-5.53,-0.84),Z=2.66,
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14381 P < 0.008]. In addition, previous studies have shown that Yintang (EX-HN3) and
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17382 Shenmen (HT7) have good sedative effects, Hegu (LI4) and Taichong (LR3) have
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19383 analgesic advantages, while Baihui (DU20) appears both sedative and analgesic
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21384 effects.^{54 57-60} With these promising results, it is meaningful to assess acupuncture as a
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23385 potential analgesia and sedation strategy in ameliorating the clinical outcomes in
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25386 mechanically ventilated critically ill patients.

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28387 RCT has been recognized as the gold standard for clinical trials since the late 20th
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30388 century.⁶¹ Another important designed technique to improve the quality of clinical trials
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32389 is blinding. Over the past several decades, RCT and blinding have been used to avoid
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34390 bias (selection bias, performance bias, and ascertainment bias) in clinical trials and
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36391 improve the reliability of effects assessment. Sham acupuncture, aiming to blind the
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38392 participants and control therapeutic components, is designed as a placebo control.
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40393 However, this acupuncture technique is relatively difficult to fabricate because it should
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42394 be both biologically inert and psychologically indistinguishable.⁶² Even previous
43
44395 experience of acupuncture feeling might impact the present perception of verum and
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46396 sham acupuncture intervention.

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49397 In PASSION study, we utilize a rigorous set of methods to minimize bias, such as
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51398 computer-generated central randomization, parallel control design, and statistical
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53399 analysis according to the intent-to-treat principle. In control design, the superficial
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55400 needle insertion without manual or electrical stimulation at the non-point is applied to
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57401 simulate deep skin penetration in the SAC group, which is used as the most predominant
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59402 type of sham electropuncture method to ensure blinding according to the published
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4 403 literature.⁶³ However, a few studies reported that superficial needle insertion at non-
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6 404 acupoints might not be physiologically inert since the locations of points are nearby true
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8 405 acupoints.^{64 65} Moreover, researchers found that even mechanical non-penetration can
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10406 evoke slight acupressure effects and physiological activity.⁶⁶ Both of these factors will
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12407 affect the effect assessment of acupuncture. Thus, the NA group, avoiding all
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14408 therapeutic components, is designed to clarify whether the sham acupuncture can be
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16409 regarded as physiologically inert, as well as compared with the results of the AC group.

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19410 A potential limitation of this trial is blinding. Given the nature of acupuncture, the
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21411 patients and members of the medical team in the NA group are impossible to be blinded
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23412 throughout the entire duration of this trial. However, adequate measures will be taken
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25413 to put the patients and medical team members of the other two groups in a masked state.
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27414 For example, we will formulate a set of isolation and secrecy strategies for the study
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29415 coordinator and acupuncturists to achieve satisfactory blinding levels in treatment
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31416 administration. Thus, in both AC and SAC groups, patients and their medical team
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33417 members will be blinded to the patients' acupuncture method. The data collectors and
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35418 the biostatisticians will also be masked from the treatment assignment.

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37
38419 The PASSION study is designed to demonstrate the efficacy of acupuncture on sedation
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40420 and analgesia in mechanically ventilated critically ill patients. We expect the finding
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42421 can provide evidence-based recommendations for acupuncture use for sedation and
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44422 analgesia in critically ill patients with mechanical ventilation.

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50
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55
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PATIENT CONSENT FOR PUBLICATION

Consent obtained from parent(s)/guardian(s).

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

ETHICS AND DISSEMINATION

The study was reviewed and approved by Ethics Committee of Guangdong Province Hospital of Chinese Medicine at Guangzhou University of Chinese Medicine (ZF2021-144-01) and performed in accordance with Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (publication No. 85-23, revised 1996).

COMPETING INTERESTS STATEMENT

All authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

YZ & SM drafted this manuscript; GY, JW & FC made statistical analysis; MZZ made a critical revision of the manuscript and contributed to the rationalization of the study.

All authors read and approved the final manuscript.

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633 Figure legend:

634 Figure 1. Trial design of PASSION study

635 Figure 2. Illustration of the sham points

636 Figure 3. Forest plot of AC group versus NAC group.

637 Figure 4. Forest plot of AC group versus NAC group.

For peer review only

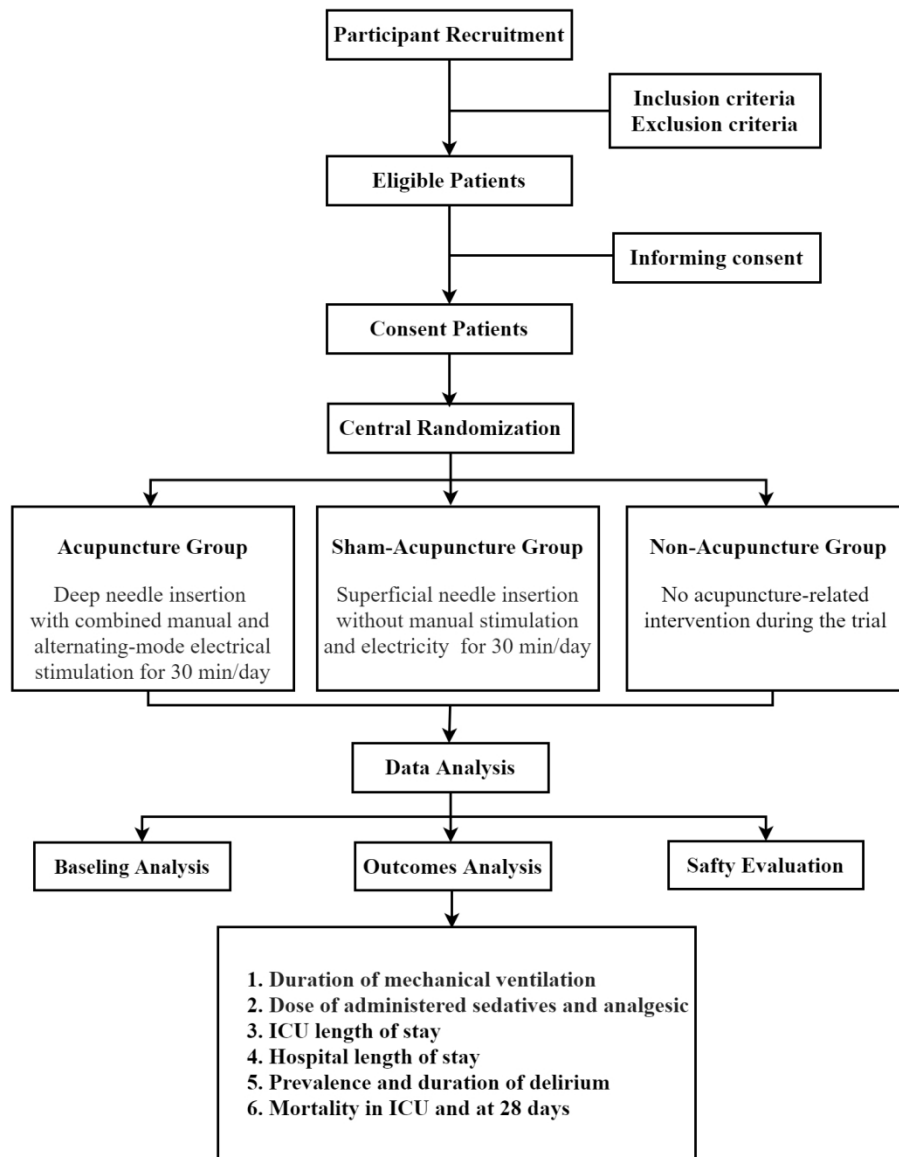


Figure 1

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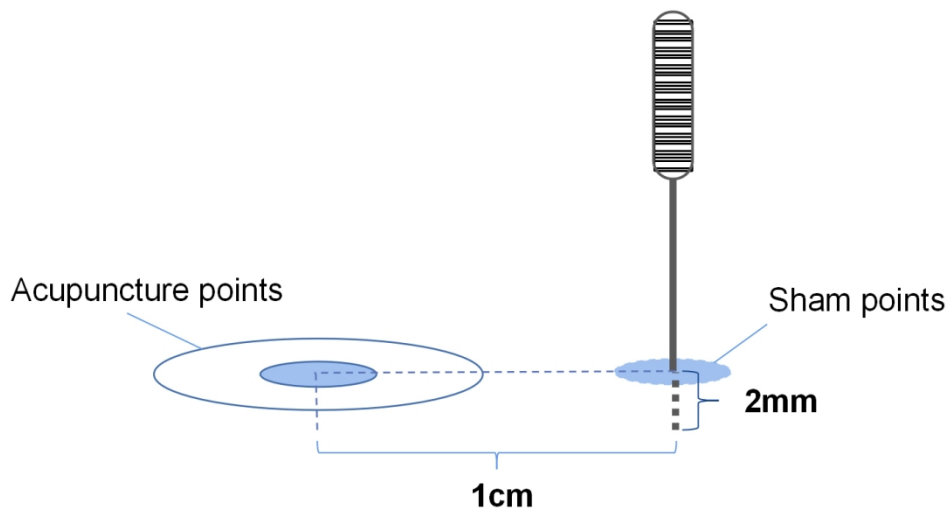


Figure 2

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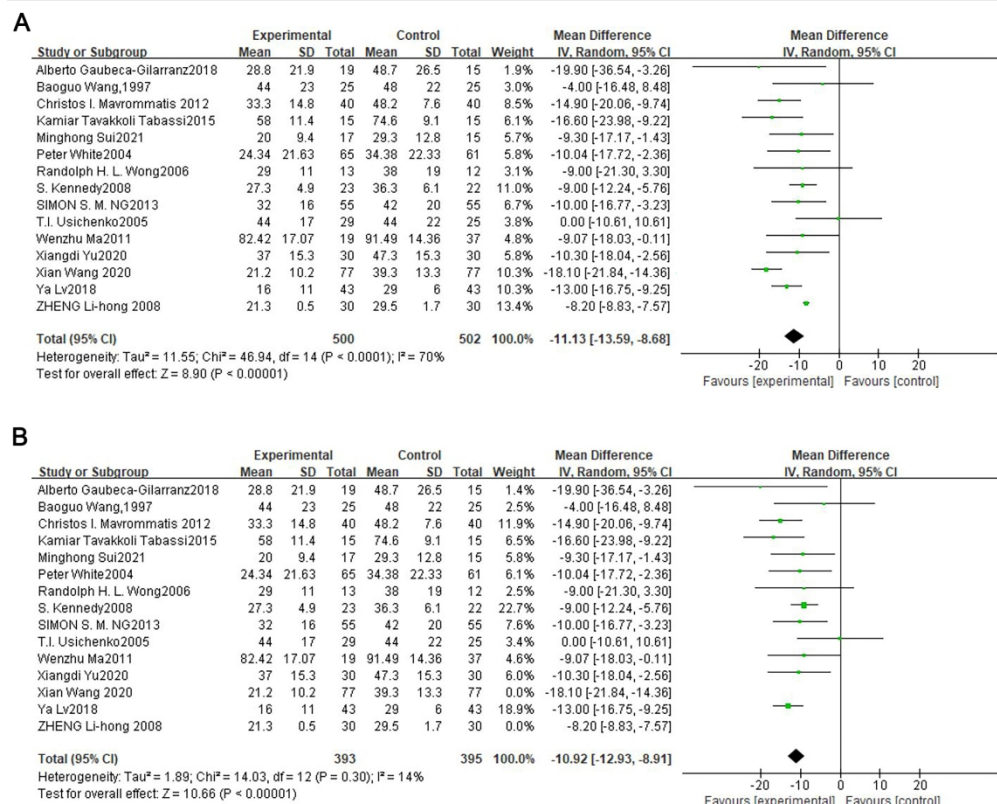


Figure3

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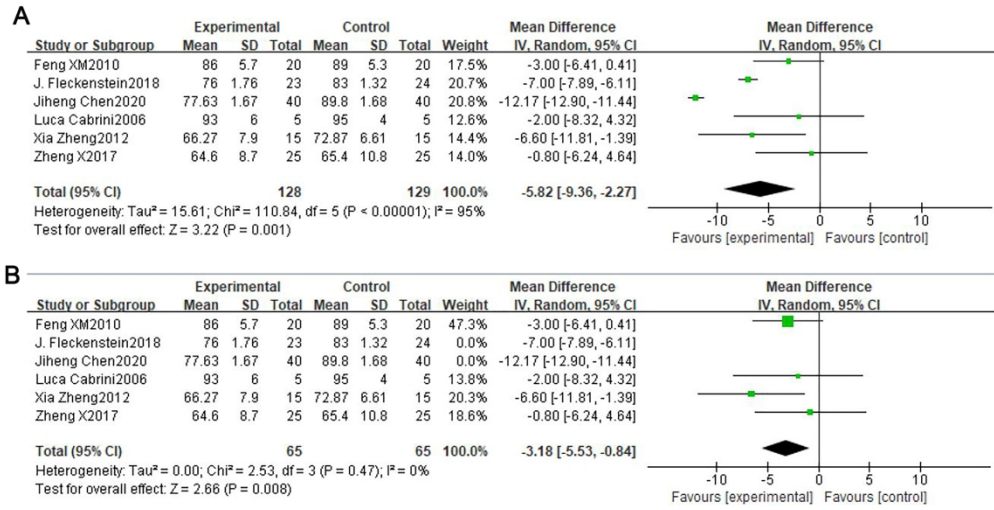


Figure 4

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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, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line 1-4.
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3, line 58; Page 7, line 130.
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	Page 18, line 427-434.

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	Page 1;
2	responsibilities:			Page 18-
3	contributorship			19, line
4				444-449.
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8	Roles and	#5b	Name and contact information for the trial sponsor	Page 18,
9	responsibilities:			line 427-
10	sponsor contact			434.
11	information			
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15	Roles and	#5c	Role of study sponsor and funders, if any, in study	Page 18,
16	responsibilities:		design; collection, management, analysis, and	line 435-
17	sponsor and funder		interpretation of data; writing of the report; and the	438.
18			decision to submit the report for publication, including	
19			whether they will have ultimate authority over any of	
20			these activities	
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25	Roles and	#5d	Composition, roles, and responsibilities of the	Page 13,
26	responsibilities:		coordinating centre, steering committee, endpoint	line 290-
27	committees		adjudication committee, data management team, and	292.
28			other individuals or groups overseeing the trial, if	
29			applicable (see Item 21a for data monitoring committee)	
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33	Introduction			
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35				
36	Background and	#6a	Description of research question and justification for	Page 5,
37	rationale		undertaking the trial, including summary of relevant	line 77-
38			studies (published and unpublished) examining benefits	100.
39			and harms for each intervention	
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42				
43	Background and	#6b	Explanation for choice of comparators	Page 6,
44	rationale: choice of			line 106-
45	comparators			107.
46				
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48	Objectives	#7	Specific objectives or hypotheses	Page 6,
49				line 103-
50				107.
51				
52				
53	Trial design	#8	Description of trial design including type of trial (eg,	Page 5-6,
54			parallel group, crossover, factorial, single group),	line 101-
55			allocation ratio, and framework (eg, superiority,	103.
56			equivalence, non-inferiority, exploratory)	
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1 **Methods:**

2 **Participants,**

3 **interventions, and**

4 **outcomes**

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8	Study setting	#9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6, line 112-113.
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14	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7-8, line 144-157.
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20			Page 8, line 159-164;
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25			Page 10, line 210-213;
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33	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-10, line 188-213;
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40	Interventions: modifications	#11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 13, line 286-290;
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48	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 8, line 207-209.
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56	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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1	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 13, line 294-302;
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12	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 9, line 183-187.
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20	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 14, line 325-331;
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28	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 14, line 330-331.
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35	Methods:			
36	Assignment of interventions (for controlled trials)			
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42	Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8, line 166-175.
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53	Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 8, line 166-175.
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1	Allocation:	#16c	Who will generate the allocation sequence, who will	Page 8,
2	implementation		enrol participants, and who will assign participants to	line 169-
3			interventions	175.
4				
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6	Blinding (masking)	#17a	Who will be blinded after assignment to interventions	Page 8,
7			(eg, trial participants, care providers, outcome	line 179-
8			assessors, data analysts), and how	181.
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	Page 13,
15	emergency unblinding		permissible, and procedure for revealing a participant's	line 286-
16			allocated intervention during the trial	290.
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22	Methods: Data			
23	collection,			
24	management, and			
25	analysis			
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28	Data collection plan	#18a	Plans for assessment and collection of outcome,	Page 13-
29			baseline, and other trial data, including any related	14,
30			processes to promote data quality (eg, duplicate	line309-
31			measurements, training of assessors) and a description	320.
32			of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known.	
34			Reference to where data collection forms can be found,	
35			if not in the protocol	
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41	Data collection plan:	#18b	Plans to promote participant retention and complete	Page 10,
42	retention		follow-up, including list of any outcome data to be	line 207-
43			collected for participants who discontinue or deviate from	209.
44			intervention protocols	
45				
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49	Data management	#19	Plans for data entry, coding, security, and storage,	Page 14,
50			including any related processes to promote data quality	line 320
51			(eg, double data entry; range checks for data values).	
52			Reference to where details of data management	
53			procedures can be found, if not in the protocol	
54				
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57	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	Page14-
58			outcomes. Reference to where other details of the	15, line
59				
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1		statistical analysis plan can be found, if not in the	332-349.
2		protocol	
3			
4			
5	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	Page14,
6	analyses	adjusted analyses)	line 337-
7			338.
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12	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	Page14,
13	population and	adherence (eg, as randomised analysis), and any	line 337-
14	missing data	statistical methods to handle missing data (eg, multiple	338.
15		imputation)	
16			
17			
18			
19	Methods: Monitoring		
20			
21	Data monitoring:	#21a Composition of data monitoring committee (DMC);	Page13,
22	formal committee	summary of its role and reporting structure; statement of	line 290-
23		whether it is independent from the sponsor and	292.
24		competing interests; and reference to where further	
25		details about its charter can be found, if not in the	
26		protocol. Alternatively, an explanation of why a DMC is	
27		not needed	
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33	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
34	interim analysis	guidelines, including who will have access to these	
35		interim results and make the final decision to terminate	
36		the trial	
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40	Harms	#22 Plans for collecting, assessing, reporting, and managing	Page12,
41		solicited and spontaneously reported adverse events	line 286-
42		and other unintended effects of trial interventions or trial	292.
43		conduct	
44			
45			
46	Auditing	#23 Frequency and procedures for auditing trial conduct, if	n/a
47		any, and whether the process will be independent from	
48		investigators and the sponsor	
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52	Ethics and		
53	dissemination		
54			
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56	Research ethics	#24 Plans for seeking research ethics committee /	Page 6-7,
57	approval	institutional review board (REC / IRB) approval	line127-
58			129.
59			
60			

1	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
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9	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7, line135-137.
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14	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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20	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page13-14, line 309-320.
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27	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
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31	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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36	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
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41	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
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49	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
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53	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
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Appendices

1	Informed consent	#32	Model consent form and other related documentation	n/a
2	materials		given to participants and authorised surrogates	
3				
4				
5	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
6			biological specimens for genetic or molecular analysis in	
7			the current trial and for future use in ancillary studies, if	
8			applicable	
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13 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with
14 [Penelope.ai](#)
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