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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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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

administered sedatives and analgesic at comparable sedation levels throughout the study period, ICU length of stay, hospital length of stay.

Ethics and dissemination The 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

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.

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

ventilation and drug accumulation. Furthermore, there is no evidence for an effect of "true" acupuncture over "sham" acupuncture (superficial needle insertion without manual stimulation at "non-points" or electrical stimulation) on clinical outcomes in critically ill patients needing mechanical ventilation.

Therefore, the PASSION study is designed to 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 sedation and analgesia therapies, could reduce the duration of mechanical ventilation, the dose of administered sedatives and analgesic, and subsequently improve other clinical outcomes for critically ill patients when compared with sham acupuncture or non-acupuncture.

METHODS

Study Design Overview

This is a prospective, parallel-group, controlled trial that will recruit 180 patients with a computer-generated allocation sequence and centralized randomization at tertiary and regional ICUs in 3 hospital (Guangdong Provincial Hospital of Chinese Medicine, Charity Hospital of Guangzhou, University Hospital) in South China. Eligible 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, n =60), superficial needle insertion without manual or electrical stimulation on non-acupoints (SAC group, n =60) for 30 min/day, or no acupuncture intervention (NAC group, n =60) .

Participants will be assessed the duration of mechanical ventilation, as well as the dose of administered sedatives and analgesic at comparable sedation levels, from randomization until patients were free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours. They will be also assessed if acupuncture could achieve better clinical outcomes than SAC or NAC treatment. The design of the trial is summarized in Figure 1.

Ethical Requirements and Registration

This protocol and statistical analysis plan was approved by the institutional human Clinical Research Ethical Committee at Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China) in October 2021 with permission number ZF2021-144-01. The PASSION study was registered on Nov 3, 2021 (ClinicalTrials.gov, number ChiCTR2100052650) and will be conducted following the Declaration of Helsinki from December 2021 to December 2022.

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. The investigational nature and details of the study, together with the possible risks and all the benefits, will be informed to patients or their authorized surrogates. Written informed consent will be subsequently obtained from either of them. Patients for whom surrogate consent was obtained were 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).

Exclusion criteria include skin lesions near the acupuncture points; coagulopathy (bleeding time >4 min, thrombocytes <50,000/μl), 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 participated in any other investigational therapeutic or device trial (Table 1).

ICU standard treatment

As is 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 a patient's response in time. A team of medical officers will review patient care every day.

Randomization and blinding

Eligible patients will be stratified by participating sites to avoid patient-level contamination from the systems-level organizational change in sedation practice and, within each ICU, assigned to the AC, SAC, or NAC group in an equal ratio via computer-generated randomization. In detail, an independent study coordinator will log into the central randomization system using a password-protected account and enter inclusion and exclusion criteria to ensure eligibility. After entering a patient's name and identification card number, a randomization sequence will be generated in blocks of varying sizes and stratified by the site under the control of the central computer system. The random sequence will then be concealed in sealed envelopes and sent to an acupuncturist from the assigned patient's site by the study coordinator.

Allocation of participants will be known to the study coordinator and acupuncturists who will not be involved in outcome assessment and be required to sign a confidentiality agreement about patient allocation. All patients will be treated in a single treatment room. In both AC and SAC groups, patients, bedside nurses, and physicians will be blinded to which acupuncture method the patients would receive. The data collectors and the biostatisticians will be masked from the treatment assignment.

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).[13] Patients will be assigned in a ratio of 1:1:1 to AC group (n=60), SAC group (n=60), 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.

Patients in the NAC group will receive no acupuncture-related intervention during the trial. But they could receive a free 12-session daily acupuncture treatment after completing the study at their convenience.

Each Site will be required to have 2 licensed acupuncturists with more than 3 years of experience and specialized training in the acupuncture protocols before starting the study. The acupuncturists will be responsible for the whole acupuncture process but are not further involved in this study.

Basic Sedation Analgesia Strategy

In this study, diagnosis and therapeutic management of agitation and pain will be prescribed by the physicians responsible for the clinical care of each patient according to recommended guidelines[14]. An interruptive sedation strategy was used by bedside nurses, and sedation levels and pain intensity were assessed with the Richmond Agitation Sedation Scale (RASS)[15 16], the Behavioral Pain Scale (BPS) ,or the Numeric Rating Scale (NRS) [17 18] every 4 h in objective to adapt sedatives and analgesics to avoid overuse. Authorized nurses will titrate infusions, including benzodiazepines, propofol, and dexmedetomidine for sedatives and opiates for analgesia, instead of bolus dosing to minimize potential adverse effects.

The sedation analgesia strategy is designed to consider pain treatment before increasing sedatives to minimize the risk of oversedation. The pain will be assessed either by the

BPS in patients unable to communicate or by the NRS, a 1-10 numeric rating scale, in those sufficiently oriented and awake to communicate with the medical staff. Efficacy of the study analgesics drug will be defined as the ability to achieve a score < 3 in both of the pain scoring systems above, evaluated by the bedside nurse. Efficacy of the study sedative drug will be defined as the ability to achieve a sedation score between -2 and 1, set by the patient's medical team using the RASS, a highly reliable and well-validated sedation scale for use within patients over time in the ICU.

Each morning, a daily interruption of sedation (DIS) will be performed at the clinical medical team's discretion. Major opioid infusions needed for active pain will be continued. Recommended criteria to interrupt sedation is used: no drug-induced paralysis, no intracranial hypertension, no myocardial ischemia in the previous 24 h, primary disease healing in progress, hemodynamic stability, the partial pressure of arterial oxygen ≥ 60 mmHg, the fraction of inspired oxygen ≤ 50%, and positive end-expiratory pressure ≤ 8 cmH_2O. The interruption of continuous sedation will be coupled with an assessment hourly for wakefulness, defined as the RASS score 1 to 4, and the ability to perform at least 3 of the following requests: eye-opening, tracking, hand squeezing, and toe moving. With the criteria recommended, patients will be able to pass the DIS if they can tolerate it for 4 h and awakening enough. Then, a spontaneous breathing trial (SBT) will immediately be managed. [19] If patients are insufficient for the DIS, sedatives will be restarted at half the previous dose and then titrated to achieve 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 H_2O PSV, 0 PEEP, and unchanged FiO_2 from the mechanical ventilation period leading up to the SBT.[20] Criteria for a successful SBT were: 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 pass the SBT if they complete a 60 min trial with the success 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 did not participate in decisions to extubate patients.

The clinical research team should 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.[21] 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

Feature 2: inattention

Feature 3: disorganized thinking

Feature 4: altered level of consciousness

Adverse Event Monitoring

Adverse events will also be defined a priori and prospectively monitored. Adverse events associated with acupuncture include bleeding, hematoma, and local infection. Adverse events related to sedation and analgesia include inadequate pain and sedation management (either pain score > 4 and RASS > 1 for 2 consecutive hours or pain and agitation assumed present if receiving neuromuscular blockade), clinically significant iatrogenic withdrawal. Adverse events associated with mechanical ventilation include accidental removal of medical devices, extubation failure (reintubation within 24 hours), pressure ulcers, catheter-associated bloodstream infections, ventilator-associated pneumonia. Every day, study personnel will monitor and assess the seriousness of all adverse events and document all details to determine whether or not any of the events would be related to acupuncture interventions or the study procedure. A report of all

serious, unexpected, and study-related adverse events will be presented to an independent data and safety monitoring board and the institutional review board within 7 days of occurrence.

Outcomes and Data Collection

The primary outcome is the duration of mechanical ventilation, defined as the time from randomization to successful extubation without reinstitution for the following 48 hours. The secondary outcomes will include the dose of administered sedatives and opiate (absolute value as well as indexed value [total drug in mg/kg ÷ total number of hours from the start of infusion to its ultimate discontinuation]) at comparable clinically individualized target sedation goals throughout the study period, the duration of ICU length of stay, and hospital length of stay. Additional outcomes include the prevalence and days of delirium in ICU, mortality in ICU, and within 28 days after randomization.

The day of extubation was considered as the day of death for patients who died while still intubated. Censoring for ICU or hospital length analyses occurred at the time of death or study withdrawal. The number of ventilator free days at 28 days is defined as days alive and not using mechanical ventilation between days 1 and 28. For the 28-day mortality analyses, patients were censored at the time of the last contact alive or at 28 days from enrollment, whichever was first.

Baseline demographic data will be collected from the patients' record by the medical team, including the reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure

Assessment (SOFA) scores, hematological and blood chemistry data, and clinical data (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.

Patient and public involvement statement

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

Statistical Analysis

Statistical power was estimated using the reduction in duration of mechanical ventilation as the primary outcome. According to Carrasco and colleagues, the mean (±standard deviation) time for current sedation was 54.7 ± 12.3 hours.[22] We calculated that a sample size of 48 patients in each group would 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 for the study.

The per-protocol set (PPS), including patients who completed 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 underwent 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 number and proportions. Normal distribution will be checked by the Kolmogorov test. For continuous variables, normal distributed data will be compared using one-way analysis of variance among three groups, and independent Student's t-test between any of the two groups. While the comparison of non-normally distributed parameters among three groups will be applied by ANOVA (Kruska Wallis), and then Mann-Whitney U-test between any of the two groups. Categorical data will be compared by using Fisher's exact test or the chi-square test. Other factors that might affect the efficacy will be considered as co-variants for covariance analysis or Cox proportional hazards regression model. $P \leq 0.05$ will be considered to indicate statistical significance. All analyses will be done with R statistical software, version 4.0.2.

DISCUSSION

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

General analgesia and sedation are necessary for mechanically ventilated critically ill patients. However, overuse of sedative and analgesic medications may cause varying degrees of side effects, like respiratory drive reduction.[23] These side effects are associated with worsened clinical outcomes, such as a prolonged time of mechanical ventilation and hospital length of stay, an increased risk of delirium, and even mortality.[24 25] With many sophisticated attempts to mitigate this clinical problem, it has thus far been identified that optimizing analgesia and sedation strategy is able to prevent excessive sedation and analgesia and improve the clinical outcome by reducing the duration and dosage of sedative and analgesic medications.[26-28] Thus, it become a key objective to formulate an intensive sedative and analgesic medications strategy when caring for critically ill patients.

The rationale for evaluating the ability of acupuncture on this subject is based on research findings that acupuncture could manage pain relief and facilitate opioid tapering by increasing the μ-opioid receptor binding ability and the opioid peptides release.[29 30] According to the meta-analysis of electroacupuncture on pain relief, the dosage of analgesics needed in AC group was lower than that in NAC group [MD=-6.33,95%CI (-7.20,-5.46), Z=14.24,P<0.00001] (Figure 2). [31-35] Meanwhile, acupuncture, without adverse effect, has been shown to exert sedation effects in various medical conditions. As it shown in meta-analysis, the bispectral index (BIS) values in AC group was also lower than that in NAC group [MD=-9.98,95%CI(-10.54,-9.42),Z=34.84,P<0.00001] (Figure 3).[33 36-38] With these promising results, it is

meaningful to assess acupuncture as a potential analgesia and sedation strategy in ameliorating the clinical outcomes in mechanically ventilated critically ill patients.

RCT has been recognized as the gold standard for clinical trials since the late 20th century.[39] Another important designed technique to improve the quality of clinical trials is blinding. Over the past several decades, RCT and blinding have been used to avoid bias (selection bias, performance bias, and ascertainment bias) in clinical trials and improve the reliability of effects assessment. Sham acupuncture, aiming to blind the participants and control therapeutic components, is designed as a placebo control. However, this acupuncture technique is relatively difficult to fabricate because it should be both biologically inert and psychologically indistinguishable.[40] Even previous experience of acupuncture feeling might impact the present perception of verum and sham acupuncture intervention.

In PASSION study, we utilize a rigorous set of methods to minimize bias, such as computer-generated central randomization, parallel control design, and statistical analysis according to the intent-to-treat principle. In control design, the superficial needle insertion without manual or electrical stimulation at non-point is applied to simulate deep skin penetration in the SAC group, which is used as the most predominant type of sham electropuncture method to ensure blinding according to the published literature.[41] However, a few studies reported that superficial needle insertion at non-acupoints might not be physiologically inert since the locations of points are nearby true acupoints.[42 43] Moreover, researchers found that even mechanical non-penetration can evoke slight acupressure effects and physiological activity.[44] Both of these factors will

affect the effect assessment of acupuncture. Thus, the NA group, avoiding all therapeutic components, is designed to clarify if the sham acupuncture could be regarded as physiologically inert, as well as compared with the results of the AC group.

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

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

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DISCLAIMER

The sponsors have had no role in the project development, in the collection of data, in the preparation of this manuscript, nor the decision to publish. The researchers have complete independence from the sources of funding in all aspects of this study.

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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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/µl;
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.

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.

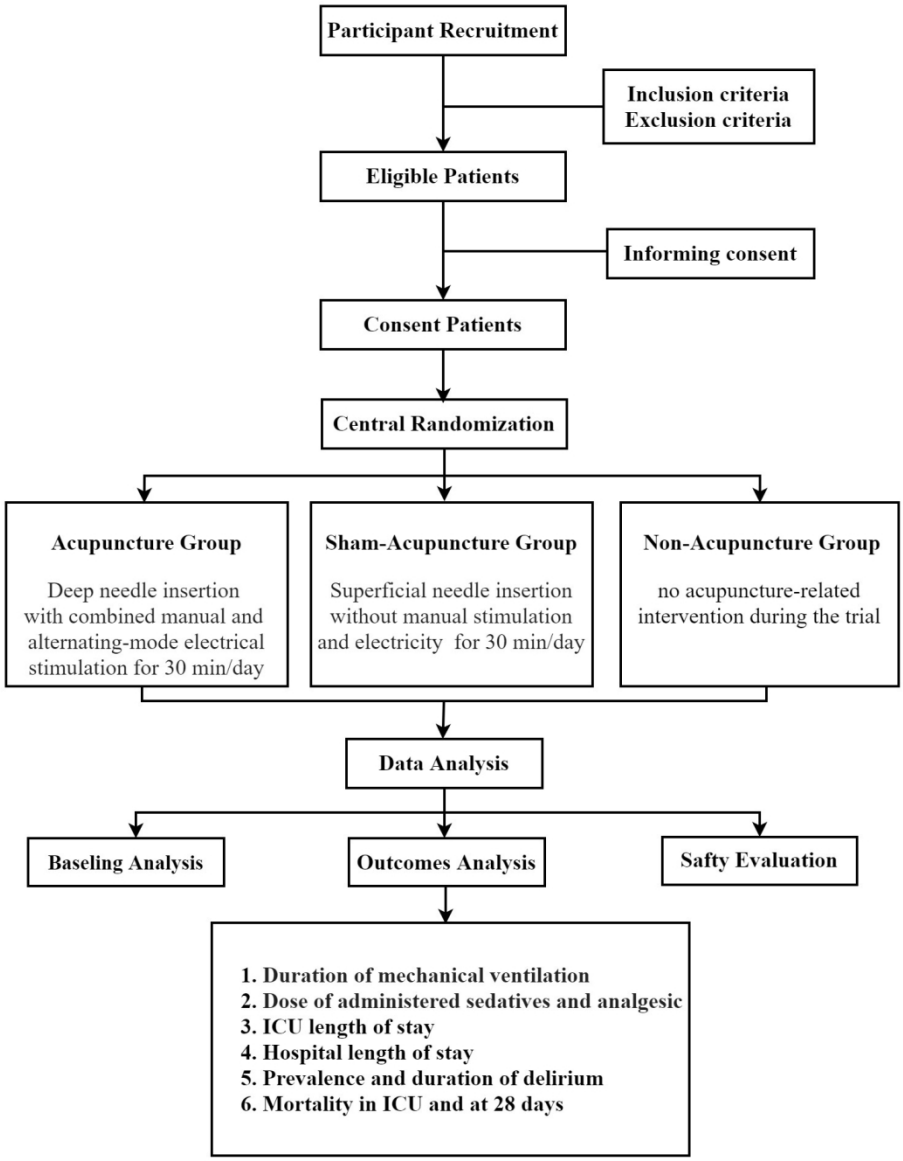

Figure 1

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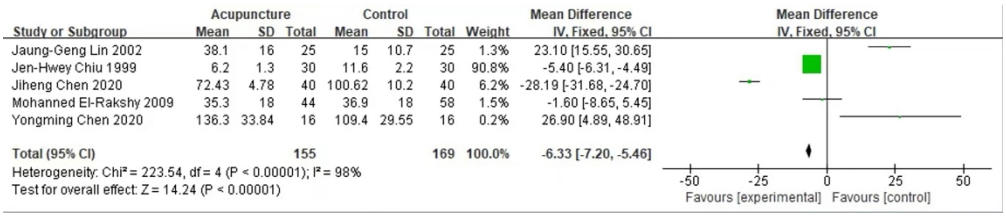

Figure 2

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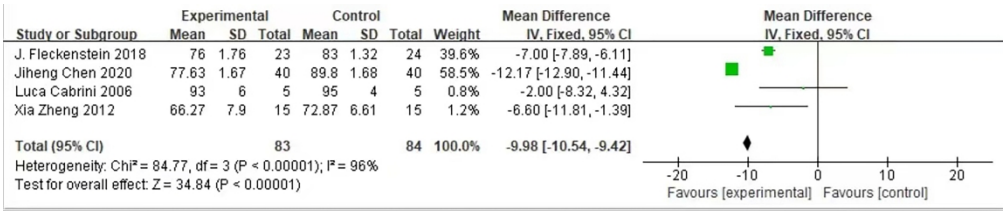

Figure 3

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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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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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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 and16 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.

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

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

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

METHODS

Study Design Overview

This is a prospective, parallel-group, controlled trial will recruit 180 patients with a computer-generated allocation sequence and centralized randomization at tertiary and regional ICUs in 3 hospitals (Guangdong Provincial Hospital of Chinese Medicine, Charity Hospital of Guangzhou, University Hospital) in South China. Recruitment officially began on 03 November 2021, and the final follow-up of the last subject will not exceed 16 August 2023. Eligible 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, n =60), superficial needle insertion without manual or electrical stimulation on non-acupoints (SAC group, n =60) for 30 min/day, or no acupuncture intervention (NAC group, n =60), respectively.

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

Ethical Requirements and Registration

This protocol is approved by the Institutional Human Clinical Research Ethical Committee at Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China) in October 2021 with permission number ZF2021-144-01. The PASSION study was

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).

Exclusion criteria include skin lesions near the acupuncture points, coagulopathy (bleeding time >4 min, thrombocytes <50,000/μl), 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

Eligible patients will be stratified by participating sites to avoid patient-level contamination from the systems-level organizational change in sedation practice and, within each ICU, assigned to the AC, SAC, or NAC group in an equal ratio via computer-generated randomization. In detail, an independent study coordinator will log into the central randomization system using a password-protected account and enter inclusion and exclusion criteria to ensure eligibility. After entering a patient's name and identification card number, a randomization sequence will be generated in blocks of varying sizes and stratified by the site under the control of the central computer system. The random sequence will then be concealed in sealed envelopes and sent to an acupuncturist from the assigned patient's site by the study coordinator.

Allocation of participants will be known to the study coordinator and acupuncturists who will not be involved in outcome assessment and be required to sign a confidentiality agreement about patient allocation. All patients will be treated in a single treatment room. In both AC and SAC groups, patients, bedside nurses, and physicians will be blinded to which acupuncture method the patients will receive. The data collectors and the biostatisticians will be masked from the treatment assignment.

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)

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

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

Basic Sedation Analgesia Strategy

In this study, diagnosis and therapeutic management of agitation and pain will be prescribed by the physicians responsible for the clinical care of each patient according to recommended guidelines[19]. An interruptive sedation strategy will be adopted by bedside nurses, and sedation levels and pain intensity will be assessed with the Richmond Agitation Sedation Scale (RASS)[20 21], the Behavioral Pain Scale (BPS), or the Numeric Rating Scale (NRS) [22 23] every 4 h in order to adapt sedatives and analgesics to avoid overuse. Authorized nurses will titrate infusions, including benzodiazepines, propofol, and dexmedetomidine for sedatives and opiates for analgesia, instead of bolus dosing to minimize potential adverse effects.

The sedation analgesia strategy is designed to consider pain treatment before increasing sedatives to minimize the risk of oversedation. The pain will be assessed either by the BPS in patients unable to communicate or by the NRS, a 1-10 numeric rating scale, in those sufficiently oriented and awake to communicate with the medical staff. Efficacy of the study analgesics drug will be defined as the ability to achieve a score < 3 in both of the pain scoring systems above, evaluated by the bedside nurse. Efficacy of the sedative drug will be defined as the ability to achieve a sedation score between -2 and 1, set by the patient's medical team using the RASS (a highly reliable and well-validated sedation scale for use within patients) over time in the ICU.

Each morning, a daily interruption of sedation (DIS) will be performed at the clinical medical team's discretion. Major opioid infusions needed for active pain will be continued. Recommended criteria to interrupt sedation are used: no drug-induced paralysis, no intracranial hypertension, no myocardial ischemia in the previous 24 h, primary disease healing in progress, hemodynamic stability, the partial pressure of arterial oxygen ≥ 60 mmHg, the fraction of inspired oxygen ≤ 50%, and positive end-expiratory pressure ≤ 8 cmH_2O. The interruption of continuous sedation will be coupled with an assessment hourly for wakefulness, defined as the RASS score 1 to 4, and the ability to perform at least 3 of the following requests: eye-opening, tracking, hand squeezing, and toe moving. With the criteria recommended, patients will be able to pass the DIS if they can tolerate it for 4 h and keep awakening enough. Then, a spontaneous breathing trial (SBT) will immediately be managed. [24] If patients are insufficient for the DIS, sedatives will be restarted at half the previous dose and then titrated to achieve 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 H_2O PSV, 0 PEEP, and unchanged FiO_2 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

Feature 2: inattention

Feature 3: disorganized thinking

Feature 4: altered level of consciousness

Adverse Event Monitoring

Adverse events will also be defined a priori and prospectively monitored. Adverse events associated with acupuncture include bleeding, hematoma, and local infection. Adverse events related to sedation and analgesia include inadequate pain and sedation management (either pain score > 4 and RASS > 1 for 2 consecutive hours or pain and agitation assumed present if receiving neuromuscular blockade), clinically significant iatrogenic withdrawal. Adverse events associated with mechanical ventilation include accidental removal of medical devices, extubation failure (reintubation within 24 hours), pressure ulcers, catheter-associated bloodstream infections, ventilator-associated

pneumonia. Every day, research personnel will monitor and assess the seriousness of all adverse events and document all details to determine whether the events are related to acupuncture interventions or the study procedure, as well as developing further treatment strategies including whether it is necessary to uncover blindness. A report of all serious, unexpected, and study-related adverse events will be presented to an independent data and safety monitoring board and the institutional review board within 7 days of occurrence.

Outcomes and Data Collection

The primary outcome is the duration of mechanical ventilation, defined as the time from randomization to successful extubation without reinstitution for the following 48 hours. The secondary outcomes will include the dose of administered sedatives and opiate (absolute value as well as indexed value [total drug in mg/kg ÷ total number of hours from the start of infusion to its ultimate discontinuation]) at comparable clinically individualized target sedation goals throughout the study, the duration of ICU length of stay, and 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.

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

Baseline demographic data will be collected from patients' records by the medical team, including the reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure Assessment (SOFA) scores, hematological and blood chemistry data, and clinical data

(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 (±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.

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

DISCUSSION

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

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

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

RCT has been recognized as the gold standard for clinical trials since the late 20th century.[61] Another important designed technique to improve the quality of clinical trials is blinding. Over the past several decades, RCT and blinding have been used to avoid bias (selection bias, performance bias, and ascertainment bias) in clinical trials and

improve the reliability of effects assessment. Sham acupuncture, aiming to blind the participants and control therapeutic components, is designed as a placebo control. However, this acupuncture technique is relatively difficult to fabricate because it should be both biologically inert and psychologically indistinguishable.[62] Even previous experience of acupuncture feeling might impact the present perception of verum and sham acupuncture intervention.

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

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

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

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DISCLAIMER

The sponsors have had no role in the project development, in the collection of data, in the preparation of this manuscript, nor the decision to publish. The researchers have complete independence from the sources of funding in all aspects of this study.

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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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/μl;
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.

Figure legend:

Figure 1. Trial design of PASSION study

Figure 2. Illustration of the sham points

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

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

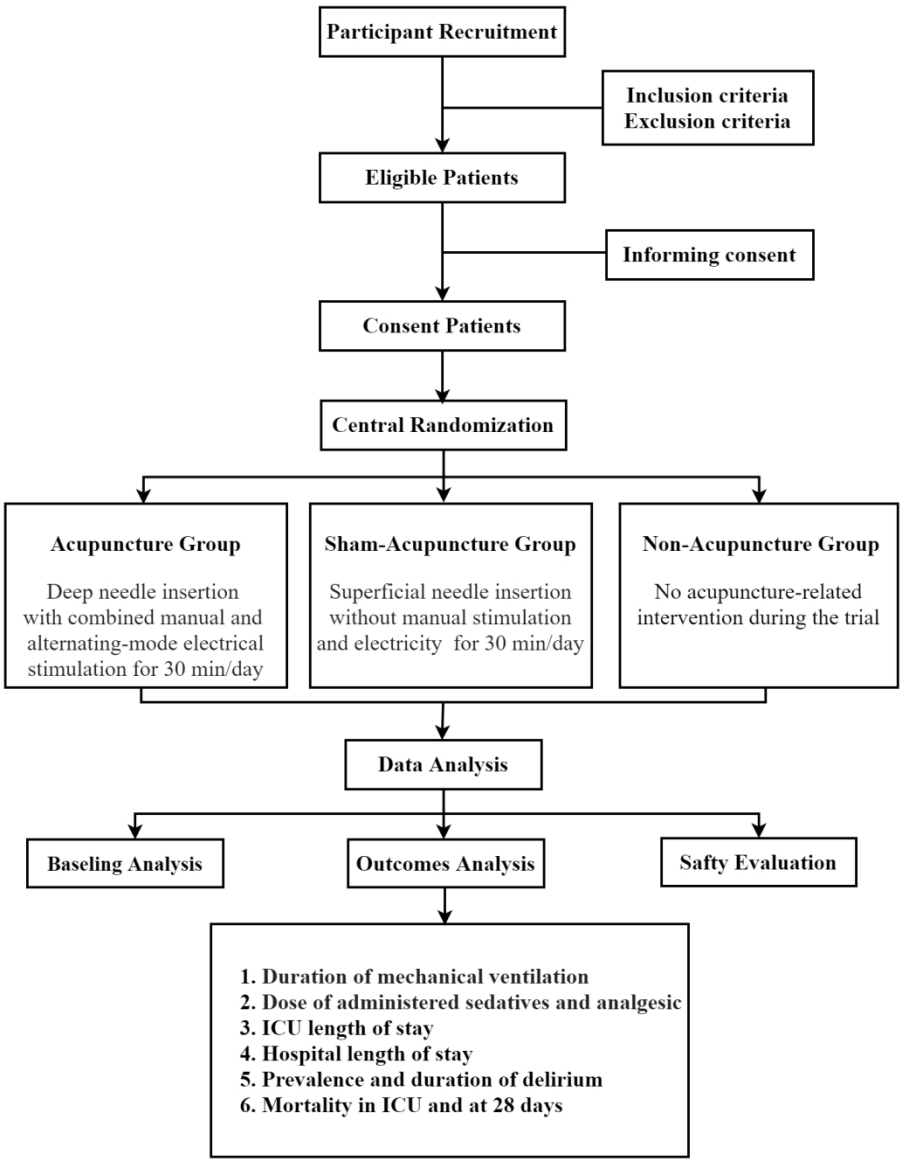

Figure1

543x691mm (72 x 72 DPI)

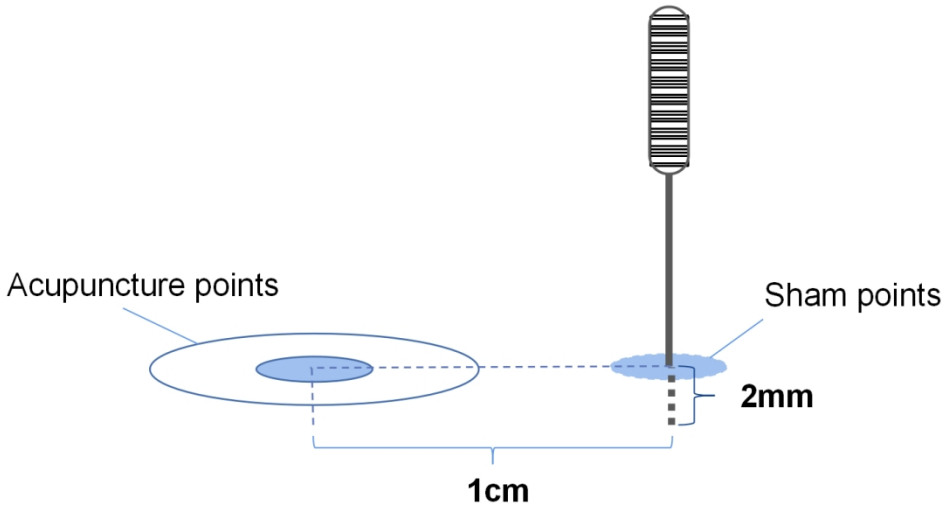

Figure2

1005x559mm (38 x 38 DPI)

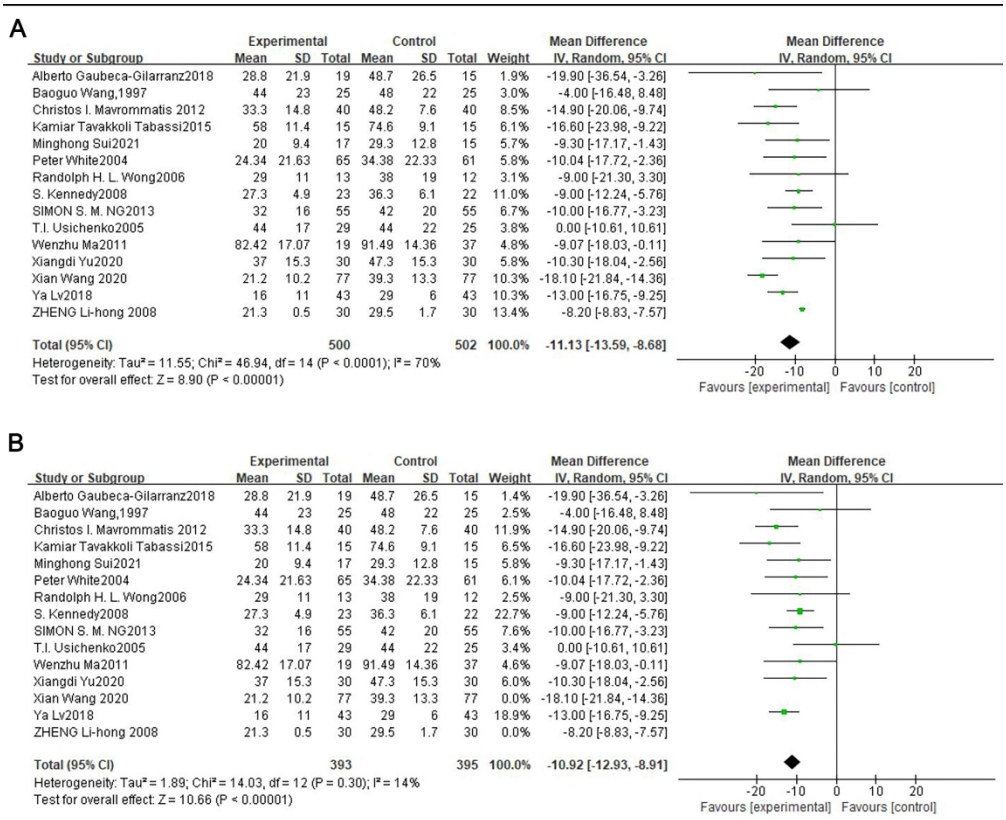

Figure3

199x162mm (300 x 300 DPI)

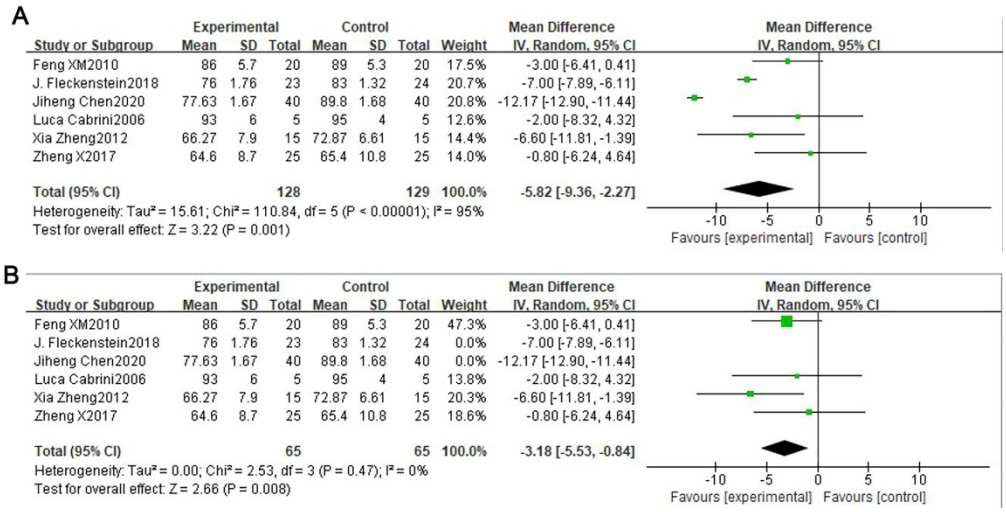

Figure4

199x101mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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

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

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In your methods section, say that you used the SPIRITreporting 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,line1-4.
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.

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1; Page 18-19, line 444-449.
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 18, line 427-434.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 18, line 435-438.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 13, line 290-292.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 5, line 77-100.
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 6, line 106-107.
Objectives	#7	Specific objectives or hypotheses	Page 6, line 103-107.
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 5-6, line 101-103.

Methods: Participants, interventions, and outcomes			
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.
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. Page 8, line 159-164; Page 10, line 210-213;
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;
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;
Interventions: adherance	#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.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

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;
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, line183-187.
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;
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 14, line 330-331.
Methods: Assignment of interventions (for controlled trials)			
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.
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.

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8, line 169-175.
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8, line 179-181.
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 13, line 286-290.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 13-14, line309-320.
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10, line 207-209.
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 14, line 320
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	Page14-15, line

		statistical analysis plan can be found, if not in the protocol	332-349.
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page14, line 337-338.
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page14, line 337-338.
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page13, line 290-292.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page12, line 286-292.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 6-7, line127-129.

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
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.
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
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.
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
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
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
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
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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

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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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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 and16 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.

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

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

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

METHODS

Study Design Overview

This is a prospective, parallel-group, controlled trial will recruit 180 patients with a computer-generated allocation sequence and centralized randomization at tertiary and regional ICUs in 3 hospitals (Guangdong Provincial Hospital of Chinese Medicine, Charity Hospital of Guangzhou, University Hospital) in South China. Recruitment officially began on 03 November 2021, and the final follow-up of the last subject will not exceed 16 August 2023. Eligible 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, n =60), superficial needle insertion without manual or electrical stimulation on non-acupoints (SAC group, n =60) for 30 min/day, or no acupuncture intervention (NAC group, n =60), respectively.

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

Ethical Requirements and Registration

This protocol is approved by the Institutional Human Clinical Research Ethical Committee at Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China) in October 2021 with permission number ZF2021-144-01. The PASSION study was

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/μl;
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/μl), 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

Eligible patients will be stratified by participating sites to avoid patient-level contamination from the systems-level organizational change in sedation practice and, within each ICU, assigned to the AC, SAC, or NAC group in an equal ratio via computer-generated randomization. In detail, an independent study coordinator will log into the central randomization system using a password-protected account and enter inclusion and exclusion criteria to ensure eligibility. After entering a patient's name and identification card number, a randomization sequence will be generated in blocks of varying sizes and stratified by the site under the control of the central computer system. The random sequence will then be concealed in sealed envelopes and sent to an acupuncturist from the assigned patient's site by the study coordinator.

Allocation of participants will be known to the study coordinator and acupuncturists who will not be involved in outcome assessment and be required to sign a confidentiality agreement about patient allocation. All patients will be treated in a single treatment room. In both AC and SAC groups, patients, bedside nurses, and physicians will be blinded to which acupuncture method the patients will receive. The data collectors and the biostatisticians will be masked from the treatment assignment.

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)

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

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

Basic Sedation Analgesia Strategy

In this study, diagnosis and therapeutic management of agitation and pain will be prescribed by the physicians responsible for the clinical care of each patient according to recommended guidelines[19]. An interruptive sedation strategy will be adopted by bedside nurses, and sedation levels and pain intensity will be assessed with the Richmond Agitation Sedation Scale (RASS)[20 21], the Behavioral Pain Scale (BPS), or

the Numeric Rating Scale (NRS) [22 23] every 4 h in order to adapt sedatives and analgesics to avoid overuse. Authorized nurses will titrate infusions, including benzodiazepines, propofol, and dexmedetomidine for sedatives and opiates for analgesia, instead of bolus dosing to minimize potential adverse effects.

The sedation analgesia strategy is designed to consider pain treatment before increasing sedatives to minimize the risk of oversedation. The pain will be assessed either by the BPS in patients unable to communicate or by the NRS, a 1-10 numeric rating scale, in those sufficiently oriented and awake to communicate with the medical staff. Efficacy of the study analgesics drug will be defined as the ability to achieve a score < 3 in both of the pain scoring systems above, evaluated by the bedside nurse. Efficacy of the sedative drug will be defined as the ability to achieve a sedation score between -2 and 1, set by the patient's medical team using the RASS (a highly reliable and well-validated sedation scale for use within patients) over time in the ICU.

Each morning, a daily interruption of sedation (DIS) will be performed at the clinical medical team's discretion. Major opioid infusions needed for active pain will be continued. Recommended criteria to interrupt sedation are used: no drug-induced paralysis, no intracranial hypertension, no myocardial ischemia in the previous 24 h, primary disease healing in progress, hemodynamic stability, the partial pressure of arterial oxygen ≥ 60 mmHg, the fraction of inspired oxygen ≤ 50%, and positive end-expiratory pressure ≤ 8 cmH_2O. The interruption of continuous sedation will be coupled with an assessment hourly for wakefulness, defined as the RASS score 1 to 4, and the ability to perform at least 3 of the following requests: eye-opening, tracking, hand squeezing, and toe moving. With the criteria recommended, patients will be able to pass the DIS if they can tolerate it for 4 h and keep awakening enough. Then, a spontaneous breathing trial (SBT) will immediately be managed. [24] If patients are insufficient for the DIS, sedatives will be restarted at half the previous dose and then titrated to achieve 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 H_2O PSV, 0 PEEP, and unchanged FiO_2 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

Feature 2: inattention

Feature 3: disorganized thinking

Feature 4: altered level of consciousness

Adverse Event Monitoring

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

Outcomes and Data Collection

The primary outcome is the duration of mechanical ventilation, defined as the time from randomization to successful extubation without reinstitution for the following 48 hours. The secondary outcomes will include the dose of administered sedatives and opiate (absolute value as well as indexed value [total drug in mg/kg ÷ total number of hours from the start of infusion to its ultimate discontinuation]) at comparable clinically individualized target sedation goals throughout the study, the duration of ICU length of

stay, and 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.

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

Baseline demographic data will be collected from patients' records by the medical team, including the reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and diagnostic classification, Sequential Organ Failure Assessment (SOFA) scores, hematological and blood chemistry data, and clinical data (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 (±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 by Markov Chain Monte Carlo (MCMC) method with 5-10 iterations according to the principle of multiple imputation. Continuous data will be presented as median and interquartile range, while categorical data as numbers and proportion. Normal distribution will be checked by the Kolmogorov test. For continuous variables, normal distributed data will be compared using one-way analysis of variance among three groups, and independent Student's t-test between any of the two groups. While the comparison of non-normally distributed parameters among three groups will be applied by ANOVA (Kruska Wallis), and then the Mann-Whitney U-test between any of the two groups. Categorical data will be compared by using Fisher's exact test or the chi-square test. Other factors that may affect the efficacy will be considered as co-variants for covariance analysis or Cox proportional hazards regression model. $P \leq 0.05$ will be considered to indicate statistical significance. All analyses will be done with R statistical software, version 4.0.2.

DISCUSSION

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

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

The rationale for evaluating the ability of acupuncture on this subject is based on research findings that acupuncture can manage pain relief and facilitate opioid tapering by increasing the μ-opioid receptor binding ability and the release of the opioid peptide.[34 35] According to the meta-analysis of acupuncture on pain relief, visual analog scale (VAS) pain scores in the AC group is lower than that in the NAC group [MD=-11.13, 95%CI(-13.59,-8.68), Z=8.9, P＜0.00001], Figure 3A.[36-50] However, there is a substantial heterogeneity of results in these trials (I^2 = 70%). As shown in Figure 3B, heterogeneity decreases (I^2 = 14%) when the studies by Xian Wang and Zheng Lihong are excluded, and the AC group consistently shows a greater pain relief compared to NAC group [MD=-10.92, 95%CI(-12.93,-8.91), Z=10.66, P＜0.00001]. Meanwhile, acupuncture, without adverse effects, has been shown to exert sedation effects in various medical conditions. As it shown in the meta-analysis, with a high heterogeneity(I^2 =

95%), the bispectral index (BIS) value in the AC group is also lower than that in the NAC group [MD=-5.82,95%CI (-9.36, -2.27), Z=3.22, P=0.001], Figure 4A.[51-56] As shown in Figure 4B, heterogeneity decreases (I^2 = 0%) when the studies by J. Fleckenstein and Jiheng Chen are excluded, and the AC group consistently shows a better sedative effect compared to NAC group [MD=-3.18,95%CI(-5.53,-0.84),Z=2.66, $P < 0.008$]. In addition, previous studies have shown that Yintang (EX-HN3) and Shenmen (HT7) have good sedative effects, Hegu (LI4) and Taichong (LR3) have analgesic advantages, while Baihui (DU20) appears both sedative and analgesic effects.[54 57-60] With these promising results, it is meaningful to assess acupuncture as a potential analgesia and sedation strategy in ameliorating the clinical outcomes in mechanically ventilated critically ill patients.

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

In PASSION study, we utilize a rigorous set of methods to minimize bias, such as computer-generated central randomization, parallel control design, and statistical analysis according to the intent-to-treat principle. In control design, the superficial needle insertion without manual or electrical stimulation at the non-point is applied to simulate deep skin penetration in the SAC group, which is used as the most predominant type of sham electropuncture method to ensure blinding according to the published

literature.[63] However, a few studies reported that superficial needle insertion at non-acupoints might not be physiologically inert since the locations of points are nearby true acupoints.[64 65] Moreover, researchers found that even mechanical non-penetration can evoke slight acupressure effects and physiological activity.[66] Both of these factors will affect the effect assessment of acupuncture. Thus, the NA group, avoiding all therapeutic components, is designed to clarify whether the sham acupuncture can be regarded as physiologically inert, as well as compared with the results of the AC group.

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

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

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DISCLAIMER

The sponsors have had no role in the project development, in the collection of data, in the preparation of this manuscript, nor the decision to publish. The researchers have complete independence from the sources of funding in all aspects of this study.

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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Figure legend:

Figure 1. Trial design of PASSION study

Figure 2. Illustration of the sham points

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

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

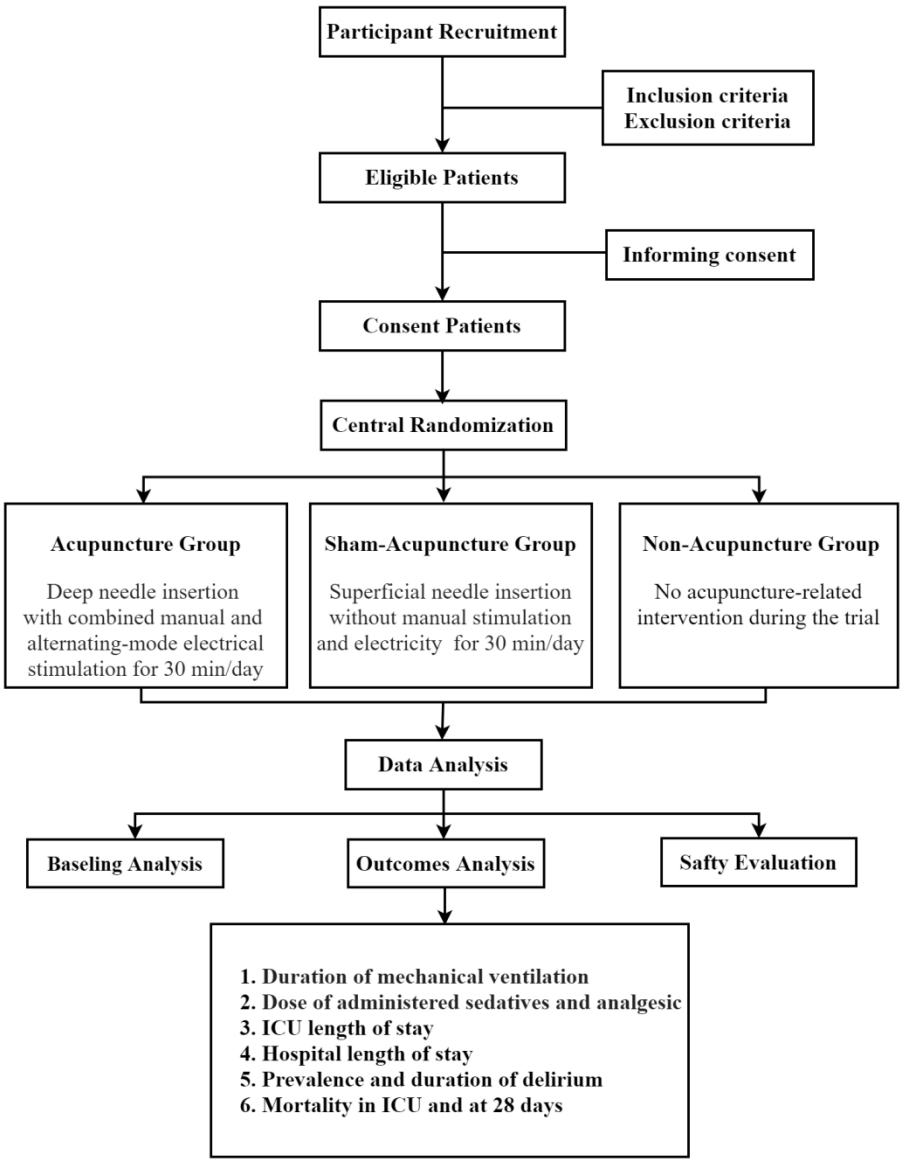

Figure 1

543x691mm (72 x 72 DPI)

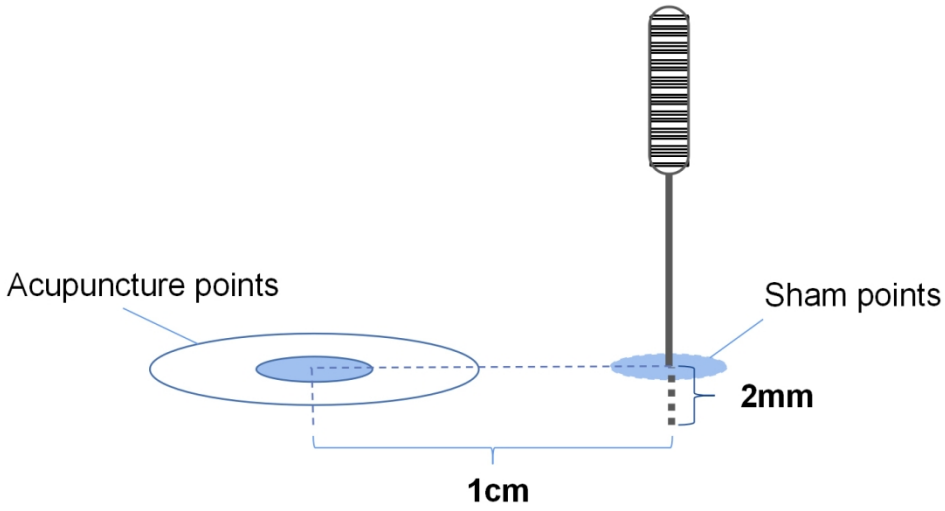

Figure 2

398x221mm (96 x 96 DPI)

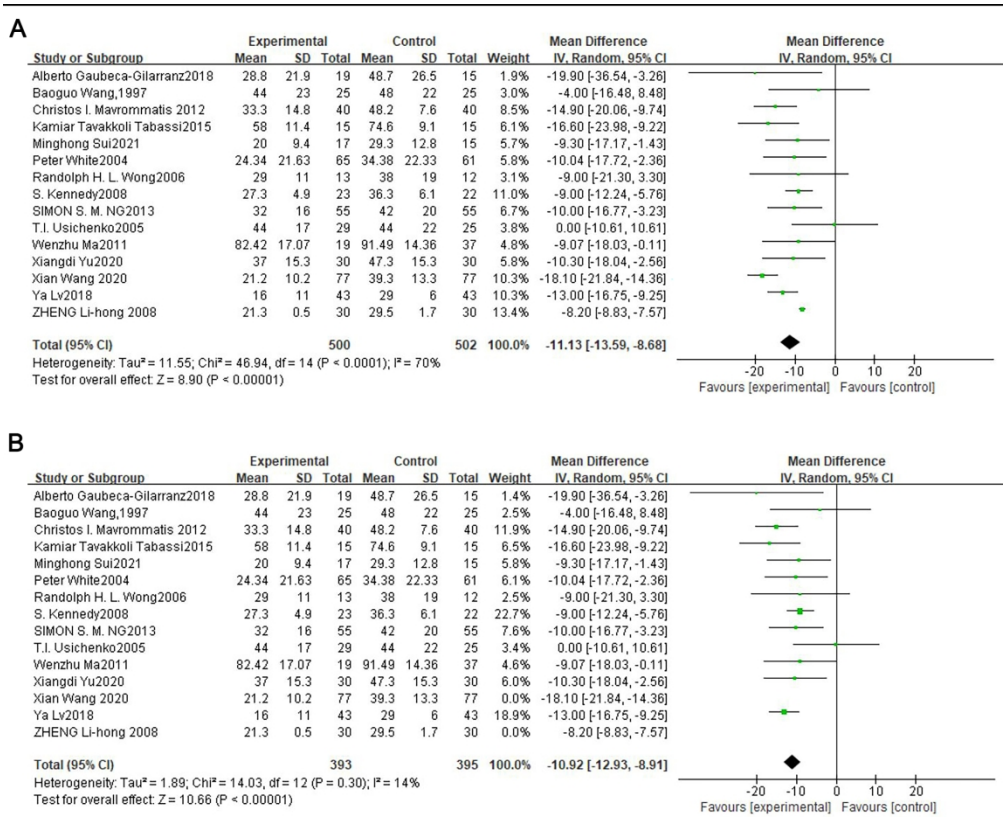

Figure3

199x162mm (300 x 300 DPI)

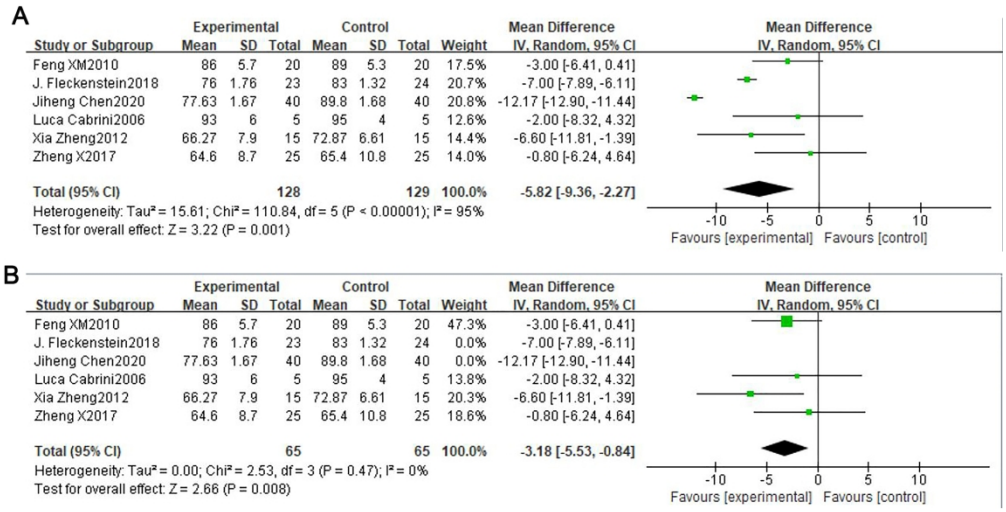

Figure4

199x101mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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

In your methods section, say that you used the SPIRITreporting 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,line1-4.
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.

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1; Page 18-19, line 444-449.
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 18, line 427-434.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 18, line 435-438.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 13, line 290-292.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 5, line 77-100.
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 6, line 106-107.
Objectives	#7	Specific objectives or hypotheses	Page 6, line 103-107.
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 5-6, line 101-103.

Methods: Participants, interventions, and outcomes			
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.
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. Page 8, line 159-164; Page 10, line 210-213;
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;
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;
Interventions: adherance	#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.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

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;
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, line183-187.
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;
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 14, line 330-331.
Methods: Assignment of interventions (for controlled trials)			
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.
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.

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8, line 169-175.
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8, line 179-181.
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 13, line 286-290.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 13-14, line309-320.
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10, line 207-209.
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 14, line 320
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	Page14-15, line

		statistical analysis plan can be found, if not in the protocol	332-349.
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page14, line 337-338.
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page14, line 337-338.
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page13, line 290-292.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page12, line 286-292.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 6-7, line127-129.

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
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.
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
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.
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
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
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
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
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a