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Dry cupping as an adjuvant treatment of individuals with severe pneumonia: study protocol for a placebo-controlled, randomised study

Wen Li,[1] Shuet Ling Chung ,[1] Ming Lei,[2] Xiaofang Yang,[2] Zhu Jin[1]

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WL and SLC contributed equally.

WL and SLC are joint first authors.

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[1]Department of Acupuncture, Moxibustion and Tuina, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai, China
[2]Department of Emergency Medical Center, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai, China

Correspondence to
Dr Zhu Jin;
112706196@qq.com

ABSTRACT

Background Severe pneumonia (SP) stands as one of the most prevalent critical illnesses encountered in clinical practice, characterised by its rapid onset and progression, numerous complications and elevated mortality rates. While modern medical interventions primarily focus on symptomatic management such as anti-infective therapy and mechanical ventilation, challenges including high drug resistance and suboptimal therapeutic outcomes for certain patients persist. Dry cupping as an ancient practice with over a millennium of clinical use in China is renowned for its convenience and perceived clinical efficacy in various illnesses. Nevertheless, the lack of well-designed studies assessing its effects remains a notable gap in the literature. This protocol describes a placebo-controlled, randomised, single-blind study to evaluate the efficacy and safety of dry cupping as an adjuvant treatment for SP.

Methods and analysis 66 patients diagnosed with SP, aged 18–80 years, will be randomly divided into two groups: intervention group, receiving 10 times of dry cupping treatment; control group, receiving placebo dry cupping therapy. Both applications are used in bilateral Fei Shu (BL13), Pi Shu (BL21) and Shen Shu (BL22) cupping. The application will be conducted once a day for 10 days. Participants will be assessed before treatment (D0), after the first intervention (D1), after the fifth intervention (D5) and after treatment ended (D10). The assessments include blood oxygen saturation, respiratory rate, traditional Chinese medicine symptom score, inflammatory response, mechanical ventilation time and oxygen condition.

Ethics and dissemination This protocol has been approved by the Ethics Committee of Shanghai Seventh People's Hospital (2023-7th-HIBR-070). The results of the study will be disseminated to participants through social networks and will be submitted to a peer-reviewed journal and scientific meetings.

Trial registration number ChiCTR2300076958.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of dry cupping to assist the treatment of severe pneumonia will not have any impact on conventional basic treatment, ensuring that patients will not have conflicts of interest and issues related to ethical principles.
⇒ This study is a placebo-controlled study, and information bias may be introduced if the patient understands the difference in treatment.
⇒ This study is not double blinded, which may introduce researcher bias.
⇒ Given the variability in drug dosages and treatment plans based on individual clinical contexts, this leads to uncertainties which may influence the outcome.

INTRODUCTION

Severe pneumonia (SP) is a prevalent and severe respiratory illness encountered in clinics. It mainly arises from lung infections caused by pathogenic microorganisms, which then followed by a series of critical clinical manifestations.[1] It is reported that around 450 million people worldwide contract pneumonia each year, about 4 million of them died from SP.[2] With the acceleration of population ageing, the prevalence rate of SP continues to rise. Considering its characteristics of rapid onset, high fatality rate and poor prognosis, raising awareness about this issue is crucial.

To date, the primary approaches in modern medicine for treating SP include anti-inflammatory medications, mechanical ventilation, hormone therapy, nutritional support and symptomatic treatment.[3] It is important to state that there is currently no specific targeted treatment for SP. Apart from that, the emergence of multidrug-resistant bacteria complicates clinical management, often rendering conventional treatments ineffective.[4] Therefore, there is a pressing need in seeking adjuvant treatment options to enhance the prognosis of SP. Traditional Chinese dry cupping therapy has a rich historical background. By applying mechanical or warm stimulation, a vacuum pressure is created during cupping, which stimulates subcutaneous capillaries and peripheral nerves. This treatment induces capillary dilation, leading to microruptures, further

promoting blood circulation and encouraging improved blood supply to the affected area.

From the perspective of traditional Chinese medicine (TCM), SP is categorised under 'wind-warming lung heat', typically addressed by clearing 'lung heat'. In this study, Back Shu points were primarily selected as the acupuncture points of focus, considering the ganglion segment correlation. The ganglion segment innervating the lung originated from T_1-T_5,[5] and acupoints within this segment have been historically used for the treatment of lung-related ailments, offering anatomical evidence for their distribution. Therefore, it is believed that applying dry cupping therapy at Back Shu points could significantly improve lung function, regulate cellular and humoral immunity, as well as alleviate bronchial smooth muscle contraction.[6]

Dry cupping is gaining recognition as a significant complementary and alternative medicine (CAM) therapy used globally. However, its efficacy remains a subject of controversy due to the scarcity of high-quality studies assessing its effects. This indicates that more clinical trials with high methodological quality are necessary to elucidate its impact on clinical outcomes in patients with SP. Consequently, a placebo-controlled, randomised clinical trial has been devised to comprehensively evaluate the safety and efficacy of dry cupping as an adjuvant treatment for SP, and these findings may provide valuable insights for clinicians and researchers, aiding in the optimisation of dry cupping in the management of SP.

Therefore, this randomised controlled trial (RCT) aims to evaluate the efficacy of dry cupping as an adjunct to the treatment of SP. The hypothesis of this study is that patients with SP receiving dry cupping therapy will exhibit better improvements in blood oxygen saturation, respiratory rate (RR), TCM symptom score, inflammatory response, mechanical ventilation time and oxygen condition compared with those who receive placebo therapy.

METHODS

Ethics statements

Ethical approval for this study has been granted by the Ethics Committee of Shanghai Seventh People's Hospital (2023-7th-HIBR-070) on 19 October 2023. This clinical study plan based on the Chinese Clinical Trial Registry (https://www.chictr.org.cn/) (ChiCTR2300076958) was registered on 25 October 2023.

Study design and population

This study is a placebo-controlled, randomised clinical trial which aims to investigate the efficacy and safety of dry cupping in the adjuvant treatment of SP. The target population will include patients with SP who meet the inclusion criteria for this study. The study will be conducted in the intensive care ward of Shanghai Seventh People's Hospital.

To ensure the integrity of blinding, only patients with SP with no prior experience on dry cupping will be included in the study. This study will be conducted by an independent acupuncturist responsible for administering the dry cupping treatment, along with another intensive care physician to evaluate its efficacy.

Emergency unblinding only occurs when the vital signs of participants show critical value. Emergency measures should be taken immediately by the medical workers of intensive care ward of the hospital.

This study was designed as a superiority trial with a level of significance set at α=0.05, a type II error (β) of 0.2 and a power of the test of 80%. The sample size was calculated based on similar studies,[7] with a 1:1 ratio between the intervention and control groups, and a dropout rate of 15% was considered. 66 patients with SP will be assigned to either intervention or control group and will undergo assessments on the 1st, 5th and 10th days of the treatment.

Participant recruitment

Participants will be recruited at the intensive care ward of Shanghai Seventh People's Hospital. The study will be explained to participants or their guardians by their attending physicians, and written informed consent will be obtained from those who are willing to participate.

Inclusion criteria

- Individuals with SP who meet the definition of Infectious Disease Society of America/American Thoracic Society.[8]
- Individuals aged 18 years or older but under 80 years of age, male or female.
- Individuals who agree to fully cooperate and undergo treatment on a regular basis and agree to signing the informed consent. (In reference to this, the family members of the patient shall step in and decide on behalf of the patient, if the patient is unresponsive or physically unable to decide on their own.)

Exclusion criteria

- Individuals have contraindications to prone position, such as facial or pelvic fractures, spinal injury or poor stability, multiple injuries and abdominal trauma.
- Individuals who cannot receive cupping treatment for various reasons, such as pneumothorax, airway injury, local skin injury or skin disease.
- Individuals with severe allergies.
- Individuals with mental illness, pulmonary encephalopathy, in coma, shock, or with serious heart, brain, liver, kidney and other complications such as malignant tumours.
- Pregnant or lactating women or women planning for pregnancy.
- Individuals participating in other clinical trials.

Study protocol

Table 1 presents the comprehensive study schedule. Each participant will receive an explanation of the study protocol from a physician. Subsequently, they will be requested to provide informed consent by signing a consent form before proceeding with the treatment.

Table 1 Study schedule

	Study period			
	Screening period	Treatment phase		
Time points	Baseline	1st day	5th day	10th day
Enrolment				
General condition	√			
Clinical symptoms	√			
Medical history	√			
Fulfilling inclusion and exclusion criteria	√			
Sign informed consent	√			
Assessment				
Primary outcome				
Saturation of peripheral oxygen (SpO_2)	√	√	√	√
Respiratory rate (RR)	√	√	√	√
Secondary outcomes				
The TCM syndrome score	√			√
Infection-related index	√			√
Ventilator-related indicators	√			√
Blood gas analysis-related indicators	√			√
Record of adverse events		√	√	√
Compliance evaluation				√
Safety assessment				√

TCM, traditional Chinese medicine.

This study employs a simple randomisation method for assigning enrolled participants to either the treatment or control group during their initial visit. Initially, a series of random numbers will be generated using SPSS V.25.0 software. These numbers will then be printed on cards and the cards will be sealed in opaque envelopes. Eligible participants who agree to take part in the study will receive these envelopes. On receiving the envelope, participants will be allocated to either the treatment or control group, in accordance with the group assignment enclosed in the envelope, and will receive the corresponding intervention. After each treatment session, relevant data will be collected, and any adverse events (AE) will be closely monitored by the attending physician during each visit.

Intervention

A manual suction pump and six acrylic cups (Hwato brand, produced by Suzhou Medical Supplies Factory, China; registration licence number: Su Su appliance 20152003) will be needed for each group to apply the dry cupping technique. Both groups will receive dry cupping therapy applications for 8 min every day for 10 consecutive days. The cups will be fixed by means of adhesive tapes so that they do not fall. Participants will be divided into intervention group with dry cupping therapy and control group with placebo therapy.

In this study trial, dry cupping therapy is considered as an adjuvant therapy which does not interfere with the basic treatment of the patient. If symptoms remain, participants of both groups will receive conventional therapy by the medical workers of intensive care ward after the study period ends.

Intervention group (dry cupping therapy)

During the intervention period, the participants are required to lay prone on the hospital bed. The patient's head is tilted to one side with a nursing pillow, and pressure relief pillow placed under the head to ensure adequate height to keep the airway clear for suctioning. Next, several pillows are placed under the patient's chest, knees and lower legs to maintain functional position. After the point selection site was disinfected, six small disposable cups (with an inner diameter of about 3.4 cm) were located on the bilateral acupoints Fei Shu (BL13), Pi Shu (BL21) and Shen Shu (BL22), with two suctions on each cup pot (figure 1). The location of acupoints is referred to the national standard of the People's Republic of China 'Name and Location of Acupoints' (GB/T 12346-2006).[9] The treatment was performed once a day for 8 min for 10 consecutive days. Physicians will keep an eye on the patients during the treatment to prevent blistering and infection.

Control group (placebo therapy)

The same procedure will be performed as in the Intervention group (dry cupping therapy) section. However, the cups will be prepared with small holes <2 mm in diameter to release the pressure. Double-sided tapes will be used so that the cup pots do not fall off and lose contact with the skin (figure 2).[10]

Basic treatment

Basic treatment for patients with SP includes anti-infection measures, oxygen therapy or ventilator support, acid suppression, fluid rehydration, nutritional support and symptomatic treatment such as fever reduction, cough and phlegm management, alleviation of spasms and asthma symptoms.

Adverse events

Possible AEs related to dry cupping may include local reactions such as itching, blister formation, subcutaneous bruises, persistent pain and infection at the treatment site. Any significant AEs occurring between the time of

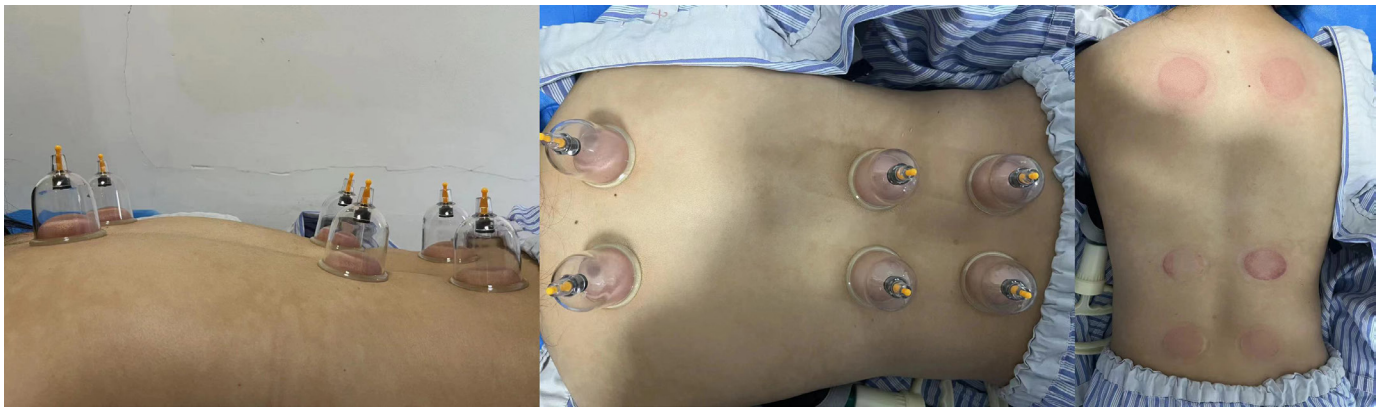

Figure 1 Dry cupping therapy on intervention group.

obtaining informed consent and the end of the trial will be recorded in the patients' medical records. If AEs occur, consultation with a dermatologist for appropriate treatment is recommended, and compensation for medical expenses should be provided.

Primary and secondary outcomes

Primary outcomes

To assess the efficacy of the measures, a specific index was applied. After finishing the treatment, it would be considered effective when the patients met the following criteria: (1) RR≤24 breaths per minute; (2) saturation of peripheral oxygen (SpO_2) ≥90% (table 2).

Secondary outcomes

- TCM symptom rating table: developed with reference to the Guiding Principles for Clinical Research of New Chinese Medicine published in 2002.
- Infection-related indicators: including leucocyte (white blood cell), C reactive protein, procalcitonin, tumour necrosis factor-alpha, interleukin-6 (IL-6) and interleukin-10 (IL-10).
- Ventilator-related indicators: including tidal volume, platform pressure, positive end-expiratory pressure and mechanical ventilation time.
- Blood gas analysis indicators: including partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), Oxygenation Index and lactic acid.

Data collection and management

In order to completely preserve the first-hand data of clinical trials, a study case report form (CRF) for this trial was specially designed. CRF is a source document for clinical trial subjects and should be kept at the hospital. Data will be collected by the appointed physician during the study. The laboratory department of the Seventh People's Hospital is fully in charge of the handling of the biological specimens of the test subjects. The laboratory department of the Seventh People's Hospital is accredited by ISO15189.

All study results and records will be kept strictly confidential and patients could only be identified by patient number, not by name. To protect the anonymity of participants, patient identification documents will be kept confidential. All data will be kept confidential and only the research team are able to access the information throughout the trial.

Data monitoring and auditing

The study will establish the Data and Safety Monitoring Board (DSMB), which will be composed of a three-member team, including acupuncturists, critical care physicians and statisticians. All members must declare any conflict of interest during the trial. The DSMB will monitor the progress of the trial and review the safety and quality of the data. A meeting will be held quarterly

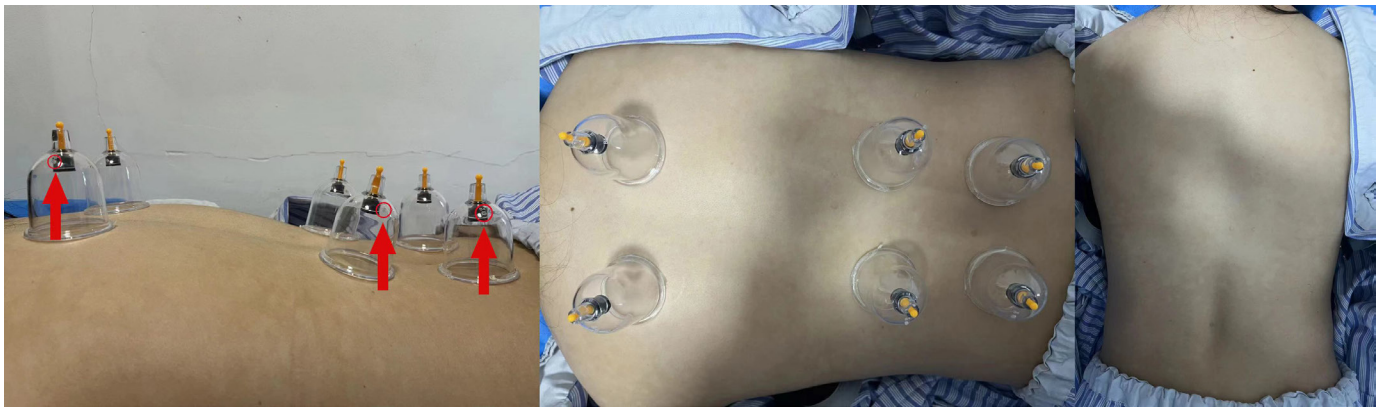

Figure 2 Placebo therapy on control group.

Table 2 Evaluation time of primary and secondary outcomes

Outcomes	Before treatment, D0	Immediately after the 1st intervention, D1	Immediately after the 5th intervention, D5	Immediately after the 10th intervention, D10
Primary outcomes				
SpO_2	√	√	√	√
RR	√	√	√	√
Secondary outcomes				
The TCM syndrome score	√			√
Infection-related index				
WBC, CRP, PCT, TNF-α, IL-6, IL-10	√			√
Ventilator-related indicators				
VT, platform pressure, PEEP, mechanical ventilation time	√			√
Blood gas analysis-related indicators				
PaO_2, $PaCO_2$, OI, Lac	√			√

CRP, C reactive protein; IL, interleukin; Lac, lactic acid; OI, Oxygenation Index; PCT, procalcitonin; PEEP, positive end-expiratory pressure; RR, respiratory rate; TCM, traditional Chinese medicine; TNF-α, tumour necrosis factor alpha; VT, tidal volume; WBC, white blood cell.

and participated by all the members to review any AEs and safety issues. All AEs and severe AEs will be reported to the main researchers and DSMB within 24 hours. The primary investigator will receive the interim results and make the final decision regarding study termination.

Statistical analyses

SPSS V.26.0 statistical software was used for statistical analysis, and the measurement data were tested for normality and homogeneity of variance first. Those who met the conditions were represented by mean and SD ($\bar{x} \pm s$), while those who did not were represented by median (quartile). If normal distribution and homogeneity of variance were met, the independent samples t-test was used for intergroup comparison. The paired t-test was used for intragroup comparison. Non-parametric test is adopted for those who do not meet the conditions. Counting data is represented by case number and compared by χ^2 test. Taking into account statistical inferences at multiple time points, repeated measures analysis of variance or mixed effects model would be used and the test level was set at α=0.05. P<0.05 was considered statistically significant.

Patient and public involvement

None.

DISCUSSION

In modern medicine, the treatment of SP primarily involves symptomatic approaches such as anti-inflammatory medication and mechanical ventilation, but certain patients exhibit high levels of drug resistance while some medications show limited therapeutic efficacy,[11] and the clinical fatality rate remains elevated, and achieving satisfactory outcomes as proven challenging. Therefore, there is an increasing concern regarding the current combinations of CAM in modern medical practice. Cupping is a form of CAM that has existed for thousands of years in various civilisations. It plays a unique role in relieving symptoms caused by lung diseases including pneumonia and bronchial asthma. Studies have found that cupping therapy can reduce the levels of serum inflammatory factors IL-1β and IL-25, and thereby reducing inflammation.[12] In addition, cupping therapy can be applied through either mechanical or warm stimulation. The formation of vacuum negative pressure stimulates the subcutaneous capillaries and peripheral nerves, leading to capillary dilation and subsequent minor bleeding, enhancing blood circulation, which facilitates improved local blood supply.[13] Cupping therapy, as an auxiliary treatment, is gradually being applied in acute and severe respiratory diseases. Clinical studies have shown that patients with COVID-19 with acute respiratory distress syndrome (ARDS) who undergo posterior thoracic cupping therapy 21 times experience improvements in symptoms including cough, breathlessness, chest tightness and SpO_2 levels. Notably, these patients did not require mechanical ventilation after discharge, indicating that integrating cupping therapy with conventional treatment may offer a favourable prognosis for individuals with acute respiratory conditions.[14] Although the mechanism of cupping therapy for SP remains unclear, there are indications that cupping therapy may improve lung function and inflammatory cytokine levels in patients with SP. The combined effect of conventional treatment with cupping therapy shows promise, yet further rigorous clinical trials are needed to fully demonstrate its effectiveness.

Currently, only small-scale clinical studies have been conducted on cupping therapy for pneumonia. In addition to conventional basic treatment, it is mostly combined with TCM and acupuncture, and no relevant clinical studies have been conducted on SP. Relevant RCT studies were not blinded, and most of them lacked placebo groups as control.[15–17] Therefore, RCTs with large sample sizes are needed to evaluate the efficacy and possible adverse outcomes of dry cupping therapy as an adjunctive treatment for SP.

This study will be the first placebo-controlled, randomised trial examining the efficacy of dry cupping as an adjunctive therapy. It offers several notable advantages. First, by employing a placebo control, it aims to mitigate the placebo effect, minimise bias and accurately determine the clinical efficacy of dry cupping in treating SP. Second, the integration of dry cupping alongside conventional basic treatment ensures that patients will not encounter conflicts of interest or ethical concerns, safeguarding the integrity of the study.

Some limitations are expected in this study. First, even though it is a placebo-controlled study, information bias may be introduced if the patient understands the difference in treatment. However, we have controlled participants' expectations by excluding those who have experienced dry cupping, plus offering a sham treatment similar to the actual procedure. Furthermore, this trial is not double blinded, which may lead to researcher bias. Finally, there is no standardised interventional protocol for the application of cupping therapy in SP. Given the variability in drug dosages and treatment plans based on individual clinical contexts, this may lead to the risk of bias.

There exists a lack of consensus regarding the utilisation of dry cupping therapy in patients with SP, nor is there sufficient evidence for the effectiveness of this technique in this population. Therefore, it is believed that this protocol will provide the basis for new research on dry cupping-assisted treatment of SP.

X Shuet Ling Chung @sharyn227

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Contributors Conceptualisation: WL, ZJ. Project implementation: WL. Data curation: SLC, XY. Formal analysis: SLC. Project administration: WL, ZJ. Resources: SLC. Supervision: ML. Writing—original draft: WL, SLC. Writing—review and editing: WL, SLC, XY, ML, ZJ.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Shuet Ling Chung http://orcid.org/0009-0007-7386-7173

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