

# Acupuncture as Adjunctive Therapy for Acute Renal Colic Caused by Urinary Calculi: Study Protocol for a Randomized Controlled Trial

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## Study protocol

**Keywords:** Acupuncture, Acute renal colic, Urinary calculi, Randomized controlled trial, sham acupuncture

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# Abstract

## Background

Acute renal colic caused by urinary calculi (ARCUC) has a considerable impact on quality of life. Acupuncture might be a potential treatment option. However, the evidence is limited. We will conduct this trial to evaluate the efficacy and safety of acupuncture as adjunctive treatment to diclofenac for ARCUC.

## Methods/design

A total of 80 eligible patients who are diagnosed of urinary stone renal colic will be randomly allocated to the acupuncture group or the sham acupuncture group. Each patient will receive 1 session of acupuncture or sham acupuncture. The primary outcome will be the response rate of patients achieving a reduction of >50% on visual analogue score (VAS) from baseline to 10 minutes after treatment. Secondary outcomes will include the VAS, remedial analgesia, re-visit and admission rate, blinding assessment, credibility and expectancy, and adverse event. All patients who receive randomization will be included in the intent-to-treat analysis.

## Discussion

The finding of this trial will provide evidence on the efficacy and safety of acupuncture for treatment of ARCUC. The results of this study will be published in peer-reviewed journals.

## Trial registration number

ChiCTR 1900025202. Registered on 16 August 2019. (<http://www.chictr.org.cn/showproj.aspx?proj=40496>)

# Background

Acute renal colic caused by urinary calculi (ARCUC) is described as acute unbearable paroxysmal pain in the lower back or upper abdomen, with or without hematuria, nausea, and vomiting. [1] Urinary stone disease was increasingly prevalent, with a lifetime risk of about 12% in men and 6% in women. [2] The prevalence of kidney stones in China was 6.4% (6.5% in men and 5.1% in women). [3] In the USA, more than one million patients visit the emergency department for the ARCUC every year. [4] It is described as one of the worst pains a patient could have and has a considerable impact on quality of life.

Pain relief is the primary goal in the management of patients with ARCUC. [1] NSAIDs offer effective sustained analgesia for ARCUC in the emergency department [5] and result in a lower need for rescue analgesia. [6] The 2017 update of the European Association of Urology (EAU) guidelines recommends NSAIDs as the first-line analgesic. [1] However, its clinical application is partly limited for the increased risk of major coronary events which increase with dose and duration. [7, 8] Furthermore, the onset time of NSAIDs is relatively slow, with the time to peak plasma concentration of 10–30 minutes [9].

Acupuncture is a complementary therapy from traditional Chinese medicine, which has the advantages of quick analgesia [10]. A meta-analysis suggested that acupuncture may be a potential therapy for ARCUC. [11] However, to our knowledge, there is no randomized controlled trial (RCT) to measure the efficacy of acupuncture as adjunctive treatment to NSAIDs for ARCUC. This randomized, participant-blind, sham-controlled trial is designed to evaluate the efficacy and safety of acupuncture as adjunctive treatment to diclofenac for ARCUC.

## Methods/design

### Study design

This study is a single-center, randomized, participant-blind, sham-controlled trial. Each participant will receive one session of acupuncture or sham acupuncture and be followed up for one week after treatment. The current protocol (version v1.0, 2019.4.21) has been approved by the ethics committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ER.03.03-V1.04) and registered with Chinese Clinical Trial Registry (ChiCTR 1900025202; registration date: 16 August 2019) before recruiting the first participant. Figure 1 shows the flow diagram of the study. The study is guided by the Declaration of Helsinki and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Additional file 1). [12]

### Patient recruitment

Participants who are diagnosed as ARCUC according to the guideline of European Association of Urology will be recruited at Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University. [1] The recruitment strategy will primarily contain advertisements on hospital social Internet media (WeChat), outpatient clinics, and the emergency room. Written informed consent will be provided by each patient through research assistant before randomization.

#### Inclusion criteria

1. Diagnosed as ARCUC according to the guideline of European Association of Urology (2017) [1]
2. Aged 18–75 years (either sex)
3. Pain intensity of 4 or more out of 10 on a visual analogue scale (VAS) [13]
4. Written informed consent

#### Exclusion criteria

1. Use of any analgesia in the last 6 hours
2. Allergic to diclofenac sodium, morphine, or anisodamine; history of asthma, urticaria or allergic rhinitis ascribed to acetylsalicylic acid or other drugs containing prostaglandin synthase inhibitors
3. Congestive heart failure, acute ischemic heart disease, or peripheral vascular disease; acute cerebrovascular disease, increased intracranial pressure; renal or liver failure
4. Active digestive ulcer, pyloric obstruction, or intestinal obstruction

5. Blood system diseases: such as hemophilia, coagulation disorders in patients; Thrombocytopenia ( $< 50 \times 10^9/L$ ); using anticoagulants
6. Glaucoma, elevated intraocular pressure
7. Serious adverse reactions to acupuncture; skin infection at acupuncture site
8. History of mental illness or substance abuse, or have severe cognitive impairment
9. Pregnant or lactating.

## Randomization, allocation concealment and masking

Eighty eligible patients will be randomly assigned to the acupuncture group or the sham acupuncture group in a 1:1 ratio. The blocked randomization sequence will be computer-generated with the SAS 9.4 software by an independent professional statistician (Li-Qiong Wang, Beijing University of Chinese Medicine), who is not involved in the implementation and statistical analysis of the trial. The sealed envelopes will be numbered in sequential order from 1 to 80 to hide the group assignments and be saved by a research assistant who does not take part in enrolling patients. When eligible patients are enrolled into the trial, envelopes will be successively opened by the clinical research coordinators who are responsible for enrolling the patients. Due to the responsibility of providing acupuncture and sham acupuncture, the acupuncturists will not be masked. Patients in the two acupuncture groups will be treated in a single treatment room and be blinded to which acupuncture method they would receive. In addition, outcome assessors, and statisticians who perform the statistical analyses will be blinded. The group assignments will be revealed after the statistical analysis is completed.

## Interventions

Patients in both acupuncture group and sham acupuncture group will receive 50 mg/2 mL diclofenac sodium intramuscular injection after randomization (Guangdong Bangmin Pharmaceutical Co, LTD). Meanwhile, acupuncture will be performed by the licensed doctors of traditional Chinese medicine who have been trained how to locate acupoints and non-acupoints, puncture, and manipulate needles before the trial. Sterile disposable acupuncture needles (length: 40 mm, diameter: 0.3 mm; Hwato, Suzhou, China) will be used. Both acupuncture and sham acupuncture treatment will only consist of 1 session treatment with 30 minutes. Needles will be removed if the patients suffer from any adverse events (AEs). Patients will receive 0.1 mg/kg intravenous morphine (Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co, LTD) and 10 mg intramuscular racanisodamine (Tianjin KingYork Pharmaceutical Co, LTD) if they report the severity of pain more than 8 points on the VAS after puncturing the needles. No additional intravenous fluid will be administered in the first 60 minutes after administration of the diclofenac sodium.

## Acupuncture

Patients allocated to the acupuncture group will be punctured at the pre-specified acupoints. Based on the clinical experience, bilateral Yaotongdian (EX-UE 7) will be used. According to the National standard of the People's Republic of China, EX-UE 7 will contain two points on the dorsum of the hand. The one is

between the second and the third metacarpal bones, and the other is between the fourth and the fifth metacarpal bones. These two points are of the same distance to the metacarpophalangeal joints and the transverse crease of the wrist. The localization of EX-UE 7 is exhibited in Fig. 2. Manipulations of twirling, lifting, and thrusting will be performed on all needles for at least 30 s to reach De qi (a compositional sensation including soreness, numbness, distention, and heaviness), which is believed to be an essential component for acupuncture efficacy.

## **Sham acupuncture**

A superficial skin penetration (1–4 mm in depth) at non-acupoints will be performed in the sham acupuncture group, without needle manipulation for De qi. Based on the search and analyses of traditional Chinese medicine reference books and acupuncture modern articles, the acupoints with effects on alleviating ARCUC or pain have been screened. After excluding these acupoints, 16 points without effects on ARCUC and pain are extracted and the locations 3 mm apart from these 16 acupoints are defined as non-acupoints, which are used in the sham acupuncture group. The locations of these non-acupoints are shown in Table 1 and Fig. 2. The 16 non-acupoints will be randomly assigned to 8 subgroups and will be recorded in predetermined computer-made randomization sealed envelopes. Each subgroup has bilateral 2 non-acupoints on the arms. The patients in the sham acupuncture group will be assigned into 1 of these 8 subgroups.

Table 1  
Locations of non-acupoints in the sham acupuncture group

Subgroup	Non-Acupoints	Locations
1	NA 1	3 mm lateral to the Shanglian (LI9) horizontally
	NA 3	3 mm lateral to the Pianli (LI6) horizontally
2	NA 4	3 mm lateral to the Sidu (TE9) horizontally
	NA 16	3 mm lateral to the Yinxi (HT6) horizontally
3	NA 6	3 mm lateral to the Zhigou (TE6) horizontally
	NA 8	3 mm lateral to the Kongzui (LU6) horizontally
4	NA 12	3 mm lateral to the Jianshi (PC5) horizontally
	NA 2	3 mm lateral to the Xialian (LI8) horizontally
5	NA 7	3 mm lateral to the Zhizheng (SI7) horizontally
	NA 11	3 mm lateral to the Erbai (EX-UE2) horizontally
6	NA 5	3 mm lateral to the Sanyangluo (TE8) horizontally
	NA 13	3 mm lateral to the Jingqu (LU8) horizontally
7	NA 9	3 mm lateral to the Ximen (PC4) horizontally
	NA 15	3 mm lateral to the Tongli (HT5) horizontally
8	NA 14	3 mm lateral to the Lingdao (HT4) horizontally
	NA 10	3 mm internal to the Erbai (EX-UE2) horizontally
NA, non-Acupoint.		

## Outcomes

### Primary outcome

The primary outcome will be the response rate after 10 minutes of the puncturing the needles, which is defined as the proportion of participants whose pain score on VAS reduces at least 50% compared with baseline. [5]

### Secondary outcomes

**Total pain** The total pain will be defined by the area under the curve during the 60 minutes after puncturing the needles. [14] The pain will be assessed using a VAS [13] with scores ranging from 0 to 10 after 0, 1, 5, 10, 15, 20, 30, 45, and 60 minutes of the puncturing the needles. The bigger of the area under the curve indicate worse pain.

**Response rate at other times** The proportion of participants achieving significant pain reduction will also be measured after 1, 5, 15, 20, 30, 45, and 60 minutes of the puncturing the needles.

**Remedial analgesia** The number of patients who receive intravenous morphine and intramuscular racanisodamine will be recorded after 60 minutes of the puncturing the needles.

**Re-visit and admission rate** The numbers of patients who re-visit the emergency department or are hospitalized will be evaluated during 72 hours after puncturing the needles.

**Blinding assessment** All patients will be asked to guess whether they receive acupuncture or sham acupuncture after acupuncture treatment to measure the patient-blinding effects.

**Credibility and expectancy** The Credibility and expectancy of patients will be assessed using the Credibility/Expectancy Questionnaire [15] after removing the needles. Items will be converted to Z scores before averaging, and the scale has a mean of 0.0 (SD, 1.0). The Z score is negative when the credibility/expectancy is below the mean and positive when it is above the mean.

**Adverse events** All adverse events will be recorded by outcome assessors during 7 days after treatment. Based on the potential relationship between needling and adverse events, adverse events will be categorized as treatment-related or not.

The schedule of enrolment, intervention, and assessments is shown in Fig. 3.

## Quality control

Both paper files and electronic documents will be preserved for at least 5 years after publication. If readers have any questions, they can contact the corresponding author for access to the original data. Patient information will remain anonymous, including name, ID number and telephone number. The protocol will be reviewed and revised by experts in acupuncture, emergency, urinary surgery, methodology and statistics. We will perform a pre-specified standard operating procedure, which includes screening patients, improve relevant inspection, intramuscular injection of diclofenac, acupuncture, filling out the CRF, assessing outcomes and data management. On-site monitoring will be adopted in this trial per three months. The ethics committee of Beijing University of Chinese medicine will audit trial conduct per 12 months.

## Sample size

Based on the previous literature [16] and our clinical experience, the response rates in the acupuncture group and sham acupuncture group are expected to be 70% and 40%, respectively. A sample size of 80 patients (40 in each group) is estimated to have at least 80% power to detect difference between groups at a 2-sided significance level of 5% based on the primary outcome. Because there is only one session of acupuncture treatment and almost no shedding, no loss to follow-up is considered.

## Statistical analysis

Patients' baseline characteristics will be summarized based on groups. Continuous variables will be described using the mean (standard deviation), or the median (interquartile range) if the normality assumption is violated. Student's t test or Wilcoxon rank sum test (if normality is violated) will be used for comparison of continuous variables among the two groups. Categorical variables will be described using the frequency (percentage) and compared using the chi-squared test.

For the primary comparison, the chi-squared test will be used for the response rate (the proportion of participants whose pain reduced  $\geq 50\%$  compared with baseline). For the secondary outcomes, Student's t test, chi-squared test, Fisher's exact test or the Wilcoxon rank sum test will be used to test the difference of the outcomes including the total pain, remedial analgesia, re-visit and admission rate, blinding assessment, credibility and expectancy and adverse events, between groups according to the distribution of variables. There is no interim analysis or additional analysis in this trial.

All efficacy analyses will be performed using the intention-to-treat set, which includes all randomized patients. Missing data will be dealt with the last observation carried forward (LOCF). All analyses will be performed using SPSS version 23.0 (IBM SPSS Statistics, New York, USA). The level of significance will be established at  $\alpha < 0.05$  with a two-sided test.

## Discussion

ARCUC is one of the worst pains a patient could experience and causes considerable burden for the patients and the society. This trial will evaluate the efficacy of acupuncture in improving the symptoms of ARCUC compared with sham acupuncture.

The effect of NSAIDs has been confirmed by recent meta-analysis. [6] Thus, it is recommended as first-line drugs by international guidelines. [1, 17] However, its application is partly limited for the relatively slow onset time. Previous trial carried out by Lee YH et al suggested that acupuncture had a more rapid analgesic onset compared with Avafortan ( $3.14 \pm 2.88$  minutes versus  $15.44 \pm 7.55$  minutes). [18] Kaynar M's study also found similar phenomenon in comparing acupuncture with diclofenac. [19] Furthermore, the analgesic effect of diclofenac only last about 7 hours based on its half-life elimination of 1.4 hours for injection. [9] Interestingly, the persistence of the analgesic effects of acupuncture was found by an individual patient data meta-Analysis. [20] Approximately 90% of the benefit of acupuncture would be sustained at 12 months. Combining acupuncture with NSAIDs may be an optional strategy for NSAIDs.

This trial meets the methodological demand for adequate randomization, allocation concealment, and blinding of patients, outcome assessors and statisticians. Although it is difficult to set a psychologically credible yet physiologically inert control in acupuncture study, superficial insertion at non-acupoints is the most commonly used approach for administering sham treatments. [21] Moreover, all participants will be asked to guess which treatment they have received to test the patient-blinding effects. Blinding patients to interventions is more important, especially when the primary outcome is subjective, such as alleviation of pain. To avoid effects on ARCUC as far as possible, we searched points without effect on ARCUC from both ancient and modern literature. This method of selecting sham points can be seen in Alecrim. [22]

There are 16 non-points, but only 2 non-points will be used to each patient in sham acupuncture group. This process of confirming non-points could further eliminate potential effects on ARCUC. After that, the prescription of acupuncture only includes one acupoint, which is very suitable for application in the emergency department due to its simplicity of operator.

This trial has limitations. First, the acupuncturists will not be masked due to the responsibility of providing the intervention. However, the patients and outcome assessors will be blinded to reduce the bias for the subjective symptom. Second, because this study is a single-center trial, the generalization of results to other medical facilities is unknown. At the end of this trial, we hope the results will provide more reliable evidence on acupuncture as an adjunctive therapy for ARCUC.

## **Trial status**

Protocol: version 1.0, 21 April 2019

Date opened to recruitment: 18 March 2020

Expected recruitment closure: 31 March 2021

## **Abbreviations**

ARCUC

Acute renal colic caused by urinary calculi; AE:Adverse events; EAU:European Association of Urology; LOCF:Last observation carried forward; NSAIDs:Nonsteroidal anti-inflammatory drugs; RCT:Randomized controlled trial; SPIRIT:Standard Protocol Items:Recommendations for Interventional Trials; VAS:Visual analogue scale.

## **Declarations**

### **Acknowledgements**

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### **Availability of data and materials**

The corresponding authors will have access to the final trial dataset. All of the individual participant data collected during the trial will be available after deidentification for anyone who wishes to access the data immediately following publication by contact the corresponding authors.

## Contributors

YC conceived of the study. YC, BLL, ZCQ, and CZL initiated the study design. YC and JFT drafted this manuscript. JFT, GXS, LQW, and BL drew up the statistical plan. YC, LCJ, WHY, and XLP helped with its implementation. YC and ZCQ sought the funding. All authors contributed to the refinement of the study protocol and approved the final manuscript.

## Ethics approval and consent to participate

This trial (version v1.0, 2019.4.21) has been approved by the ethics committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ER.03.03-V1.04). Written informed consent will be obtained from patients before randomization. If we have important changes to the protocol, the principal investigator will notify the center and that a copy of the revised protocol will be sent to the principal investigator to add to the Investigator Site File. What is more, we will also update the protocol in the clinical trial registry if there is any change. Any deviations from the protocol will be fully documented using a breach report form.

## Consent for publication

None declared.

## Competing interests

None declared.

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## Figures

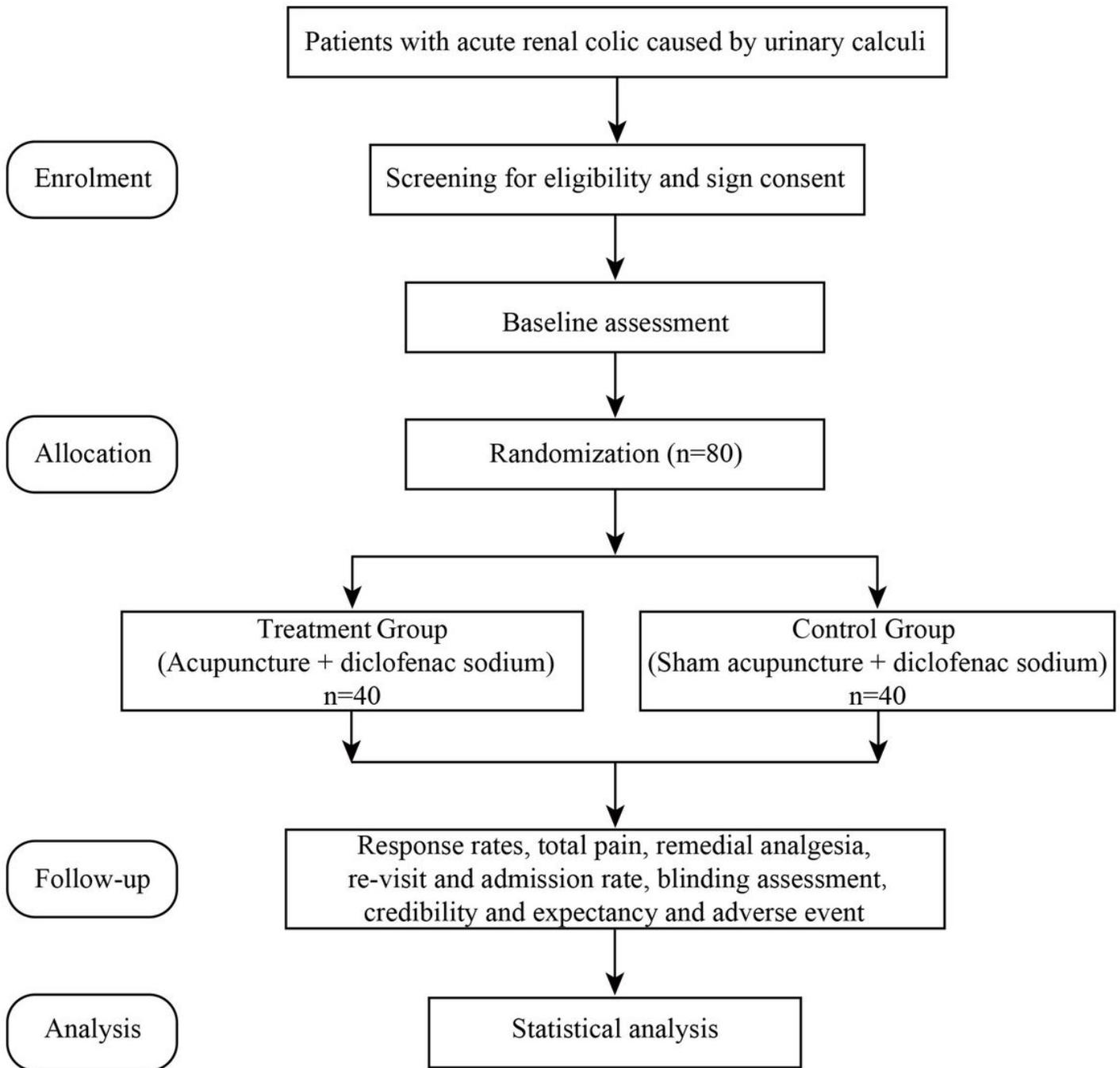
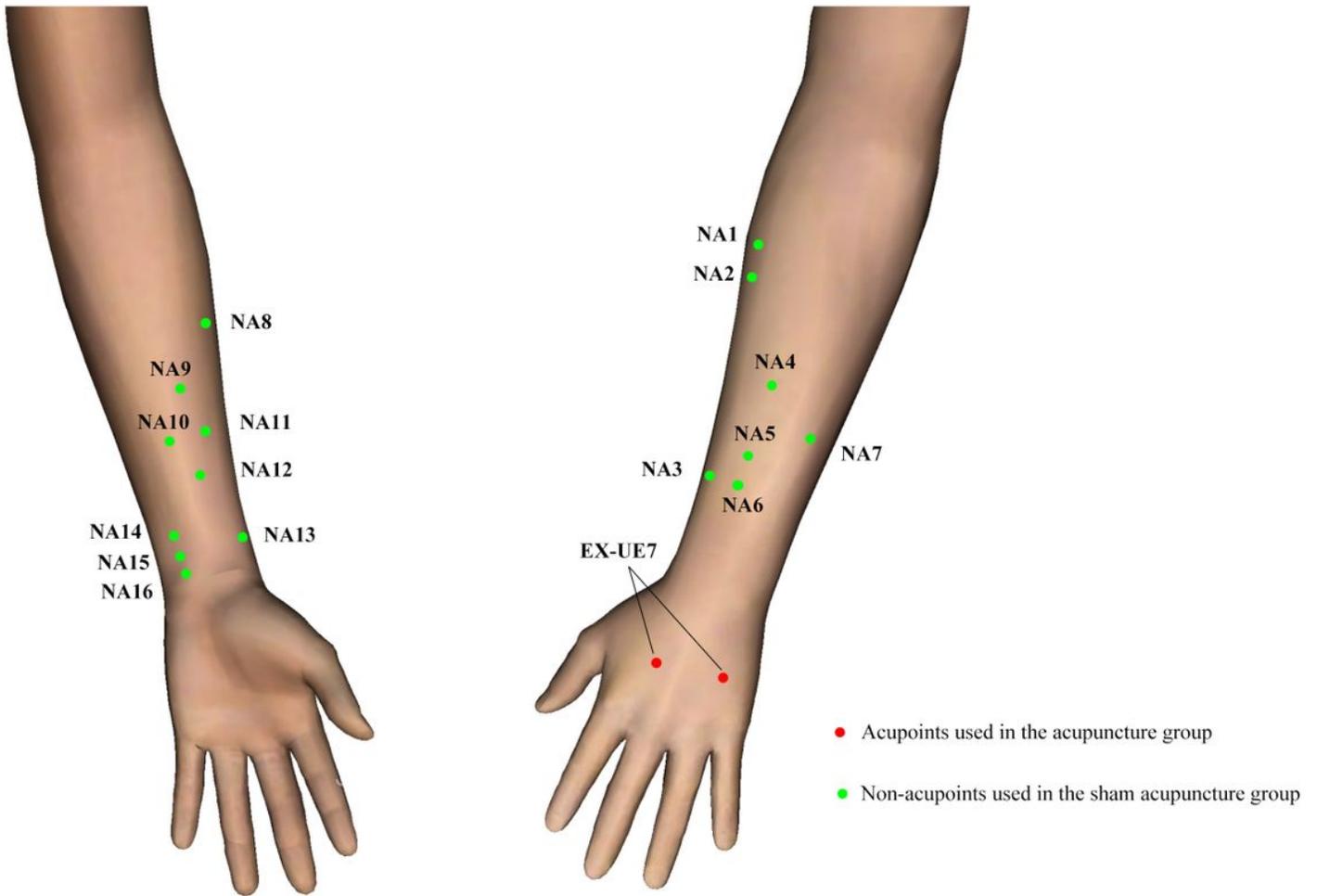


Figure 1

Flow diagram



**Figure 2**

Locations of acupoints and non-acupoints Red points are the acupoints used in the acupuncture group; green points are the non-acupoints used in the sham acupuncture group. The 16 non-acupoints will be randomly assigned to 8 subgroups. The patients in the sham acupuncture group will be assigned into 1 of these 8 subgroups and the 2 non-acupoints in this subgroup will be used on this patient in the whole treatment period. NA, non-acupoint.

TIME POINT	STUDY PERIOD												
	Enrolment	Allocation	Post-allocation									Closeout	
		0	1 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min	3 days	7 days	
ENROLLMENT:													
[Eligibility screen]	×												
[Informed consent]	×												
[Randomization]		×											
INTERVENTION:													
[Acupuncture]			◆—————◆										
[Sham acupuncture]			◆—————◆										
ASSESSMENTS:													
[Response rate]			×	×	×	×	×	×	×	×			
[Total pain]		×	×	×	×	×	×	×	×	×			
[Remedial analgesia]										×			
[Re-visit and admission rate]											×		
[Blinding assessment]								×					
[Credibility and expectancy]								×					
[Adverse events]												×	

**Figure 3**

Schedule of enrollment, intervention and assessments of this study protocol Min, minutes.