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Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial

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ABSTRACT

Introduction

Electroacupuncture at 'four sacral points', also known as electrical pudendal nerve stimulation therapy, combines the advantages of pudendal nerve neuromodulation (PNM) and the technique of deep insertion of long acupuncture needles. It has been used to treat stress urinary incontinence, female urgency-frequency syndrome, idiopathic urgency urinary incontinence, and neurological bladders in previous studies. Here we describe the protocol for a randomized controlled trial for evaluation of the efficacy and safety of electroacupuncture at 'four sacral points' for the management of urinary incontinence after stroke.

Methods and Analysis

This is an open-label randomized controlled trial with blinded assessments and analyses. A total of 140 eligible patients will be randomly allocated to two groups. The treatment group (n = 70) will receive electroacupuncture at 'four sacral points' along with routine medical care, while the control group will receive conventional electroacupuncture along with routine medical care. Twenty treatment sessions will occur over a period of 4 weeks. The primary outcome measures will be the self-recorded findings in an incontinent episode diary and the findings of the 24-hour pad test at baseline and at 4 weeks after baseline. The secondary outcome measures will be the International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) score and the Barthel Activities of Daily Living Index (Barthel ADL Index) score at baseline and at 4 and 28 weeks after baseline.

Ethics and dissemination: This protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (approval No. 2018-K-059-01). Written informed consent will be obtained from each participant. The results of the study will be published in peer-reviewed journals.

Trial registration number: ChiCTR-IOR-17012847

Strengths and limitations of this study

First pilot study to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the treatment of urinary incontinence after stroke.

Randomised clinical trial with pragmatic design, blinded assessment and analysis.

A novel acupuncture intervention versus conventional acupuncture for the treatment of urinary incontinence after stroke.

Lack of blinding of acupuncturists and participants due to the nature of acupuncture.

INTRODUCTION

The International Continence Society (ICS) has defined urinary incontinence (UI) as the involuntary loss of urine [1]. In a systematic review, a random-effects meta-analysis determined the prevalence of UI after stroke to be 23.6% [2]. Post-stroke UI may develop because of various reasons, although direct stroke-induced damage to the neuromicturition pathways is considered the most common cause. Typical symptoms include the involuntary leakage of urine accompanied or immediately preceded by urgency. Urodynamic evaluation often reveals uninhibited detrusor contraction [3]. Physical consequences include skin dermatitis and urinary tract infections, while psychological consequences include embarrassment and low self-esteem [4]. In addition, UI is a powerful prognostic indicator of survival and eventual functional dependence [5]. The most recent research on this topic demonstrated a higher mortality rate for stroke patients with UI (56.8%) than for stroke patients without UI (11.9%) [6]. Therefore, the management of UI after stroke is of great importance.

Evidence-based interventions for post-stroke UI are somewhat limited, but include behavioural and pharmacological interventions, as well as individually tailored structured management plans, or the aid of continence nurse specialists, in order to promote continence [3]. Trials of behavioural and pharmacological therapies have provided insufficient evidence to guide the management of post-stroke UI in adults [7]. Furthermore, side effect profiles and anticholinergic burden should be considered before medications are prescribed [8].

Neuromodulation therapies, which involve the electrical stimulation of target-specific nerves, are reportedly effective for overactive bladder (OAB) or urgency UI (UUI) [9]. Neuromodulation includes transvaginal or transanal electrical stimulation (TES), percutaneous tibial nerve stimulation (PTNS), sacral nerve neuromodulation (SNM), and pudendal nerve (PN) neuromodulation (PNM) [10]. Although TES is an easy procedure, it is not tolerated by several patients because of discomfort, mucosal injury, and the necessity for high-intensity stimulation to achieve an acceptable outcome [11]. SNM with the InterStim device (Medtronic, Minneapolis, MN) provides continuous stimulation and close nerve contact; thus, it is different from TES. The success rate is high [12, 13]; however, at least 20% of initially tested patients do not respond to the test procedure [14]. The disadvantages of SNM include the invasiveness of the procedure, the high cost of treatment, the high rate of revision surgery, the requirement for device replacement on battery exhaustion, and adverse events (pain and infection) [15, 16]. PN afferents play a particularly important role in the inhibition of the voiding reflex. Because SNM only excites a portion of PN afferents, direct PN stimulation may be more effective [10]. PNM with the Interstim device or the Bion device (selective PN stimulation) can be used to treat UUI refractory to SNM [10, 17, 18], although its disadvantages are similar to those of SNM

[10, 18]. PTNS with needle electrodes is minimally invasive, effective, easy to perform, and well tolerated [8]; however, its effect diminishes over time [15, 17].

According to the theory of traditional Chinese medicine (TCM), UI is primarily caused by kidney qi deficiency, which often causes bladder dysfunction in terms of urine control. Accordingly, the principle of acupuncture treatment for UI is to reinforce kidney qi and promote the recovery of bladder function [19]. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33 (Zhongliao), and BL 35 (Huiyang), are generally selected for the reinforcement of kidney qi and regulation of the bladder voiding function [20-22]. A literature review showed that acupuncture demonstrated more favourable effects than did antimuscarinic drugs for the treatment of OAB and alleviation of symptoms in some comparative trials [23]. In addition, acupuncture reportedly improved the quality of life (QoL) and urodynamic testing parameters in patients with OAB [23, 24]. In a randomized, double-blind, placebo-controlled study, electroacupuncture significantly increased the maximum cystometric capacity and bladder compliance, decreased the detrusor leak point pressure, alleviated lower urinary tract symptoms, and decreased the risk of upper urinary tract damage in patients with post-stroke detrusor overactivity [22]. However, high-quality clinical trials with appropriate inclusion criteria, sample size, control design, acupoint selection, depth of needle insertion, and efficacy and safety evaluations are necessary to properly evaluate the efficacy of acupuncture for the treatment of post-stroke UI [7, 25, 26].

On the basis of the theory of nerve stimulation, we developed electroacupuncture at 'four sacral points' [27, 28], also known as electroacupuncture neurostimulation therapy or electrical PN stimulation therapy. This approach involves the insertion of long needles at 'four sacral points,' with electricity to stimulate specific nerves under the sacral region [28, 29]. When it was first developed, this treatment was used to treat stress UI (SUI) in women, and radiographic evidence with simultaneous records of perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure, and pelvic floor surface electromyography have shown that it causes PN excitation [29]. In addition, it has been used for the treatment of female urgency-frequency syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological conditions [28, 30, 31]. The mechanism of action of electroacupuncture at 'four sacral points' for post-stroke UI can be explained by the modulation of reflex pathways at spinal or supraspinal levels [3]. Electrical stimulation of the afferent branches of the PN can induce strong inhibition of the micturition reflex and detrusor hyper-reflexia [10], resulting in the effective treatment of post-stroke UI [31, 32].

The effectiveness of post-stroke UI treatment using alternative medicine approaches is worthy of investigation in a well-designed study. To the best of our

knowledge, no randomized controlled trials (RCT) comparing the efficacy and safety of electroacupuncture at 'four sacral points' with those of conventional electroacupuncture for the treatment of post-stroke UI have been conducted. Here we describe a protocol for an RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the management of post-stroke UI.

METHODS AND ANALYSIS

Objectives

This is a protocol for an RCT designed to compare the efficacy and safety of electroacupuncture at 'four sacral points' with those of conventional electroacupuncture for the treatment of post-stroke UI.

Recruitment

This is a pragmatic RCT comparing electroacupuncture at 'four sacral points' with conventional electroacupuncture for the treatment of post-stroke UI. The research structure is shown in Figure 1. A total of 140 eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University according to the inclusion and exclusion criteria. At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form. This will be followed by baseline assessment and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks will follow the recruitment procedure.

Design

Randomization and allocation concealment

The randomization scheme has been created by the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University, where professionals used SPSS Statistics 22.0 to generate a random allocation sequence using a computer. Professionals involved in allocation will not be recruited in the study. The random allocation is strictly kept in an opaque envelope and is inaccessible to other research staff. After baseline assessment, the envelope will be opened by an independent staff member in the participant's presence, in order to determine the group assignment for that participant.

Blinding

Considering the nature of acupuncture, therapists and participants cannot be blinded to the treatment allocation. Data managers and statisticians will be blinded throughout the trial. Telephone interviewers who collect follow-up information will also be blinded. Data managers, statisticians, and telephone interviewers are restricted from

discussing the treatment allocations with each other. The therapists will not be permitted to communicate with any data managers, statisticians, or telephone interviewers. If an unblinding event occurs among data managers, statisticians, or telephone interviewers, the relevant work will be transferred to other appropriately blinded data managers, statisticians, or telephone interviewers.

Participants

Sample size

With reference to a similar study with 120 women (efficacy rate, 70.1%:45%), the sample size has been calculated, using PASS 11 software, as 120 patients for a power (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With consideration of the estimated dropout rate (15%), the total sample size will be 140 (70 in each group).

Inclusion criteria

1. Male or female patients aged 30–85 years
2. Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association [33] and the International Continence Society [34]
3. Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years
4. Stable vital signs, normal consciousness, and compliance with treatment
5. Refractoriness to medications (antimuscarinic agents)
6. Provision of written informed consent

Exclusion criteria

1. UI caused by other diseases such as Parkinson's disease, multiple sclerosis, spinal injury, or Alzheimer's disease
2. SUI or mixed UI
3. Urinary retention concomitant with UI
4. Urethral injury, lower urinary tract obstruction, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours
5. Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 [35]
6. Insufficiency of the heart, lungs, liver, and/or kidneys
7. Presence of an implantable electronic device

Elimination criteria

1. Inclusion despite non-fulfillment of the inclusion criteria
2. Lack of exclusion despite fulfilment of the exclusion criteria
3. Eligible participants who receive no interventions

Dropout criteria

1. Poor participant compliance
2. Serious adverse events (SAE), complications, or special physiological changes

necessitating discontinuation of the intervention

3. Voluntary dropout

Intervention

All participants will receive routine medical care for stroke recovery, including the control of blood pressure, blood sugar, and blood lipids and routine rehabilitation training. All of the study-related treatments will be provided by skilled acupuncturists who will strictly follow the detailed procedures for each group.

Standard operating procedure

1. Needle requirements

   Disposable sterile acupuncture needles in accordance with national standards within the validity period will be used.

2. Hand hygiene of the operator

   The operator is required to sterilize his or her hands with a sanitizer before the acupuncture procedure.

3. Sterilization of the acupuncture points

   Within a 5-cm diameter with the acupoint as the centre, sterilize the skin over the acupoints using a cotton swab dipped in 0.45%–0.55% povidone iodine or 75% ethanol.

4. Procedure

   Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'.

   a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected. The two upper points are located on either side of the sacrococcygeal joint, approximately 1 cm from the joint. The two lower points are located on either side of the tip of the coccyx, approximately 1 cm from the coccyx. Acupuncture will be performed at LI15 (Jiangyu), LI11 (Quchi), LI10 (Shousanli), SJ5 (Waiguan), and LI4 (Hegu) for participants with upper limb paralysis. For participants with lower limb paralysis, ST31 (Biguan), ST34 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia, with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang) for participants with facial paralysis and drooling.

   b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong Medical Apparatus Factory, Suzhou, China) measuring 0.40 × 100 mm will be inserted perpendicularly to a depth of 80–90 mm to induce a sensation referred to the urethra or anus via stimulation of the main trunk of the PN. At the lower sacral points, a needle measuring 0.40 × 100 or 0.40 × 125 mm will

be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm to induce a sensation referred to the urethra via stimulation of the perineal nerve (Figure 4 and Figure 5). Once the sensation is induced in the respective regions, two pairs of electrodes from the G6805-A electroacupuncture device (Shantou Medical equipment factory, Shantou, China) will be connected to the two ipsilaterally inserted needles, with the anode connected to the upper needle and the cathode connected to the lower needle. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be performed for 20 min during each treatment. PFM contraction around the urethra (often comfortable) must be maintained during the entire electrostimulation procedure. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

Control group: Participants in this group will receive conventional electroacupuncture.

a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao, both sides), corresponding to the conventional electroacupuncture treatment of UI. The point selection procedure for participants with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the same as that used for the treatment group.

b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao), a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the electrodes from the G6805-A electroacupuncture device will be connected to the needles at these points. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity that is tolerable by the participants. Electrostimulation will be performed for 20 min during each treatment. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

5. Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks).

Outcome measures

Primary outcome measures

1. The incontinent episode diary

The incontinent episode diary (table 1) will be used to derive the primary outcome measure. The number of incontinent episodes will be recorded by the participants

over a period of 3 days at baseline. A template will be provided for patient use. This data will be recorded again at the end of treatment.

Table 1 The incontinent episode diary

Name		Date			
Record every accidental loss of urine over 3 consecutive days with an X.					
Start at baseline and continue recording for 3 days					
Day 1		Day 2		Day 3	
eg X					

2. 24-hour pad test

The 24-hour pad test findings will be used as the other primary outcome measure. This test quantitatively assesses the amount of urine leakage for an individual with UI. At baseline and at the end of treatment, wet pads will be collected by the patient over a 24-hour period and stored in an airtight plastic bag. The equivalent number of dry pads will be placed in a similar plastic bag. Each bag will be weighed by the patient or brought into the clinic for weighing.

Secondary outcome measures

1. International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF)[36] (Table 2)

2. Barthel Activities of Daily Living Index (Barthel ADL Index) [37] (Table 3)

The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and psychometrically robust patient-completed questionnaire for evaluating the frequency and severity of UI in men and women and its impact on quality of life (QoL). The ICIQ-UI SF score ranges from 0 to 21 [38]. The Barthel ADL Index is a 10-item measure of activities of daily living (ADL) that is frequently used in clinical practice and as a trial outcome measure in stroke medicine [37]. It is used to assess baseline abilities to quantify functional changes, including UI, after rehabilitation in stroke patients.

The above outcome measures will be assessed at baseline and at 4 and 28 weeks after baseline.

Table 2 International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF)

1. Please write in your date of birth:	□□ □□ □□ date month year	
2. Are you	Female □ Male □	
3. How often do you leak urine? (Tick one box)		
	never	□ 0
	about once a week or less often	□ 1
	two or three times a week	□ 2
	about once a day	□ 3
	several times a day	□ 4
	all the time	□ 5
4. We would like to know how much urine you think leaks. How much urine do you usually leak (whether you wear protection or not)? (Tick one box)		
	None	□ 0
	a small amount	□ 2
	a moderate amount	□ 4
	a large amount	□ 6
5. Overall, how much does leaking urine interfere with your everyday life? Please ring a number between 0 (not at all) and 10 (a great deal) 0 1 2 3 4 5 6 7 8 9 10 not at all a great deal		
ICIQ score: sum scores 3+4+5	□□	
6. When does urine leak? (Please tick all that apply to you)		

	never – urine does not leak	□
	leaks before you can get to the toilet	□
	leaks when you cough or sneeze	□
	leaks when you are asleep	□
	leaks when you have finished urinating and are dressed	□
	leaks for no obvious reason	□
	leaks all the time	□

Table 3 Barthel Activities of Daily Living Index (Barthel ADL Index)

The Barthel Index		Patient Name Rater Name Date:
Activity		Score
Feeding	Unable	0
	Some help required (e.g., needs help cutting, spreading butter, etc. or requires a modified diet)	5
	Independent	10
Bathing	Dependent	0
	Independent (or in shower)	5
Grooming	Needs help with personal care	0
	Independent face/hair/teeth/shaving (implements provided)	5
Dressing	Dependent	0
	Needs help but can do at least half unaided	5
	Independent (including buttons, zips, laces, etc.)	10
Bowels	Incontinent or catheterized and unable to manage alone	0

	Occasional accident	5
	Continent	10
Bladder	Incontinent or catheterized and unable to manage alone	0
	Occasional accident	5
	Continent	10
Toilet use	Dependent	0
	Needs some help, but can do some things alone	5
	Independent (can get on and off, dress and wipe unassisted)	10
Transfer (bed to chair and back)	Unable, no sitting balance	0
	Major help (one or two people, physical), can sit	5
	Minor help (verbal or physical)	10
	Independent	15
Mobility (on level surfaces)	Immobile or <50 yards	0
	Wheelchair independent, including corners; >50 yards	5
	Walks with little help from one person (verbal or physical); >50 yards	10
	Independent (but may use an aid; e.g., walking stick); >50 yards	15
Stairs	Unable	0
	Needs help (verbal, carrying aid)	5
	Independent	10
	Total	

Adverse events (AEs)

An adverse event of acupuncture is defined as symptoms or diseases that are against the purpose of the treatment during or following the acupuncture treatment [39]. The research staff will record the blood pressure, heart rate, heart rhythm, and respiration rate and observe changes in the consciousness of all participants before and after the treatment. The description of AEs, time of occurrence, location of the reaction, level of severity, corresponding management, and the necessity for patient withdrawal from the trial will be recorded on the Case Report Forms (CRFs). AEs of acupuncture will be classified according to their location as local and systemic reactions.

Local reactions:

Subcutaneous haematoma
Minor bleeding on withdrawal of the needle
Subcutaneous bruise
Pain in the punctured region after treatment
Skin allergy in the punctured region after treatment
Local infection

Systemic reactions:

Acupuncture fainting
Abdominal distention
Dizziness or vertigo
Leg weakness
Muscle spasm
Systemic allergy
Systemic infection
Organ injury

Severe AEs are defined as symptoms or diseases that result in hospitalization or that prolong hospitalization, disability, a life-threatening situation, or even death [40]. Systemic infection and organ injury are two major AEs. Severe AEs will be reported to the Ethics Committee within 24 h. The Ethics Committee will provide medical suggestions for the research team and decide whether the patient should continue the ongoing treatment.

Data management, monitoring and auditing

A research assistant will record the baseline characteristics of all participants. Trained caregivers will record the frequency of UI and conduct the 24-hour pad test at baseline and at 4 weeks after baseline. A researcher who remains blinded to treatment group allocation will collect data regarding the frequency of UI and the weight of pads from the caregivers. The participants will also complete ICIQ-UI SF and the Barthel ADL Index at baseline and at 4 weeks after baseline. A blinded telephone interviewer will interview the participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at 28 weeks after baseline. All data will be recorded on the CRFs. For participants who discontinue treatment early, their data will also be

collected and analysed.

After the completion of the CRFs, two independent researchers blinded to the group allocation will separately input data into an Excel spreadsheet. Another independent supervisor will check the two datasets for consistency. If conflicting data entries are discovered, the supervisor will compare the datasets with the original CRFs and mark the modification on the CRFs. The principal investigator of the research team will protect the electronic documents with a password and create backups of all documents. The First Affiliated Hospital of Zhejiang Chinese Medical University will be responsible for the storage and management of all data.

The First Affiliated Hospital of Zhejiang Chinese Medical University will regularly monitor the study data and audit this study.

Statistical analysis

All statistical analyses will be performed by a statistician from the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University using SPSS Statistics 22.0. Continuous variables with a normal distribution will be expressed as means ± standard deviations (SDs). Continuous variables with a non-normal distribution or ordinal variables will be expressed as medians (with lower upper quartiles). Categorical variables will be summarized as counts and proportions. Continuous variables will be compared using Student's t-test (normal distribution) or the Wilcoxon signed rank test (abnormal distribution). Ordinal variables will be compared using the Wilcoxon signed rank test. The categorical variables will be compared using Fisher's exact test or the chi-square test. All reported P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A P-value of <0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

Research ethics approval

The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University has reviewed and approved this protocol (approval No. 2018-K-059-01). This study will adhere to the principles of the Declaration of Helsinki. This study will be conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University. Each participant will voluntarily sign written informed consent forms.

Confidentiality

All study participants will be given an identification number throughout the trial to assure confidentiality.

Dissemination

The results of this study will be published in open-access and peer-reviewed journals and presented at relevant conferences.

DISCUSSION

According to the present study protocol, in addition to electroacupuncture at 'four

sacral points' in the treatment group and conventional electroacupuncture in the control group, the same acupoints for other stroke symptoms will also be selected for both groups. Other stroke symptoms include unilateral limb weakness, facial paresis, dysphasia, and dysphagia [41]. In China, acupuncture has been a primary medical intervention for stroke [42]. In fact, not providing acupuncture therapy to a stroke patient is considered impractical.

Antimuscarinic agents are considered first-line drugs for neurogenic detrusor overactivity (NDO) [43]. However, because of their moderate efficacy and troublesome side effects, quite a few patients exhibit refractory disease [44]. According to the eligibility criteria, participants who are refractory to medication will be included in this RCT.

With regard to the outcome measures, the incontinent episode diary and 24-hour pad test will be used as objective measures to record the frequency of incontinence and the severity of urine loss. Patients will record their findings in the incontinent diary for only 3 days, because a longer recording period can lead to decreased patient compliance [45, 46]. Research suggests that repeatability for the pad test is better with a long-term test than with a short-term test; however, longer tests (i.e., 48 and 72 hours) have lower adherence than the standard 24-hour pad test [47]. Therefore, we will perform the 24-hour pad test for good reproducibility. Moreover, in order to improve adherence, pads used in the test will be provided at no cost to the trial participants and 50 Renminbi (RMB) will be offered to caregivers collecting the pads. The ICIQ-UI SF and Barthel ADL Index will be used as subjective measures to investigate UI symptoms and QoL. The ICIQ-UI SF is a useful tool to assess UI with regard to the severity of symptoms and impact on QoL at baseline and at follow-up [48]. The Barthel ADL Index (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfer, mobility, and stairs) is an important predictor of stroke outcomes. Studies involving stroke survivors should include ADL assessments for better management of stroke patients [37].

In summary, we have described a protocol for a pilot RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the treatment of post-stroke UI. The results of this trial should lead to a greater understanding of promising alternative options for post-stroke UI.

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Contributors

SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript.

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Competing Interests Statement

None

Ethics approval

The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Figure legends:

Figure 1 Study flowchart

Figure 2 Locations of the ‘four sacral points’ for electroacupuncture

Figure 3 Anatomical positions of the ‘four sacral points’ for electroacupuncture

Figure 4 Acupuncture at the ‘four sacral points’

Figure 5 Transverse computed tomography (CT) image of the coccygeal apex

The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN in Alcock’s canal)

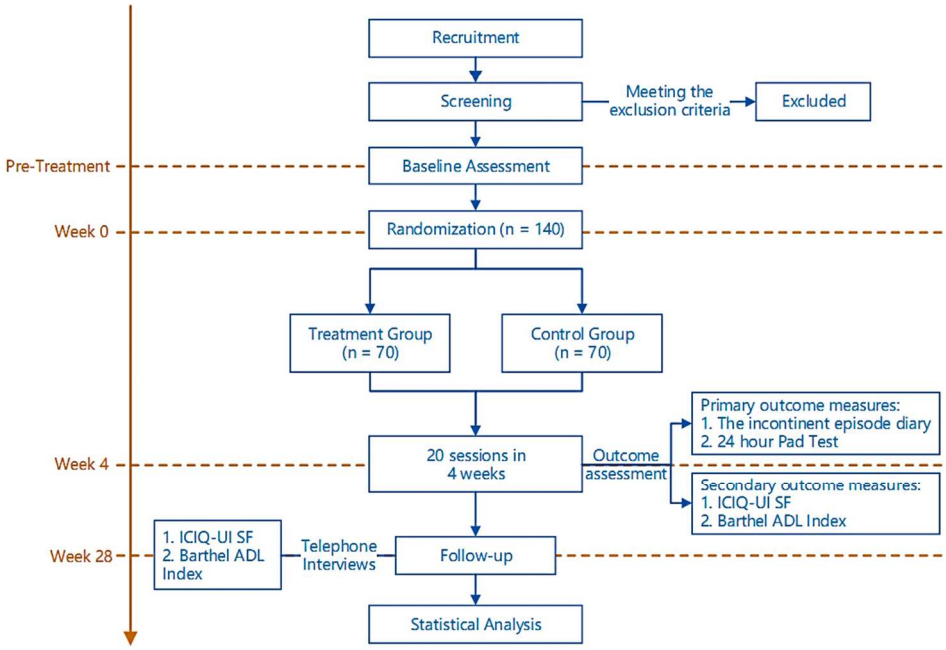

Figure 1 Study flowchart

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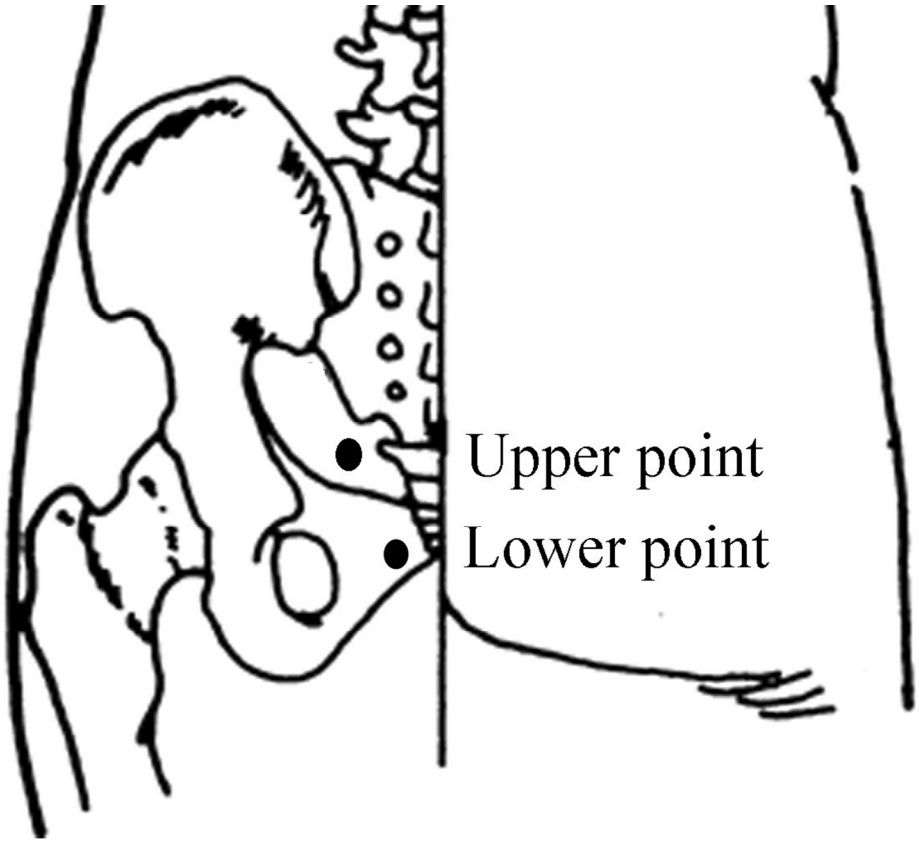

Figure 2 Locations of the 'four sacral points' for electroacupuncture

102x85mm (300 x 300 DPI)

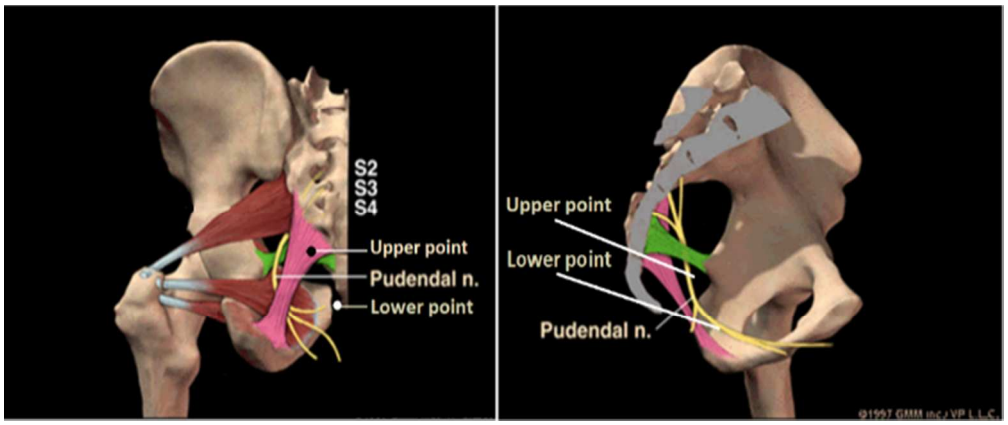

Figure 3 Anatomical positions of the 'four sacral points' for electroacupuncture

60x25mm (300 x 300 DPI)

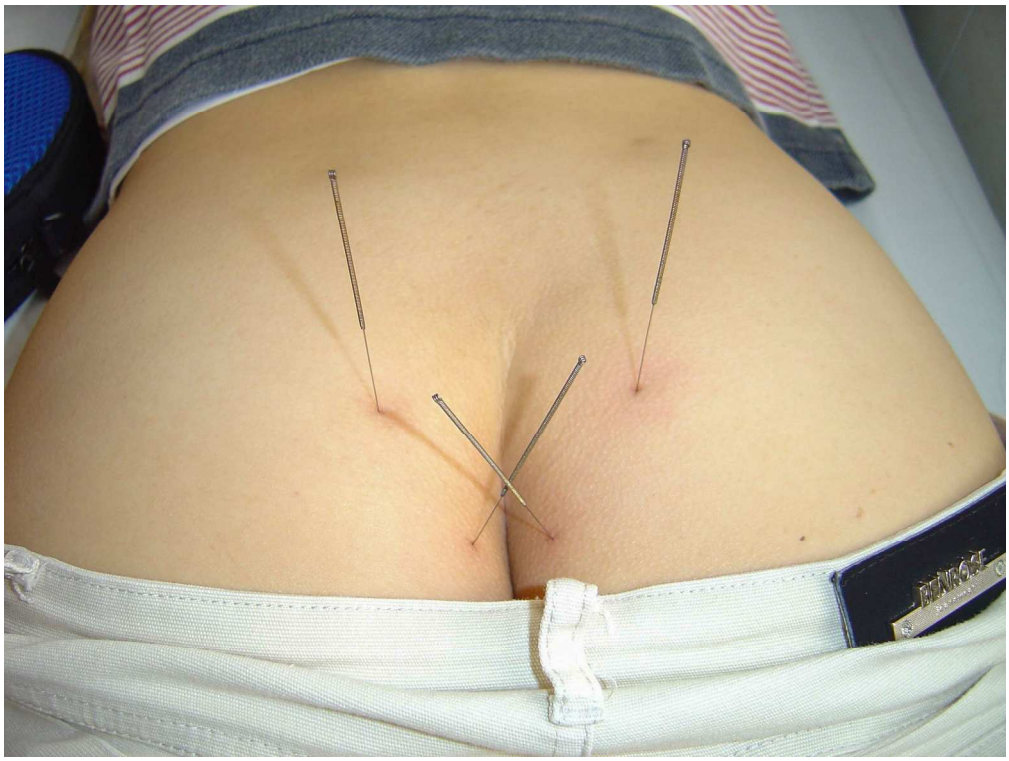

Figure 4 Acupuncture at the 'four sacral points'

219x164mm (300 x 300 DPI)

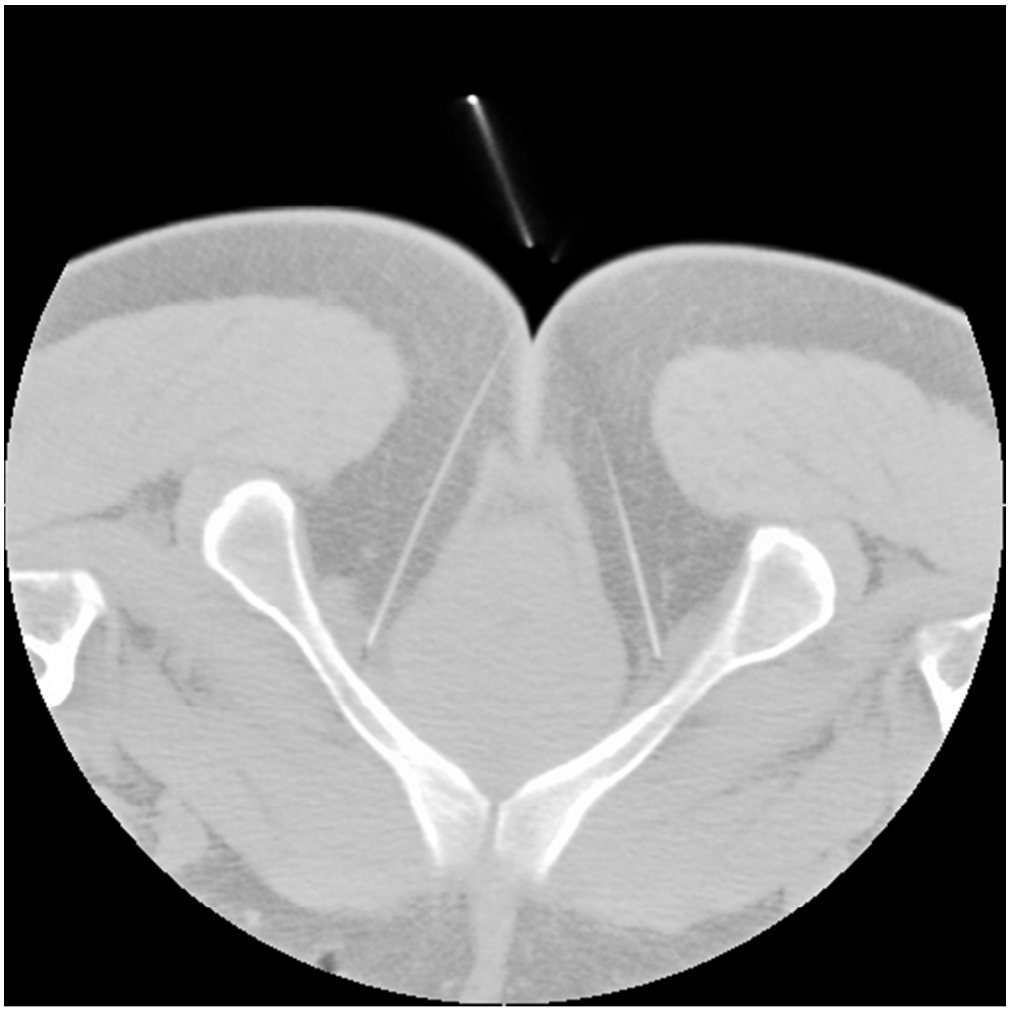

Figure 5 Transverse computed tomography (CT) image of the coccygeal apex
The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN in Alcock's canal)

43x43mm (300 x 300 DPI)

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Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial

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Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial

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Keyword: electroacupuncture; urinary incontinence; post-stroke; electrical pudendal nerve stimulation

Word count: 6585

ABSTRACT

Introduction

Electroacupuncture at 'four sacral points', also known as electrical pudendal nerve stimulation therapy, combines the advantages of pudendal nerve neuromodulation (PNM) and the technique of deep insertion of long acupuncture needles. It has been used to treat stress urinary incontinence, female urgency-frequency syndrome, idiopathic urgency urinary incontinence, and neurological bladders in previous studies. Here, we describe the protocol for a randomized controlled trial for evaluation of the efficacy and safety of electroacupuncture at 'four sacral points' for the management of urinary incontinence after stroke.

Methods and Analysis

This is an open-label randomized controlled trial with blinded assessments and analyses. A total of 140 eligible patients will be randomly allocated to two groups. The treatment group (n = 70) will receive electroacupuncture at 'four sacral points' along with routine medical care, while the control group will receive conventional electroacupuncture along with routine medical care. Twenty treatment sessions will occur over a period of 4 weeks. The primary outcome measures will be the self-recorded findings in an incontinent episode diary at baseline and at 4 weeks after baseline. The secondary outcome measures will be the International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) score and the Barthel Activities of Daily Living Index (Barthel ADL Index) score at baseline and at 4 and 28 weeks after baseline.

Ethics and dissemination: This protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (approval No. 2018-K-059-01). Written informed consent will be obtained from each participant. The results of the study will be published in peer-reviewed journals.

Trial registration number: ChiCTR-IOR-17012847

Strengths and limitations of this study

- First pilot study to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the treatment of urinary incontinence after stroke
- Randomised clinical trial with pragmatic design
- A novel acupuncture intervention for the treatment of urinary incontinence after stroke
- Lack of blinding of acupuncturists and participants due to the nature of acupuncture

INTRODUCTION

The International Continence Society (ICS) has defined urinary incontinence (UI) as the involuntary loss of urine [1]. In a systematic review, a random-effects meta-analysis determined the prevalence of UI after stroke to be 23.6% [2]. Post-stroke UI may develop because of various reasons, although direct stroke-induced damage to the neuromicturition pathways is considered the most common cause. Typical symptoms include the involuntary leakage of urine accompanied or immediately preceded by urgency. Urodynamic evaluation often reveals uninhibited detrusor contraction [3]. Physical consequences include skin dermatitis and urinary tract infections, while psychological consequences include embarrassment and low self-esteem [4]. In addition, UI is a powerful prognostic indicator of survival and eventual functional dependence [5]. The most recent research on this topic demonstrated a higher mortality rate for stroke patients with UI (56.8%) than for stroke patients without UI (11.9%) [6]. Therefore, the management of UI after stroke is of great importance.

Evidence-based interventions for post-stroke UI are somewhat limited, but include behavioural and pharmacological interventions, as well as individually tailored structured management plans, or the aid of continence nurse specialists, in order to promote continence [3]. Trials of behavioural and pharmacological therapies have provided insufficient evidence to guide the management of post-stroke UI in adults [7]. Furthermore, side effect profiles and anticholinergic burden should be considered before medications are prescribed [8].

Neuromodulation therapies, which involve the electrical stimulation of target-specific nerves, are reportedly effective for overactive bladder (OAB) or urgency UI (UUI) [9]. Neuromodulation includes transvaginal or transanal electrical stimulation (TES), percutaneous tibial nerve stimulation (PTNS), sacral nerve neuromodulation (SNM), and pudendal nerve (PN) neuromodulation (PNM) [10]. Although TES is an easy procedure, it is not tolerated by several patients because of discomfort, mucosal injury, and the necessity for high-intensity stimulation to achieve an acceptable outcome [11]. SNM with the InterStim device (Medtronic, Minneapolis, MN) provides continuous stimulation and close nerve contact; thus, it is different from TES. The success rate is high [12, 13]; however, at least 20% of initially tested patients do not respond to the test procedure [14]. The disadvantages of SNM include the invasiveness of the procedure, the high cost of treatment, the high rate of revision surgery, the requirement for device replacement on battery exhaustion, and adverse events (pain and infection) [15, 16]. PN afferents play a particularly important role in the inhibition of the voiding reflex. Because SNM only excites a portion of PN afferents, direct PN stimulation may be more effective [10]. PNM with the Interstim device or the Bion device (selective PN stimulation) can be used to treat UUI

refractory to SNM [10, 17, 18], although its disadvantages are similar to those of SNM [10, 18]. PTNS with needle electrodes is minimally invasive, effective, easy to perform, and well tolerated [8]; however, its effect diminishes over time [15, 17].

According to the theory of traditional Chinese medicine (TCM), UI is primarily caused by kidney and bladder dysfunction in terms of urine control. Accordingly, the principle of acupuncture treatment for UI is to promote the recovery of urine control [19]. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33 (Zhongliao), and BL 35 (Huiyang), are generally selected for the regulation of the bladder voiding function [20-22]. A literature review showed that acupuncture demonstrated more favourable effects than did antimuscarinic drugs for the treatment of OAB and alleviation of symptoms in some comparative trials [23]. In addition, acupuncture reportedly improved the quality of life (QoL) and urodynamic testing parameters in patients with OAB [23, 24]. In a randomized, double-blind, placebo-controlled study, electroacupuncture significantly increased the maximum cystometric capacity and bladder compliance, decreased the detrusor leak point pressure, alleviated lower urinary tract symptoms, and decreased the risk of upper urinary tract damage in patients with post-stroke detrusor overactivity [22]. However, high-quality clinical trials with appropriate inclusion criteria, sample size, control design, acupoint selection, depth of needle insertion, and efficacy and safety evaluations are necessary to properly evaluate the efficacy of acupuncture for the treatment of post-stroke UI [7, 25, 26].

On the basis of the theory of nerve stimulation, we developed electroacupuncture at ‘four sacral points’ [27, 28], also known as electroacupuncture neurostimulation therapy or electrical PN stimulation therapy. This approach involves the insertion of long needles at ‘four sacral points’, with electricity to stimulate specific nerves under the sacral region [28, 29]. When it was first developed, this treatment was used to treat stress UI (SUI) in women, and radiographic evidence with simultaneous records of perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure, and pelvic floor surface electromyography have shown that it causes PN excitation [29]. In addition, it has been used for the treatment of female urgency-frequency syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological conditions [28, 30, 31]. The mechanism of action of electroacupuncture at ‘four sacral points’ for post-stroke UI can be explained by the modulation of reflex pathways at spinal or supraspinal levels [3]. Electrical stimulation of the afferent branches of the PN can induce strong inhibition of the micturition reflex and detrusor hyper-reflexia [10], resulting in the effective treatment of post-stroke UI [31, 32].

The effectiveness of post-stroke UI treatment using alternative medicine approaches is worthy of investigation in a well-designed study. To the best of our

knowledge, no randomized controlled trials (RCT) comparing the efficacy and safety of electroacupuncture at 'four sacral points' with those of conventional electroacupuncture for the treatment of post-stroke UI have been conducted. Here we describe a protocol for an RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the management of post-stroke UI.

METHODS AND ANALYSIS

Objectives

This is a protocol comparing the efficacy and safety of electroacupuncture at 'four sacral points' with those of conventional electroacupuncture for the treatment of post-stroke UI. It is designed as a blinded randomized assessment and analysis with two parallel groups over a 4-week treatment period. Randomization will be performed in a random 1:1 allocation sequence.

Recruitment

This is a pragmatic RCT comparing electroacupuncture at 'four sacral points' with conventional electroacupuncture for the treatment of post-stroke UI. The research structure is shown in Figure 1. A total of 140 eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University according to the inclusion and exclusion criteria. At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form. This will be followed by baseline assessment and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks will follow the recruitment procedure. The neurology department of the First Affiliated Hospital of Zhejiang Chinese Medical University has the major source of patients with post-stroke UI. Our reach team includes neurological physicians and special nurses who will interview potentially eligible patients. Advertisements will be released through health education brochures, posters, and videos displayed in the outpatient and inpatient sites of the First Affiliated Hospital of Zhejiang Chinese Medical University. Recruitment information will also be issued through media (e.g. newspapers, broadcasts, and websites).

Design

Randomization and allocation concealment

The randomization scheme has been created by the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University, where professionals used SPSS Statistics 22.0 to generate a random 1:1 allocation sequence using a computer. Professionals involved in allocation will not be recruited in the

study. The random allocation is strictly kept in an opaque envelope and is inaccessible to other research staff. After baseline assessment, the envelope will be opened by an independent staff member in the participant's presence, in order to determine the group assignment for that participant. All patients who give consent for participation and who fulfil the inclusion criteria will be assigned to a group randomly. Randomisation will be requested by the staff member responsible for recruitment and clinical interviews from the First Affiliated Hospital of Zhejiang Chinese Medical University. An independent staff member will open an envelope with printed randomisation numbers in the participant's presence. The therapists will be informed about the participant's allocation at the same time. The staff member responsible for recruitment and clinical interviews is not allowed to receive information about the group allocation.

Blinding

Considering the nature of acupuncture, therapists and participants cannot be blinded to the treatment allocation. Data managers and statisticians will be blinded throughout the trial. Telephone interviewers who collect follow-up information will also be blinded. Data managers, statisticians, and telephone interviewers are restricted from discussing the treatment allocations with each other. The therapists will not be permitted to communicate with any data managers, statisticians, or telephone interviewers. If an unblinding event occurs among data managers, statisticians, or telephone interviewers, the relevant work will be transferred to other appropriately blinded data managers, statisticians, or telephone interviewers. The Investigator must report all code breaks (with reason) as they occur on the corresponding CRF page.

Participants

Sample size

With reference to a similar study [33] with 120 women (efficacy rate, 70.1%:45%), the sample size has been calculated, using PASS 11 software, as 120 patients for a power (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With consideration of the estimated dropout rate (15%), the total sample size will be 140 (70 in each group).

Inclusion criteria

1. Male or female patients aged 30–85 years
2. Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association [34] and the International Continence Society [35]
3. Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years
4. Stable vital signs, normal consciousness, and compliance with treatment
5. Refractoriness to medications (patients who have taken antimuscarinic agents with no UI improvement)

6. Provision of written informed consent

Exclusion criteria

1. UI caused by other diseases such as Parkinson's disease, multiple sclerosis, spinal injury, or Alzheimer's disease
2. Pre-stroke UI, SUI or mixed UI, or overflow incontinence
3. Urinary retention concomitant with UI
4. Urethral injury, lower urinary tract obstruction, acute urinary tract infection, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours
5. Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 [36]
6. Insufficiency of the heart, lungs, liver, and/or kidneys
7. Presence of an implantable electronic device

Elimination criteria

1. Inclusion despite non-fulfilment of the inclusion criteria
2. Lack of exclusion despite fulfilment of the exclusion criteria
3. Eligible participants who receive no interventions

Dropout criteria

1. Poor participant compliance (lack of adherence to treatment for personal reasons)
2. Serious adverse events (SAE), complications, or special physiological changes necessitating discontinuation of the intervention
3. Voluntary dropout

Intervention

All participants will receive routine medical care for stroke recovery, including the control of blood pressure, blood sugar, and blood lipids and routine rehabilitation training. All of the study-related treatments will be provided by skilled acupuncturists who will strictly follow the detailed procedures for each group. During the treatment course and 24-week follow-up time, the administration of antimuscarinic agents and other drugs for neurogenic detrusor overactivity is prohibited for all the patients. They are also not permitted to receive other acupuncture treatment or physiotherapy for UI. All of the study-related treatments will be provided by certified and skilled acupuncturists who will strictly follow the detailed procedures for each group.

Standard operating procedure

1. Needle requirements

   Disposable sterile acupuncture needles in accordance with national standards within the validity period will be used.
2. Hand hygiene of the operator

   The operator is required to sterilize his or her hands with a sanitizer before the acupuncture procedure.
3. Sterilization of the acupuncture points

Within a 5-cm diameter with the acupoint as the centre, sterilize the skin over the acupoints using a cotton swab dipped in 0.45%–0.55% povidone iodine or 75% ethanol.

4. Procedure

Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'.

a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected. The two upper points are located on either side of the sacrococcygeal joint, approximately 1 cm from the joint. The two lower points are located on either side of the tip of the coccyx, approximately 1 cm from the coccyx. Acupuncture will be performed at LI15(Jianyu), LI11 (Quchi), LI10 (Shousanli), SJ5 (Waiguan), and LI4 (Hegu) for participants with upper limb paralysis. For participants with lower limb paralysis, ST31 (Biguan), ST34 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia, with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang) for participants with facial paralysis and drooling.

b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong Medical Apparatus Factory, Suzhou, China) measuring 0.40 × 100 mm will be inserted perpendicularly to a depth of 80–90 mm to induce a sensation referred to the urethra or anus via stimulation of the main trunk of the PN. At the lower sacral points, a needle measuring 0.40 × 100 or 0.40 × 125 mm will be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm to induce a sensation referred to the urethra via stimulation of the perineal nerve (Figure 4). Once the sensation is induced in the respective regions, two pairs of electrodes from the G6805-A electroacupuncture device (Shantou Medical equipment factory, Shantou, China) will be connected to the two ipsilaterally inserted needles, with the anode connected to the upper needle and the cathode connected to the lower needle. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be performed for 20 min during each treatment. PFM contraction around the urethra (often comfortable) must be maintained during the entire electrostimulation procedure. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

Control group: Participants in this group will receive conventional electroacupuncture.

a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao, both sides), corresponding to the conventional electroacupuncture treatment of UI. The point selection procedure for participants with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the same as that used for the treatment group.

b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao), a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the electrodes from the G6805-A electroacupuncture device will be connected to the needles at these points, with the anode connected to ST28 and the cathode connected to CV6 and CV4. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity that is tolerable by the participants. Electrostimulation will be performed for 20 min during each treatment. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

5. Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks).

Outcome measures

Primary outcome measures

The incontinent episode diary

The incontinent episode diary (Table 1) will be used to derive the primary outcome measure. The number of incontinent episodes will be recorded by the participants over a period of 3 days at baseline. A template will be provided for patient use. This data will be recorded again at the end of treatment.

Table 1 The incontinent episode diary

Name		Date			
Record every accidental loss of urine over 3 consecutive days with an X.					
Start at baseline and continue recording for 3 days					
Day 1		Day 2		Day 3	
eg X					

Secondary outcome measures

1. International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) [37] (Table 2)

2. Barthel Activities of Daily Living Index (Barthel ADL Index) [38] (Table 3)

The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and psychometrically robust patient-completed questionnaire for evaluating the frequency and severity of UI in men and women and its impact on quality of life (QoL). The ICIQ-UI SF score ranges from 0 to 21 [39]. The Barthel ADL Index is a 10-item measure of activities of daily living (ADL) that is frequently used in clinical practice and as a trial outcome measure in stroke medicine [38]. It is used to assess baseline abilities to quantify functional changes, including UI, after rehabilitation in stroke patients.

The above outcome measures will be assessed at baseline and at 4 and 28 weeks after baseline.

Table 2 International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF)

1. Please write in your date of birth:	□□ □□ □□ date month year	
2. Are you	Female □ Male □	
3. How often do you leak urine? (Tick one box)		
	never	□ 0
	about once a week or less often	□ 1
	two or three times a week	□ 2
	about once a day	□ 3
	several times a day	□ 4
	all the time	□ 5
4. We would like to know how much urine you think leaks. How much urine do you usually leak (whether you wear protection or not)? (Tick one box)		
	None	□ 0
	a small amount	□ 2
	a moderate amount	□ 4
	a large amount	□ 6
5. Overall, how much does leaking urine interfere with your everyday life? Please ring a number between 0 (not at all) and 10 (a great deal) 0 1 2 3 4 5 6 7 8 9 10 not at all a great deal		

ICIQ score: sum scores 3+4+5	□□	
6. When does urine leak? (Please tick all that apply to you)		
	never – urine does not leak	□
	leaks before you can get to the toilet	□
	leaks when you cough or sneeze	□
	leaks when you are asleep	□
	leaks when you have finished urinating and are dressed	□
	leaks for no obvious reason	□
	leaks all the time	□

Table 3 Barthel Activities of Daily Living Index (Barthel ADL Index)

The Barthel Index		Patient Name Rater Name Date:
Activity		Score
Feeding	Unable	0
	Some help required (e.g., needs help cutting, spreading butter, etc. or requires a modified diet)	5
	Independent	10
Bathing	Dependent	0
	Independent (or in shower)	5
Grooming	Needs help with personal care	0

	Independent face/hair/teeth/shaving (implements provided)	5
Dressing	Dependent	0
	Needs help but can do at least half unaided	5
	Independent (including buttons, zips, laces, etc.)	10
Bowels	Incontinent or catheterized and unable to manage alone	0
	Occasional accident	5
	Continent	10
Bladder	Incontinent or catheterized and unable to manage alone	0
	Occasional accident	5
	Continent	10
Toilet use	Dependent	0
	Needs some help, but can do some things alone	5
	Independent (can get on and off, dress and wipe unassisted)	10
Transfer (bed to chair and back)	Unable, no sitting balance	0
	Major help (one or two people, physical), can sit	5
	Minor help (verbal or physical)	10
	Independent	15
Mobility (on level surfaces)	Immobile or <50 yards	0
	Wheelchair independent, including corners; >50 yards	5
	Walks with little help from one person (verbal or physical); >50 yards	10
	Independent (but may use an aid; e.g., walking stick); >50 yards	15
Stairs	Unable	0
	Needs help (verbal, carrying aid)	5
	Independent	10
	Total	

Adverse events (AEs)

An adverse event of acupuncture is defined as symptoms or diseases that are against the purpose of the treatment during or following the acupuncture treatment [40]. The research staff will record the blood pressure, heart rate, heart rhythm, and respiration rate and observe changes in the consciousness of all participants before and after the treatment. The description of AEs, time of occurrence, location of the reaction, level of severity, corresponding management, and the necessity for patient withdrawal from the trial will be recorded on the Case Report Forms (CRFs). AEs of acupuncture will be classified according to their location as local and systemic reactions.

Local reactions:

Subcutaneous haematoma
Minor bleeding on withdrawal of the needle
Subcutaneous bruise
Pain in the punctured region after treatment
Skin allergy in the punctured region after treatment
Local infection

Systemic reactions:

Acupuncture fainting
Abdominal distention
Dizziness or vertigo
Leg weakness
Muscle spasm
Systemic allergy
Systemic infection
Organ injury

Severe AEs are defined as symptoms or diseases that result in hospitalization or prolong hospitalization, disability, a life-threatening situation, or even death [41]. Systemic infection and organ injury are two major AEs. Severe AEs will be reported to the Ethics Committee within 24 h. The Ethics Committee will provide medical suggestions for the research team and decide whether the patient should continue the ongoing treatment.

For patients having common adverse reactions, appropriate medical care will be given to ease local bleeding, irritation, bruising, and so on. For those who have severe reactions leading to organ injury, systematic infection, systematic allergy, and so on, compensation will be given to cover their medical costs by our research team.

Data management, monitoring and auditing

A research assistant will record the baseline characteristics of all participants. Trained caregivers will record the frequency of UI at baseline and at 4 weeks after baseline. A researcher who remains blinded to treatment group allocation will collect data regarding the frequency of UI and the weight of pads from the caregivers. The participants will also complete ICIQ-UI SF and the Barthel ADL Index at baseline and

at 4 weeks after baseline. A blinded telephone interviewer will interview the participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at 28 weeks after baseline. All data will be recorded on the CRFs. For participants who discontinue treatment early, we will use last observation carried forward analysis to handle the missing data, meaning that we will input outcome data of patients who are lost to follow-up in our analysis.

After the completion of the CRFs, two independent researchers blinded to the group allocation will separately input data into an Excel spreadsheet. Another independent supervisor will check the two datasets for consistency. If conflicting data entries are discovered, the supervisor will compare the datasets with the original CRFs and mark the modification on the CRFs. The principal investigator of the research team will have the access to all documents and will protect the electronic documents with a password and create backups of all documents. The First Affiliated Hospital of Zhejiang Chinese Medical University will be responsible for the storage and management of all data.

An independent data monitoring committee (DMC) is made up of members from Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University. The DMC, blinded to the treatment allocations, will meet regularly to monitor the study data. The DMC will also perform interim-analysis when 50% of patients have been randomised and have completed the primary outcome measurement.

The First Affiliated Hospital of Zhejiang Chinese Medical University will audit this study mainly for participant enrolment, consent, and costs.

Statistical analysis

All statistical analyses will be performed by a statistician from the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University using SPSS Statistics 22.0. A normality test will be used to determine whether the data are normally distributed. ANCOVA (analysis of covariance) will be used if there is imbalance in the baseline characteristics and outcome measures. Continuous variables with a normal distribution will be expressed as means ± standard deviations (SDs). Continuous variables with a non-normal distribution or ordinal variables will be expressed as medians (with lower, upper quartiles). Categorical variables will be summarized as counts and proportions. A Student's t-test will be used if the primary and secondary outcome measures conform to normal distribution. A paired t-test will be used to compare pre-treatment and post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in the secondary outcome measures. The independent sample t-test will be used to compare the difference between two groups for primary and secondary outcome measures. A Wilcoxon signed rank test will be used if the primary and secondary outcome measures conform to abnormal distribution. A Wilcoxon paired test will be used to compare pre-treatment and post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in secondary outcome measures. The inter-group rank sum test will be used to compare the difference

between two groups for primary and secondary outcome measures. All reported P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A P-value of <0.05 will be considered statistically significant.

Patient and Public Involvement

Patients and the public were not directly involved in the design, recruitment or conduct of this pilot study. Since the participants in our study are under chronic conditions, the outcome measures valuated in this study was influenced by patients' priorities, experience and preferences. As most stroke patients are in great need of acupuncture treatment in China, we did not view the intervention as burdensome and the burden of the intervention was not assessed by the patients themselves. The results of this study will be disseminated in peer-reviewed journals and at academic conferences. A summary of the study report will be written for patients through online website (https://sandychenshan.haodf.com/) and WeChat (a free messaging and calling application) account or group.

ETHICS AND DISSEMINATION

Research ethics approval

The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University has reviewed and approved this protocol (approval No. 2018-K-059-01). This study will adhere to the principles of the Declaration of Helsinki. This study will be conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University. Each participant will voluntarily sign written informed consent forms.

Modification of the protocol

Any modifications to the protocol, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal application to the Zhejiang Provincial Administration of Traditional Chinese Medicine as well as the Chinese clinical trial registry.

Confidentiality

All study participants will be given an identification number throughout the trial to assure confidentiality. All participants' information will be stored in locked cabinets with limited access.

Dissemination

The initial data will be accessible via Research Manager (ResMan). The results of this study will be published in open-access and peer-reviewed journals and presented at relevant conferences.

DISCUSSION

According to the present study protocol, in addition to electroacupuncture at 'four sacral points' in the treatment group and conventional electroacupuncture in the

control group, the same acupoints for other stroke symptoms will also be selected for both groups. Other stroke symptoms include unilateral limb weakness, facial paresis, dysphasia, and dysphagia [42]. In China, acupuncture has been a primary medical intervention for stroke [43]. In fact, not providing acupuncture therapy to a stroke patient is considered impractical.

Antimuscarinic agents are considered first-line drugs for neurogenic detrusor overactivity (NDO) [44]. However, because of their moderate efficacy and troublesome side effects, quite a few patients exhibit refractory disease [45]. According to the eligibility criteria, participants who are refractory to medication will be included in this RCT.

With regard to the outcome measures, the incontinent episode diary will be used as objective measure to record the frequency of incontinence. Patients will record their findings in the incontinent diary for only 3 days, because a longer recording period can lead to decreased patient compliance [46,47]. In order to improve adherence, health education about the importance of UI management will be conducted by a special nurse and brochures on post-stroke UI will be provided to patients. The ICIQ-UI SF and Barthel ADL Index will be used as subjective measures to investigate UI symptoms and QoL. The ICIQ-UI SF is a useful tool to assess UI with regard to the severity of symptoms and impact on QoL at baseline and at follow-up [48]. The Barthel ADL Index (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfer, mobility, and stairs) is an important predictor of stroke outcomes. Studies involving stroke survivors should include ADL assessments for better management of stroke patients [38].

In summary, we have described a protocol for a pilot RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the treatment of post-stroke UI. The results of this trial should lead to a greater understanding of promising alternative options for post-stroke UI.

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Contributors
SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript.

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Competing Interests Statement
None

Ethics approval
The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University.

Provenance and peer review
Not commissioned; externally peer reviewed.

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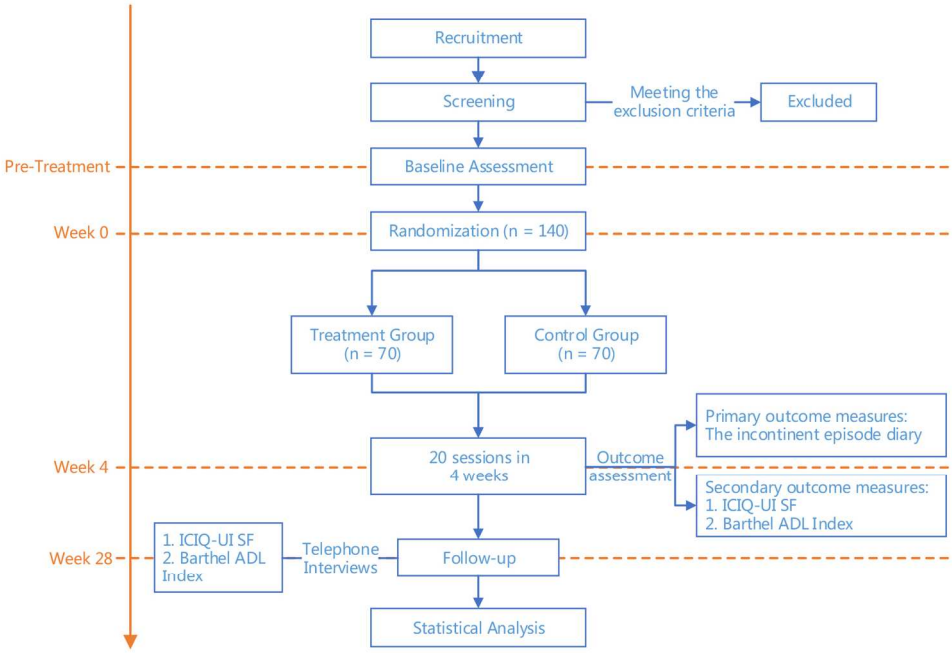
Figure legends

Figure 1 Study flowchart

Figure 2 Locations of the 'four sacral points' for electroacupuncture

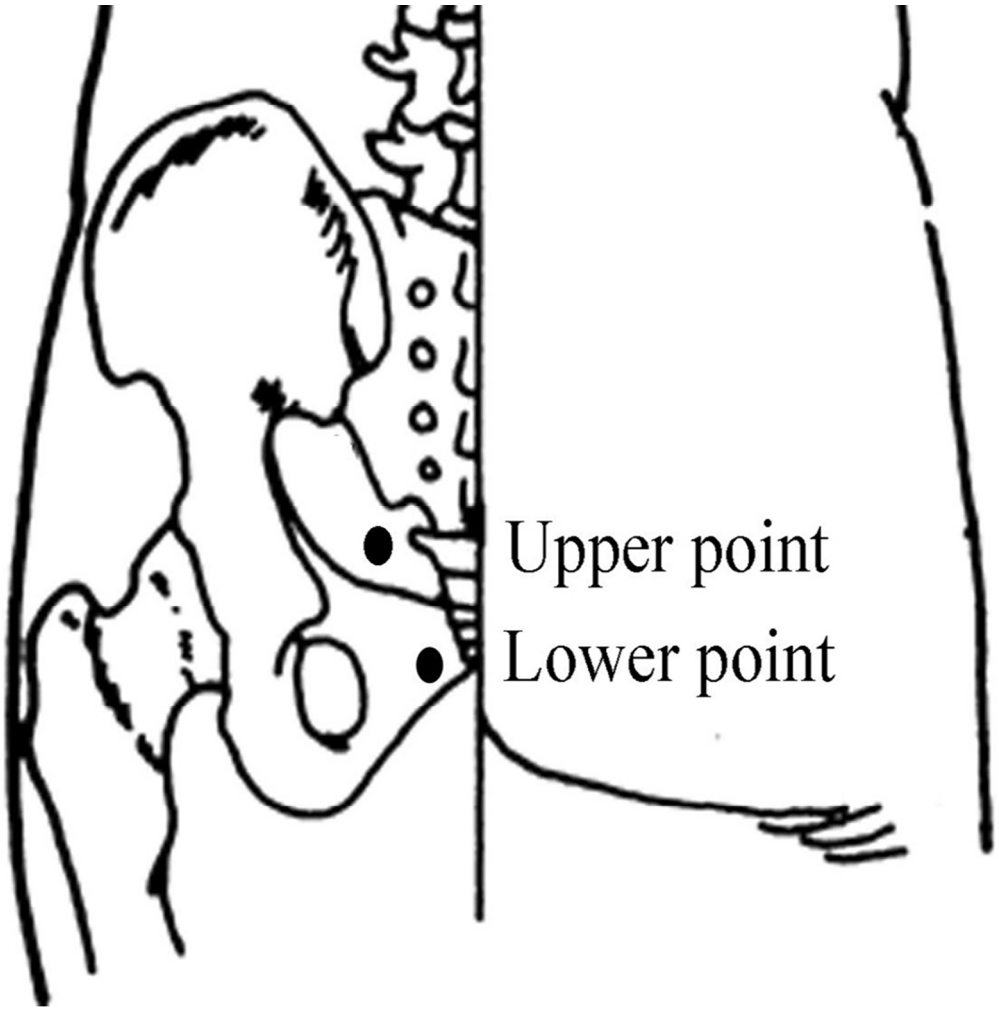
Figure 3 Anatomical positions of the 'four sacral points' for electroacupuncture

Figure 4 Transverse computed tomography (CT) image of the coccygeal apex
The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN in Alcock's canal)



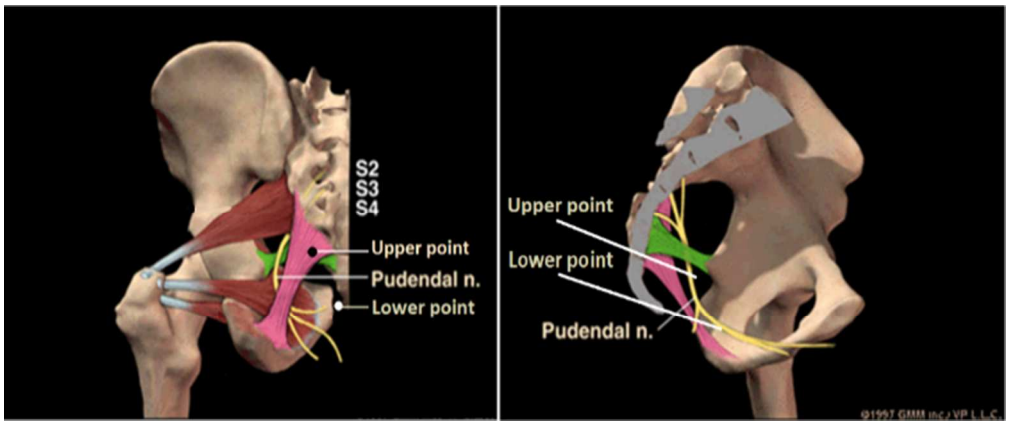
Study flowchart

151x105mm (300 x 300 DPI)



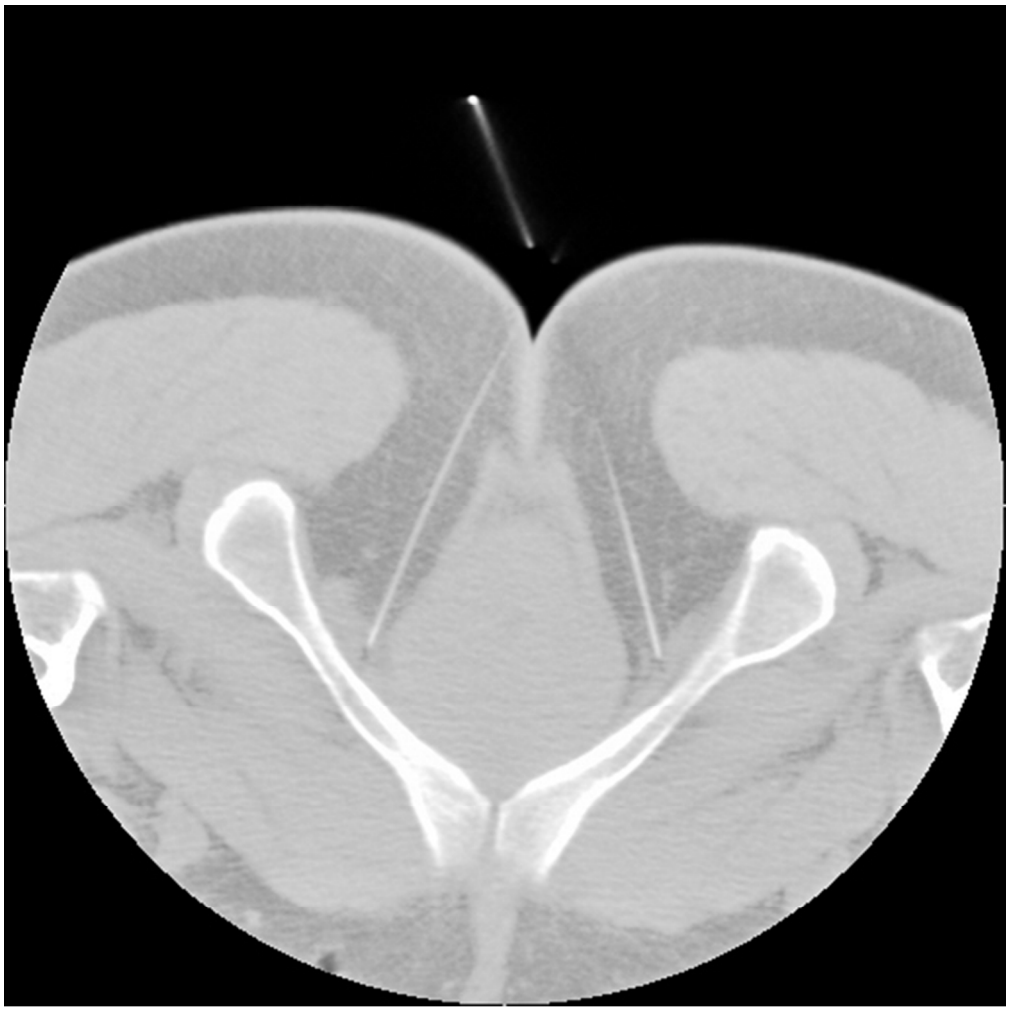
Locations of the 'four sacral points' for electroacupuncture

90x90mm (300 x 300 DPI)



Anatomical positions of the 'four sacral points' for electroacupuncture

216x90mm (300 x 300 DPI)



Transverse computed tomography (CT) image of the coccygeal apex
The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN in Alcock's canal)

90x90mm (300 x 300 DPI)

Section/item	ItemNo	Description	
Administrative Information			
Title	1	Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial [1]	
Trial registration	2a	ChiCTR-IOR-17012847 [2]	
	2b	Primary registry and trial identifying number	ChiCTR-IOR-17012847
		Date of registration in primary registry	30 Sep 2017
		Secondary identifying numbers	
		Source(s) of monetary or material support	Zhejiang Provincial Administration of Traditional Chinese Medicine
		Primary sponsor	Zhejiang Provincial Administration of Traditional Chinese Medicine
		Secondary sponsor(s)	
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		Contact for scientific queries	CZ,HFZ Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China
		Public title	Electroacupuncture at 'four sacral points' for the treatment of urinary incontinence after stroke
		Scientific title	Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial
		Countries of recruitment	China
		Health condition(s) or problem(s) studied	Acupuncture treatment; Urinary incontinence after stroke

Intervention(s)	Treatment group: electroacupuncture at ‘four sacral points’ Control group: conventional electroacupuncture
Key inclusion and exclusion criteria	Ages eligible for study: 30-85 years old; Sexes eligible for study: both; Accepts healthy volunteers: no. Inclusion criteria: Male or female patients aged 30–85 years; Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association and the International Continence Society; Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years; Stable vital signs, normal consciousness, and compliance with treatment; Refractoriness to medications (patients who have taken antimuscarinic agents with no UI improvement); Provision of written informed consent. Exclusion criteria: UI caused by other diseases such as Parkinson’s disease, multiple sclerosis, spinal injury, or Alzheimer’s disease; Pre-stroke UI, SUI or mixed UI, overflow incontinence; Urinary retention concomitant with UI; Urethral injury, lower urinary tract obstruction, acute urinary tract infection, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours; Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 ;

			Insufficiency of the heart, lungs, liver, and/or kidneys; Presence of an implantable electronic device
		Study type	Interventional Allocation: randomized; Intervention model: parallel assignment; Masking: blinded assessment and analysis. Primary purpose: treatment
		Date of first enrolment	Hasn't started
		Target sample size	140
		Recruitment status	Hasn't started
		Primary outcome(s)	The incontinent episode diary
		Key secondary outcomes	International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF); Barthel Activities of Daily Living Index (Barthel ADL Index)
Protocol version	3	Issue date: 30 Sep 2017	
		Protocol amendment number: 01	
		Authors: Chen Shan; Siyou Wang； Lihua Xuan, Hanti Lu, Zhikai Hu, Chao Zhang, Huifang Zhang [1]	
Funding	4	This work has been supported Zhejiang Provincial Administration of Traditional Chinese Medicine (grant number 2018ZA045).	
Roles and responsibilities	5a	SC[No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; SYW[No. 650 Wanpin Road, Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian, Shanghai, China]; LHX[No. 54 Youdian Road, Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; HTL[No. 54 Youdian Road, Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang Chinese Medical University,	

		Hangzhou, China]; ZKH[No. 668 Jimei Avenue, Jimei District, Department of Computer Science, Huaqiao University, Xiamen, China]; CZ[No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Rehabilitation Unit of the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; HFZ[No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China] Contributors: SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript. [17]
	5b	Trial sponsor: Zhejiang Provincial Administration of Traditional Chinese Medicine [18]
		Sponsor's Reference: grant number 2018ZA045 [18]
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		Telephone: +86 0571 8770 9076
		Email: zjtcm@zjwst.gov.cn
	5c	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
	5d	Authors in the title page are members of the steering committee
Introduction		
Background and rationale	6a	Introduction: In a systematic review, a random-effects meta-analysis determined the prevalence of UI after stroke to be 23.6%. Physical consequences include skin dermatitis and urinary tract infections, while psychological consequences include embarrassment and low self-esteem. In addition, UI is a powerful prognostic indicator of survival and eventual functional dependence. The most recent research on this topic demonstrated a higher mortality rate for stroke patients with UI (56.8%) than

for stroke patients without UI (11.9%). Therefore, the management of UI after stroke is of great importance. Post-stroke UI may develop because of various reasons, although direct stroke-induced damage to the neuromicturition pathways is considered the most common cause. Typical symptoms include the involuntary leakage of urine accompanied or immediately preceded by urgency. Urodynamic evaluation often reveals uninhibited detrusor contraction.

Evidence-based interventions for post-stroke UI include behavioural and pharmacological interventions, as well as individually tailored structured management plans, or the aid of continence nurse specialists, in order to promote continence. Trials of behavioural and pharmacological therapies have provided insufficient evidence to guide the management of post-stroke UI in adults. Furthermore, side effect profiles and anticholinergic burden should be considered before medications are prescribed. Neuromodulation therapies, which involve the electrical stimulation of target-specific nerves, are reportedly effective for overactive bladder (OAB) or urgency UI (UUI). Neuromodulation includes transvaginal or transanal electrical stimulation (TES), percutaneous tibial nerve stimulation (PTNS), sacral nerve neuromodulation (SNM), and pudendal nerve (PN) neuromodulation (PNM). TES is an easy procedure, but it is not tolerated by several patients because of discomfort, mucosal injury, and the necessity for high-intensity stimulation to achieve an acceptable outcome. SNM with the InterStim device provides continuous stimulation and close nerve contact; however, at least 20% of initially tested patients do not respond to the test procedure. The disadvantages of SNM include the invasiveness of the procedure, the high cost of treatment, the high rate of revision surgery, the requirement for device replacement on battery exhaustion, and adverse events (pain and infection). PNM with the Interstim device or the Bion device (selective PN stimulation) can be used to treat UUI refractory to SNM, although its disadvantages are similar to those of SNM. PTNS with needle electrodes is minimally invasive, effective, easy to perform, and well tolerated; however, its effect diminishes over time.

On the basis of the theory of nerve stimulation, we developed electroacupuncture at ‘four sacral points’, also known as electroacupuncture neurostimulation therapy or electrical PN stimulation therapy. This approach involves the insertion of long needles at ‘four sacral points,’ with electricity to stimulate specific nerves under the sacral region. In our previous study, this treatment has been used to treat stress UI (SUI) in women, and radiographic evidence with simultaneous records of perineal

		ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure, and pelvic floor surface electromyography have shown that it causes PN excitation. It has also been used for the treatment of female urgency-frequency syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological conditions. High quality study on electroacupuncture at 'four sacral points' for post-stroke UI need to be conducted for a better management of UI after stroke.[3-4] Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks).[9]
	6b	The principle of acupuncture treatment for UI is to promote the recovery of urine control. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33 (Zhongliao), and BL 35 (Huiyang), are generally selected for the regulation of the bladder voiding function. A literature review showed that acupuncture demonstrated more favourable effects than did antimuscarinic drugs for the treatment of OAB and alleviation of symptoms in some comparative trials.[4]
Objectives	7	The mechanism of action of electroacupuncture at 'four sacral points' for post-stroke UI can be explained by the modulation of reflex pathways at spinal or supraspinal levels. Electrical stimulation of the afferent branches of the PN can induce strong inhibition of the micturition reflex and detrusor hyper-reflexia, resulting in the effective treatment of post-stroke UI.[4]
Trial design	8	It is designed as a blinded randomized assessment and analysis with two parallel groups over a 4-week treatment period. Randomization will be performed in a random 1:1 allocation sequence.[5]
Methods: Participants, interventions, and outcomes		
Study setting	9	Eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University [5]
Eligibility criteria	10	Inclusion Criteria 1. Male or female patients aged 30–85 years 2. Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association and the International Continence

		Society 3. Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years 4. Stable vital signs, normal consciousness, and compliance with treatment 5. Refractoriness to medications(patients who have taken antimuscarinic agents with no UI improvement) 6. Provision of written informed consent Exclusion Criteria 1. UI caused by other diseases such as Parkinson's disease, multiple sclerosis, spinal injury, or Alzheimer's disease 2. Pre-stroke UI, SUI or mixed UI, or overflow incontinence. 3. Urinary retention concomitant with UI 4. Urethral injury, lower urinary tract obstruction, acute urinary tract infection, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours 5. Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 6. Insufficiency of the heart, lungs, liver, and/or kidneys 7. Presence of an implantable electronic device [6-7] Eligibility criteria for acupuncturists and training All of the study-related treatments will be provided by certified and skilled acupuncturists who will strictly follow the detailed procedures for each group.[7]
Interventions	11a	Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'. a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected. The two upper points are located on either side of the sacrococcygeal joint, approximately 1 cm from the joint. The two lower points are located on either side of the tip of the coccyx, approximately 1 cm from the coccyx. Acupuncture will be performed at LI15 (Jianyu), LI11 (Quchi), LI10 (Shousanli), SJ5 (Waiguan), and LI4 (Hegu) for participants with upper limb paralysis. For participants with lower limb paralysis, ST31 (Biguan),

ST34 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia, with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang) for participants with facial paralysis and drooling.

b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong Medical Apparatus Factory, Suzhou, China) measuring 0.40 × 100 mm will be inserted perpendicularly to a depth of 80–90 mm to induce a sensation referred to the urethra or anus via stimulation of the main trunk of the PN. At the lower sacral points, a needle measuring 0.40 × 100 or 0.40 × 125 mm will be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm to induce a sensation referred to the urethra via stimulation of the perineal nerve (Figure 4). Once the sensation is induced in the respective regions, two pairs of electrodes from the G6805-A electroacupuncture device (Shantou Medical equipment factory, Shantou, China) will be connected to the two ipsilaterally inserted needles, with the anode connected to the upper needle and the cathode connected to the lower needle. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be performed for 20 min during each treatment. PFM contraction around the urethra (often comfortable) must be maintained during the entire electrostimulation procedure. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

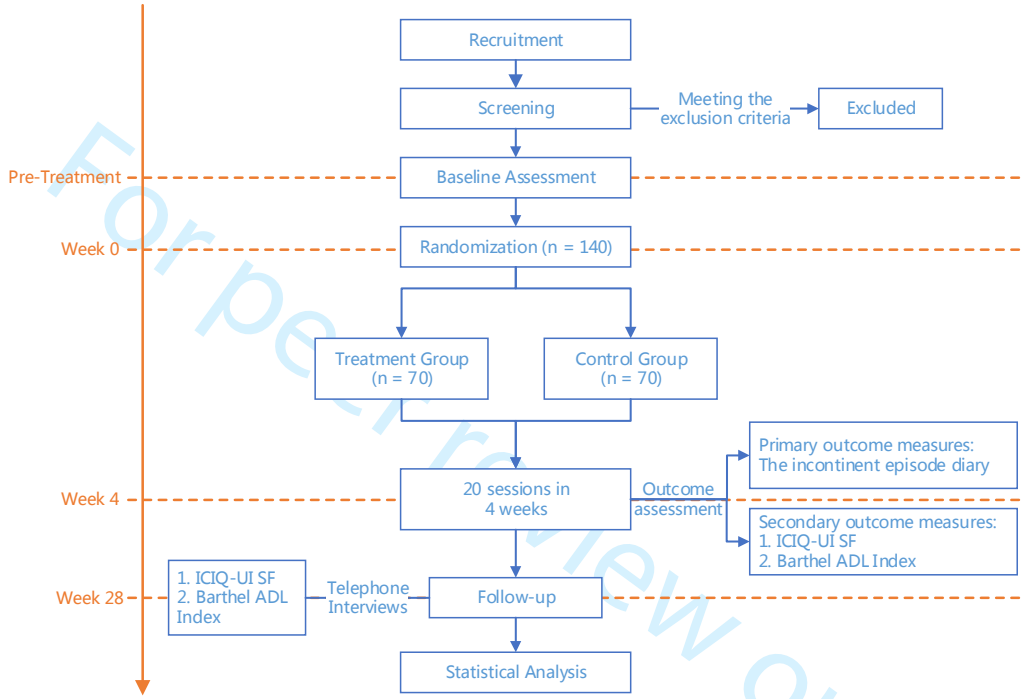
Control group: Participants in this group will receive conventional electroacupuncture.

a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao, both sides), corresponding to the conventional electroacupuncture treatment of UI. The point selection procedure for participants with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the same as that used for the treatment group.

b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao), a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the electrodes from the G6805-A electroacupuncture device will be connected to the needles at these points with the anode connected to ST28 and the cathode connected to CV6 and CV4. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity that is tolerable by the participants. Electrostimulation will be performed for 20 min

		during each treatment. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints. Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks). [8-9]
	11b	Elimination criteria 1. Inclusion despite non-fulfilment of the inclusion criteria 2. Lack of exclusion despite fulfilment of the exclusion criteria 3. Eligible participants who receive no interventions Dropout criteria 1. Poor participant compliance (lack of adherence to treatment for personal reasons) 2. Serious adverse events (SAE), complications, or special physiological changes necessitating discontinuation of the intervention 3. Voluntary dropout [7]
	11c	In order to improve adherence, health education about the importance of UI management will be conducted by a special nurse and brochures on post-stroke UI will be provided to patients.[17]
	11d	All participants will receive routine medical care for stroke recovery, including the control of blood pressure, blood sugar, and blood lipids and routine rehabilitation training. During the treatment course and 24-week follow-up time, the administration of antimuscarinic agents and other drugs for neurogenic detrusor overactivity is prohibited for all the patients. They are also not permitted to receive other acupuncture treatment or physiotherapy for UI. All of the study-related treatments will be provided by certified and skilled acupuncturists who will strictly follow the detailed procedures for each group.[7]
Outcomes	12	Primary outcome measures The incontinent episode diary The incontinent episode diary (Table 1) will be used to derive the primary outcome measure. The number of incontinent episodes will be recorded by the participants over a period of 3 days at baseline. A template will be provided for patient use. This data will

		be recorded again at the end of treatment. Secondary outcome measures 1. International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) (Table 2) 2. Barthel Activities of Daily Living Index (Barthel ADL Index) (Table 3) The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and psychometrically robust patient-completed questionnaire for evaluating the frequency and severity of UI in men and women and its impact on quality of life (QoL). The ICIQ-UI SF score ranges from 0 to 21. The Barthel ADL Index is a 10-item measure of activities of daily living (ADL) that is frequently used in clinical practice and as a trial outcome measure in stroke medicine. It is used to assess baseline abilities to quantify functional changes, including UI, after rehabilitation in stroke patients. The above outcome measures will be assessed at baseline and at 4 and 28 weeks after baseline. [9-10]
Participant timeline	13	A total of 140 eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University according to the inclusion and exclusion criteria. At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form. This will be followed by baseline assessment and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks will follow the recruitment procedure. [5] Figure1



Sample size	14	With reference to a similar study with 120 women (efficacy rate, 70.1%:45%), the sample size has been calculated, using PASS 11 software, as 120 patients for a power (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With consideration of the estimated dropout rate (15%), the total sample size will be 140 (70 in each group).[6]
Recruitment	15	The neurology department of the First Affiliated Hospital of Zhejiang Chinese Medical University has the major source of patients with post-stroke UI. Our reach team includes neurological physicians and special nurses who will interview potentially eligible

		patients. Advertisements will be released through health education brochures, posters, and videos displayed in the outpatient and inpatient sites of the First Affiliated Hospital of Zhejiang Chinese Medical University. Recruitment information will also be issued through media (e.g. newspapers, broadcasts, and websites) [5]
Methods: Assignment of interventions		
Administrative Information		
Allocation:		
Sequence generation	16a	The randomization scheme has been created by the Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang Chinese Medical University, where professionals used SPSS Statistics 22.0 to generate a random 1:1 allocation sequence using a computer.[5-6]
Allocation concealment mechanism	16b	Professionals involved in allocation will not be recruited in the study. The random allocation is strictly kept in an opaque envelope and is inaccessible to other research staff. After baseline assessment, the envelope will be opened by an independent staff member in the participant's presence, in order to determine the group assignment for that participant.[6]
Implementation	16c	All patients who give consent for participation and who fulfil the inclusion criteria will be assigned to a group randomly. Randomisation will be requested by the staff member responsible for recruitment and clinical interviews from the First Affiliated Hospital of Zhejiang Chinese Medical University. An independent staff member will open an envelope with printed randomisation numbers in the participant's presence. The therapists will be informed about the participant's allocation at the same time. The staff member responsible for recruitment and clinical interviews is not allowed to receive information about the group allocation.[6]
Blinding	17a	Considering the nature of acupuncture, therapists and participants cannot be blinded to the treatment allocation. Data managers and statisticians will be blinded throughout the trial. Telephone interviewers who collect follow-up information will also be blinded. Data managers, statisticians, and telephone interviewers are restricted from discussing the treatment allocations with each other. The therapists will not be permitted to communicate with any data managers, statisticians, or telephone interviewers.[6]
	17b	If an unblinding event occurs among data managers, statisticians, or telephone interviewers, the relevant work will be transferred to

		other appropriately blinded data managers, statisticians, or telephone interviewers. The Investigator must report all code breaks (with reason) as they occur on the corresponding CRF page.[6]
Methods: Data collection, management and analysis		
Data collection method	18a	A research assistant will record the baseline characteristics of all participants. Trained caregivers will record the frequency of UI at baseline and at 4 weeks after baseline. A researcher who remains blinded to treatment group allocation will collect data regarding the frequency of UI and the weight of pads from the caregivers. The participants will also complete ICIQ-UI SF and the Barthel ADL Index at baseline and at 4 weeks after baseline. A blinded telephone interviewer will interview the participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at 28 weeks after baseline. All data will be recorded on the CRFs. After the completion of the CRFs, two independent researchers blinded to the group allocation will separately input data into an Excel spreadsheet. Another independent supervisor will check the two datasets for consistency. If conflicting data entries are discovered, the supervisor will compare the datasets with the original CRFs and mark the modification on the CRFs.[14-15]
	18b	For participants who discontinue treatment early, we will use last observation carried forward analysis to handle the missing data, which means we will input outcome data of patients who lost follow-up to our analysis.[15]
Data management	19	The principal investigator of the research team will have the access to all documents and will protect the electronic documents with a password and create backups of all documents. The First Affiliated Hospital of Zhejiang Chinese Medical University will be responsible for the storage and management of all data.[15]
Statistical methods	20a	All statistical analyses will be performed by a statistician from the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University using SPSS Statistics 22.0. A normality test will be used to determine whether the data are normally distributed. Continuous variables with a normal distribution will be expressed as means ± standard deviations (SDs). Continuous variables with a non-normal distribution or ordinal variables will be expressed as medians (with lower, upper quartiles). Categorical variables will be summarized as counts and proportions. A Student's t-test will be used if the primary and secondary outcome measures conform to normal distribution. A paired t-test will be used to compare pre-treatment and

		post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in the secondary outcome measures. The independent sample t-test will be used to compare the difference between two groups for primary and secondary outcome measures. A Wilcoxon signed rank test will be used if the primary and secondary outcome measures conform to abnormal distribution. A Wilcoxon paired test will be used to compare pre-treatment and post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in secondary outcome measures. The inter-group rank sum test will be used to compare the difference between two groups for primary and secondary outcome measures. All reported P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A P-value of <0.05 will be considered statistically significant.[15-16]
	20b	ANCOVA (analysis of covariance) will be used if there is imbalance in the baseline characteristics and outcome measures.[15]
	20c	For participants who discontinue treatment early, we will use last observation carried forward analysis to handle the missing data, meaning that we will input outcome data of patients who are lost to follow-up in our analysis.[15]
Methods: Monitoring		
Data monitoring	21a	An independent data monitoring committee (DMC) is made up of members from Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University. The DMC, blinded to the treatment allocations, will meet regularly to monitor the study data.[15]
	21b	The DMC will also perform interim-analysis when 50% of patients have been randomised and have completed the primary outcome measurement.[15]
Harms	22	Adverse events (AEs) An adverse event of acupuncture is defined as symptoms or diseases that are against the purpose of the treatment during or following the acupuncture treatment. The research staff will record the blood pressure, heart rate, heart rhythm, and respiration rate and observe changes in the consciousness of all participants before and after the treatment. The description of AEs, time of occurrence, location of the reaction, level of severity, corresponding management, and the necessity for patient withdrawal from the

		trial will be recorded on the Case Report Forms (CRFs). AEs of acupuncture will be classified according to their location as local and systemic reactions. Local reactions: Subcutaneous haematoma Minor bleeding on withdrawal of the needle Subcutaneous bruise Pain in the punctured region after treatment Skin allergy in the punctured region after treatment Local infection Systemic reactions: Acupuncture fainting Abdominal distention Dizziness or vertigo Leg weakness Muscle spasm Systemic allergy Systemic infection Organ injury Severe AEs are defined as symptoms or diseases that result in hospitalization or prolong hospitalization, disability, a life-threatening situation, or even death. Systemic infection and organ injury are two major AEs. Severe AEs will be reported to the Ethics Committee within 24 h. The Ethics Committee will provide medical suggestions for the research team and decide whether the patient should continue the ongoing treatment. [14]
Auditing	23	The First Affiliated Hospital of Zhejiang Chinese Medical University will audit this study mainly for participant enrolment, consent, and costs.[15]
Ethics and dissemination		
Research ethics approval	24	Research ethics approval

		The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University has reviewed and approved this protocol (approval No. 2018-K-059-01). This study will adhere to the principles of the Declaration of Helsinki.[16]
Protocol amendments	25	Modification of the protocol Any modifications to the protocol, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal application to the Zhejiang Provincial Administration of Traditional Chinese Medicine as well as the Chinese clinical trial registry.[16]
Consent or assent	26a	At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form.[5]
	26b	There are no additional consent provisions for collection and use of participant data and biological specimens in ancillary studies.
Confidentiality	27	All study participants will be given an identification number throughout the trial to assure confidentiality. All participant information will be stored in locked cabinets with limited access. [16]
Declaration of interests	28	None.
Access to data	29	The principal investigator of the research team will have the access to all documents. [15]
Ancillary and post-trial care	30	For patients having common adverse reactions, appropriate medical care will be given to ease local bleeding, irritation, bruising, and so on. For those who have severe reactions leading to organ injury, systematic infection, systematic allergy, and so on, compensation will be given to cover their medical costs by our research team.[14]
Dissemination policy	31a	The results of this study will be published in open-access and peer-reviewed journals and presented at relevant conferences.[16]
	31b	SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript.[17]
	31c	The initial data will be accessible via Research Manager (ResMan).[16]

Appendices		
Informed consent materials	32	A model consent form have been made and provided to the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University
Biological specimens	33	We don't have biological specimens to collect.

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Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial

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Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial

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Keyword: electroacupuncture; urinary incontinence; post-stroke; electrical pudendal nerve stimulation

Word count: 6690

ABSTRACT

Introduction

Electroacupuncture at 'four sacral points', also known as electrical pudendal nerve stimulation therapy, combines the advantages of pudendal nerve neuromodulation (PNM) and the technique of deep insertion of long acupuncture needles. It has been used to treat stress urinary incontinence, female urgency-frequency syndrome, idiopathic urgency urinary incontinence, and neurological bladders in previous studies. Here, we describe the protocol for a randomized controlled trial for evaluation of the efficacy and safety of electroacupuncture at 'four sacral points' for the management of urinary incontinence after stroke.

Methods and Analysis

This is an open-label randomized controlled trial with blinded assessments and analyses. A total of 140 eligible patients will be randomly allocated to two groups. The treatment group (n = 70) will receive electroacupuncture at 'four sacral points' along with routine medical care, while the control group will receive conventional electroacupuncture along with routine medical care. Twenty treatment sessions will occur over a period of 4 weeks. The primary outcome measures will be the self-recorded findings in an incontinent episode diary at baseline and at 4 weeks after baseline. The secondary outcome measures will be the International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) score and the Barthel Activities of Daily Living Index (Barthel ADL Index) score at baseline and at 4 and 28 weeks after baseline.

Ethics and dissemination: This protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (approval No. 2018-K-059-01). Written informed consent will be obtained from each participant. The results of the study will be published in peer-reviewed journals.

Trial registration number: ChiCTR-IOR-17012847

Strengths and limitations of this study

- First pilot study to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the treatment of urinary incontinence after stroke
- Randomised clinical trial with pragmatic design
- A novel acupuncture intervention for the treatment of urinary incontinence after stroke
- Lack of blinding of acupuncturists and participants due to the nature of acupuncture

INTRODUCTION

The International Continence Society (ICS) has defined urinary incontinence (UI) as the involuntary loss of urine [1]. In a systematic review, a random-effects meta-analysis determined the prevalence of UI after stroke to be 23.6% [2]. Post-stroke UI may develop because of various reasons, although direct stroke-induced damage to the neuromicturition pathways is considered the most common cause. Typical symptoms include the involuntary leakage of urine accompanied or immediately preceded by urgency. Urodynamic evaluation often reveals uninhibited detrusor contraction [3]. Physical consequences include skin dermatitis and urinary tract infections, while psychological consequences include embarrassment and low self-esteem [4]. In addition, UI is a powerful prognostic indicator of survival and eventual functional dependence [5]. The most recent research on this topic demonstrated a higher mortality rate for stroke patients with UI (56.8%) than for stroke patients without UI (11.9%) [6]. Therefore, the management of UI after stroke is of great importance.

Evidence-based interventions for post-stroke UI are somewhat limited, but include behavioural and pharmacological interventions, as well as individually tailored structured management plans, or the aid of continence nurse specialists, in order to promote continence [3]. Trials of behavioural and pharmacological therapies have provided insufficient evidence to guide the management of post-stroke UI in adults [7]. Furthermore, side effect profiles and anticholinergic burden should be considered before medications are prescribed [8].

Neuromodulation therapies, which involve the electrical stimulation of target-specific nerves, are reportedly effective for overactive bladder (OAB) or urgency UI (UUI) [9]. Neuromodulation includes transvaginal or transanal electrical stimulation (TES), posterial tibial nerve stimulation (PTNS), sacral nerve neuromodulation (SNM), and pudendal nerve (PN) neuromodulation (PNM) [10]. Although TES is an easy procedure, it is not tolerated by many patients because of discomfort, mucosal injury and high intensity stimulation for an acceptable treatment result [11]. PTNS is a minimally invasive technique with needle electrodes but it is not direct PN stimulation and requires multiple treatments to maintain initial effect comparing with SNM [12, 13]. SNM requires surgical procedure with implantation of InterStim device, providing continuous stimulation by close nerve contact. It has a high success rate [14, 15]. Its common adverse events are pain (15-42%) and infection (3.4-6.1%) at the implant site and surgical revision that can mount up to 33% [13,16]. PN afferents play a particularly important role in the inhibition of the voiding reflex. PNM as direct PN stimulation may be more effective than SNM because the latter only excites a portion of PN afferents. UUI refractory to SNM can be treated by PNM with the Interstim device or the Bion device (selective PN stimulation) [10, 17, 18];

however, the performance of PNM also needs surgery so its disadvantages are similar to those of SNM [10, 18].

According to the theory of traditional Chinese medicine (TCM), UI is primarily caused by kidney and bladder dysfunction in terms of urine control. Accordingly, the principle of acupuncture treatment for UI is to promote the recovery of urine control [19]. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33 (Zhongliao), and BL 35 (Huiyang), are generally selected for the regulation of the bladder voiding function [20-22]. A literature review showed that acupuncture demonstrated more favourable effects than did antimuscarinic drugs for the treatment of OAB and alleviation of symptoms in some comparative trials [23]. In addition, acupuncture reportedly improved the quality of life (QoL) and urodynamic testing parameters in patients with OAB [23, 24]. In a randomized, double-blind, placebo-controlled study, electroacupuncture significantly increased the maximum cystometric capacity and bladder compliance, decreased the detrusor leak point pressure, alleviated lower urinary tract symptoms, and decreased the risk of upper urinary tract damage in patients with post-stroke detrusor overactivity [22]. However, high-quality clinical trials with appropriate inclusion criteria, sample size, control design, acupoint selection, depth of needle insertion, and efficacy and safety evaluations are necessary to properly evaluate the efficacy of acupuncture for the treatment of post-stroke UI [7, 25, 26].

On the basis of the theory of nerve stimulation, we developed electroacupuncture at 'four sacral points' [27, 28], also known as electroacupuncture neurostimulation therapy or electrical PN stimulation therapy. This approach involves the insertion of long needles at 'four sacral points', with electricity to stimulate specific nerves under the sacral region [28, 29]. When it was first developed, this treatment was used to treat stress UI (SUI) in women, and radiographic evidence with simultaneous records of perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure, and pelvic floor surface electromyography have shown that it causes PN excitation [29]. In addition, it has been used for the treatment of female urgency-frequency syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological conditions [28, 30, 31]. The mechanism of electroacupuncture at 'four sacral points' for the treatment of post-stroke UI is that as this therapy can stimulate PN directly, it is speculated that it is able to inhibit central hyperactivity through the vicerosomatic convergence at S2-S4 common spinal neurons of PNs and bladder nerves to relive the symptoms post-stroke UI [32,33].

The effectiveness of post-stroke UI treatment using alternative medicine approaches is worthy of investigation in a well-designed study. To the best of our knowledge, no randomized controlled trials (RCT) comparing the efficacy and safety

of electroacupuncture at 'four sacral points' with those of conventional electroacupuncture for the treatment of post-stroke UI have been conducted. Here we describe a protocol for an RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the management of post-stroke UI.

METHODS AND ANALYSIS

Objectives

This is a protocol comparing the efficacy and safety of electroacupuncture at 'four sacral points' with those of conventional electroacupuncture for the treatment of post-stroke UI. It is designed as a blinded randomized assessment and analysis with two parallel groups over a 4-week treatment period. Randomization will be performed in a random 1:1 allocation sequence.

Recruitment

This is a pragmatic RCT comparing electroacupuncture at 'four sacral points' with conventional electroacupuncture for the treatment of post-stroke UI. The research structure is shown in Figure 1. A total of 140 eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University according to the inclusion and exclusion criteria. At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form. This will be followed by baseline assessment and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks will follow the recruitment procedure. The neurology department of the First Affiliated Hospital of Zhejiang Chinese Medical University has the major source of patients with post-stroke UI. Our reach team includes neurological physicians and special nurses who will interview potentially eligible patients. Advertisements will be released through health education brochures, posters, and videos displayed in the outpatient and inpatient sites of the First Affiliated Hospital of Zhejiang Chinese Medical University. Recruitment information will also be issued through media (e.g. newspapers, broadcasts, and websites).

Design

Randomization and allocation concealment

The randomization scheme has been created by the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University, where professionals used SPSS Statistics 22.0 to generate a random 1:1 allocation sequence using a computer. Professionals involved in allocation will not be recruited in the

study. The random allocation is strictly kept in an opaque envelope and is inaccessible to other research staff. After baseline assessment, the envelope will be opened by an independent staff member in the participant's presence, in order to determine the group assignment for that participant. All patients who give consent for participation and who fulfil the inclusion criteria will be assigned to a group randomly. Randomisation will be requested by the staff member responsible for recruitment and clinical interviews from the First Affiliated Hospital of Zhejiang Chinese Medical University. An independent staff member will open an envelope with printed randomisation numbers in the participant's presence. The therapists will be informed about the participant's allocation at the same time. The staff member responsible for recruitment and clinical interviews is not allowed to receive information about the group allocation.

Blinding

Considering the nature of acupuncture, therapists and participants cannot be blinded to the treatment allocation. Data managers and statisticians will be blinded throughout the trial. Telephone interviewers who collect follow-up information will also be blinded. Data managers, statisticians, and telephone interviewers are restricted from discussing the treatment allocations with each other. The therapists will not be permitted to communicate with any data managers, statisticians, or telephone interviewers. If an unblinding event occurs among data managers, statisticians, or telephone interviewers, the relevant work will be transferred to other appropriately blinded data managers, statisticians, or telephone interviewers. The Investigator must report all code breaks (with reason) as they occur on the corresponding CRF page.

Participants

Sample size

With reference to a similar study [33] with 120 women (efficacy rate, 70.1%:45%), the sample size has been calculated, using PASS 11 software, as 120 patients for a power (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With consideration of the estimated dropout rate (15%), the total sample size will be 140 (70 in each group).

Inclusion criteria

1. Male or female patients aged 30–85 years
2. Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association [34] and the International Continence Society [35]
3. Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years
4. Stable vital signs, normal consciousness, and compliance with treatment
5. Refractoriness to medications (patients who have taken antimuscarinic agents with no UI improvement)

6. Provision of written informed consent

Exclusion criteria

1. UI caused by other diseases such as Parkinson's disease, multiple sclerosis, spinal injury, or Alzheimer's disease
2. Pre-stroke UI, SUI or mixed UI, or overflow incontinence
3. Urinary retention concomitant with UI
4. Urethral injury, lower urinary tract obstruction, acute urinary tract infection, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours
5. Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 [36]
6. Insufficiency of the heart, lungs, liver, and/or kidneys
7. Presence of an implantable electronic device

Elimination criteria

1. Inclusion despite non-fulfilment of the inclusion criteria
2. Lack of exclusion despite fulfilment of the exclusion criteria
3. Eligible participants who receive no interventions

Dropout criteria

1. Poor participant compliance (lack of adherence to treatment for personal reasons)
2. Serious adverse events (SAE), complications, or special physiological changes necessitating discontinuation of the intervention
3. Voluntary dropout

Intervention

All participants will receive routine medical care for stroke recovery, including the control of blood pressure, blood sugar, and blood lipids and routine rehabilitation training. All of the study-related treatments will be provided by skilled acupuncturists who will strictly follow the detailed procedures for each group. During the treatment course and 24-week follow-up time, the administration of antimuscarinic agents and other drugs for neurogenic detrusor overactivity is prohibited for all the patients. They are also not permitted to receive other acupuncture treatment or physiotherapy for UI. All of the study-related treatments will be provided by certified and skilled acupuncturists who will strictly follow the detailed procedures for each group.

Standard operating procedure

1. Needle requirements

   Disposable sterile acupuncture needles in accordance with national standards within the validity period will be used.
2. Hand hygiene of the operator

   The operator is required to sterilize his or her hands with a sanitizer before the acupuncture procedure.
3. Sterilization of the acupuncture points

Within a 5-cm diameter with the acupoint as the centre, sterilize the skin over the acupoints using a cotton swab dipped in 0.45%–0.55% povidone iodine or 75% ethanol.

4. Procedure

Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'.

a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected. The two upper points are located on either side of the sacrococcygeal joint, approximately 1 cm from the joint. The two lower points are located on either side of the tip of the coccyx, approximately 1 cm from the coccyx. Acupuncture will be performed at LI15 (Jianyu), LI11 (Quchi), LI10 (Shousanli), SJ5 (Waiguan), and LI4 (Hegu) for participants with upper limb paralysis. For participants with lower limb paralysis, ST31 (Biguan), ST34 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia, with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang) for participants with facial paralysis and drooling.

b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong Medical Apparatus Factory, Suzhou, China) measuring 0.40 × 100 mm will be inserted perpendicularly to a depth of 80–90 mm to induce a sensation referred to the urethra or anus via stimulation of the main trunk of the PN. At the lower sacral points, a needle measuring 0.40 × 100 or 0.40 × 125 mm will be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm to induce a sensation referred to the urethra via stimulation of the perineal nerve (Figure 4). Once the sensation is induced in the respective regions, two pairs of electrodes from the G6805-A electroacupuncture device (Shantou Medical equipment factory, Shantou, China) will be connected to the two ipsilaterally inserted needles, with the anode connected to the upper needle and the cathode connected to the lower needle. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be performed for 20 min during each treatment. PFM contraction around the urethra (often comfortable) must be maintained during the entire electrostimulation procedure. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

Control group: Participants in this group will receive conventional electroacupuncture.

a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao, both sides), corresponding to the conventional electroacupuncture treatment of UI. The point selection procedure for participants with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the same as that used for the treatment group.

b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao), a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the electrodes from the G6805-A electroacupuncture device will be connected to the needles at these points, with the anode connected to ST28 and the cathode connected to CV6 and CV4. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity that is tolerable by the participants. Electrostimulation will be performed for 20 min during each treatment. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

5. Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks).

Outcome measures

Primary outcome measures

The incontinent episode diary

The incontinent episode diary (Table 1) will be used to derive the primary outcome measure. The number of incontinent episodes will be recorded by the participants over a period of 3 days at baseline. A template will be provided for patient use. This data will be recorded again at the end of treatment.

Table 1 The incontinent episode diary

Name		Date			
Record every accidental loss of urine over 3 consecutive days with an X.					
Start at baseline and continue recording for 3 days					
Day 1		Day 2		Day 3	
eg X					

Secondary outcome measures

1. International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) [37] (Table 2)

2. Barthel Activities of Daily Living Index (Barthel ADL Index) [38] (Table 3)

The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and psychometrically robust patient-completed questionnaire for evaluating the frequency and severity of UI in men and women and its impact on quality of life (QoL). The ICIQ-UI SF score ranges from 0 to 21 [39]. The Barthel ADL Index is a 10-item measure of activities of daily living (ADL) that is frequently used in clinical practice and as a trial outcome measure in stroke medicine [38]. It is used to assess baseline abilities to quantify functional changes, including UI, after rehabilitation in stroke patients.

The above outcome measures will be assessed at baseline and at 4 and 28 weeks after baseline.

Table 2 International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF)

1. Please write in your date of birth:	□□ □□ □□ date month year	
2. Are you	Female □ Male □	
3. How often do you leak urine? (Tick one box)		
	never	□ 0
	about once a week or less often	□ 1
	two or three times a week	□ 2
	about once a day	□ 3
	several times a day	□ 4
	all the time	□ 5
4. We would like to know how much urine you think leaks. How much urine do you usually leak (whether you wear protection or not)? (Tick one box)		
	None	□ 0
	a small amount	□ 2
	a moderate amount	□ 4
	a large amount	□ 6
5. Overall, how much does leaking urine interfere with your everyday life? Please ring a number between 0 (not at all) and 10 (a great deal) 0 1 2 3 4 5 6 7 8 9 10 not at all a great deal		

ICIQ score: sum scores 3+4+5	□□	
6. When does urine leak? (Please tick all that apply to you)		
	never – urine does not leak	□
	leaks before you can get to the toilet	□
	leaks when you cough or sneeze	□
	leaks when you are asleep	□
	leaks when you have finished urinating and are dressed	□
	leaks for no obvious reason	□
	leaks all the time	□

Table 3 Barthel Activities of Daily Living Index (Barthel ADL Index)

The Barthel Index		Patient Name Rater Name Date:
Activity		Score
Feeding	Unable	0
	Some help required (e.g., needs help cutting, spreading butter, etc. or requires a modified diet)	5
	Independent	10
Bathing	Dependent	0
	Independent (or in shower)	5
Grooming	Needs help with personal care	0

	Independent face/hair/teeth/shaving (implements provided)	5
Dressing	Dependent	0
	Needs help but can do at least half unaided	5
	Independent (including buttons, zips, laces, etc.)	10
Bowels	Incontinent or catheterized and unable to manage alone	0
	Occasional accident	5
	Continent	10
Bladder	Incontinent or catheterized and unable to manage alone	0
	Occasional accident	5
	Continent	10
Toilet use	Dependent	0
	Needs some help, but can do some things alone	5
	Independent (can get on and off, dress and wipe unassisted)	10
Transfer (bed to chair and back)	Unable, no sitting balance	0
	Major help (one or two people, physical), can sit	5
	Minor help (verbal or physical)	10
	Independent	15
Mobility (on level surfaces)	Immobile or <50 yards	0
	Wheelchair independent, including corners; >50 yards	5
	Walks with little help from one person (verbal or physical); >50 yards	10
	Independent (but may use an aid; e.g., walking stick); >50 yards	15
Stairs	Unable	0
	Needs help (verbal, carrying aid)	5
	Independent	10
	Total	

Adverse events (AEs)

An adverse event of acupuncture is defined as symptoms or diseases that are against the purpose of the treatment during or following the acupuncture treatment [40]. The research staff will record the blood pressure, heart rate, heart rhythm, and respiration rate and observe changes in the consciousness of all participants before and after the treatment. The description of AEs, time of occurrence, location of the reaction, level of severity, corresponding management, and the necessity for patient withdrawal from the trial will be recorded on the Case Report Forms (CRFs). AEs of acupuncture will be classified according to their location as local and systemic reactions.

Local reactions:

Subcutaneous haematoma
Minor bleeding on withdrawal of the needle
Subcutaneous bruise
Pain in the punctured region after treatment
Skin allergy in the punctured region after treatment
Local infection

Systemic reactions:

Acupuncture fainting
Abdominal distention
Dizziness or vertigo
Leg weakness
Muscle spasm
Systemic allergy
Systemic infection
Organ injury

Severe AEs are defined as symptoms or diseases that result in hospitalization or prolong hospitalization, disability, a life-threatening situation, or even death [41]. Systemic infection and organ injury are two major AEs. Severe AEs will be reported to the Ethics Committee within 24 h. The Ethics Committee will provide medical suggestions for the research team and decide whether the patient should continue the ongoing treatment.

For patients having common adverse reactions, appropriate medical care will be given to ease local bleeding, irritation, bruising, and so on. For those who have severe reactions leading to organ injury, systematic infection, systematic allergy, and so on, compensation will be given to cover their medical costs by our research team.

Data management, monitoring and auditing

A research assistant will record the baseline characteristics of all participants. Trained caregivers will record the frequency of UI at baseline and at 4 weeks after baseline. A researcher who remains blinded to treatment group allocation will collect data regarding the frequency of UI and the weight of pads from the caregivers. The participants will also complete ICIQ-UI SF and the Barthel ADL Index at baseline and

at 4 weeks after baseline. A blinded telephone interviewer will interview the participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at 28 weeks after baseline. All data will be recorded on the CRFs. For participants who discontinue treatment early, we will use last observation carried forward analysis to handle the missing data, meaning that we will input outcome data of patients who are lost to follow-up in our analysis.

After the completion of the CRFs, two independent researchers blinded to the group allocation will separately input data into an Excel spreadsheet. Another independent supervisor will check the two datasets for consistency. If conflicting data entries are discovered, the supervisor will compare the datasets with the original CRFs and mark the modification on the CRFs. The principal investigator of the research team will have the access to all documents and will protect the electronic documents with a password and create backups of all documents. The First Affiliated Hospital of Zhejiang Chinese Medical University will be responsible for the storage and management of all data.

An independent data monitoring committee (DMC) is made up of members from Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University. The DMC, blinded to the treatment allocations, will meet regularly to monitor the study data. The DMC will also perform interim-analysis when 50% of patients have been randomised and have completed the primary outcome measurement.

The First Affiliated Hospital of Zhejiang Chinese Medical University will audit this study mainly for participant enrolment, consent, and costs.

Statistical analysis

All statistical analyses will be performed by a statistician from the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University using SPSS Statistics 22.0. A normality test will be used to determine whether the data are normally distributed. ANCOVA (analysis of covariance) will be used if there is imbalance in the baseline characteristics and outcome measures. Continuous variables with a normal distribution will be expressed as means ± standard deviations (SDs). Continuous variables with a non-normal distribution or ordinal variables will be expressed as medians (with lower, upper quartiles). Categorical variables will be summarized as counts and proportions. A Student's t-test will be used if the primary and secondary outcome measures conform to normal distribution. A paired t-test will be used to compare pre-treatment and post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in the secondary outcome measures. The independent sample t-test will be used to compare the difference between two groups for primary and secondary outcome measures. A Wilcoxon signed rank test will be used if the primary and secondary outcome measures conform to abnormal distribution. A Wilcoxon paired test will be used to compare pre-treatment and post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in secondary outcome measures. The inter-group rank sum test will be used to compare the difference

between two groups for primary and secondary outcome measures. All reported P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A P-value of <0.05 will be considered statistically significant.

Patient and Public Involvement

Patients and the public were not directly involved in the design, recruitment or conduct of this pilot study. Since the participants in our study are under chronic conditions, the outcome measures valuated in this study was influenced by patients' priorities, experience and preferences. As most stroke patients are in great need of acupuncture treatment in China, we did not view the intervention as burdensome and the burden of the intervention was not assessed by the patients themselves. The results of this study will be disseminated in peer-reviewed journals and at academic conferences. A summary of the study report will be written for patients through online website (https://sandychenshan.haodf.com/) and WeChat (a free messaging and calling application) account or group.

ETHICS AND DISSEMINATION

Research ethics approval

The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University has reviewed and approved this protocol (approval No. 2018-K-059-01). This study will adhere to the principles of the Declaration of Helsinki. This study will be conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University. Each participant will voluntarily sign written informed consent forms.

Modification of the protocol

Any modifications to the protocol, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal application to the Zhejiang Provincial Administration of Traditional Chinese Medicine as well as the Chinese clinical trial registry.

Confidentiality

All study participants will be given an identification number throughout the trial to assure confidentiality. All participants' information will be stored in locked cabinets with limited access.

Dissemination

The initial data will be accessible via Research Manager (ResMan). The results of this study will be published in open-access and peer-reviewed journals and presented at relevant conferences.

DISCUSSION

According to the present study protocol, in addition to electroacupuncture at 'four sacral points' in the treatment group and conventional electroacupuncture in the

control group, the same acupoints for other stroke symptoms will also be selected for both groups. Other stroke symptoms include unilateral limb weakness, facial paresis, dysphasia, and dysphagia [42]. In China, acupuncture has been a primary medical intervention for stroke [43]. In fact, not providing acupuncture therapy to a stroke patient is considered impractical.

Antimuscarinic agents are considered first-line drugs for neurogenic detrusor overactivity (NDO) [44]. However, because of their moderate efficacy and troublesome side effects, quite a few patients exhibit refractory disease [45]. According to the eligibility criteria, participants who are refractory to medication will be included in this RCT.

With regard to the outcome measures, the incontinent episode diary will be used as objective measure to record the frequency of incontinence. Patients will record their findings in the incontinent diary for only 3 days, because a longer recording period can lead to decreased patient compliance [46,47]. In order to improve adherence, health education about the importance of UI management will be conducted by a special nurse and brochures on post-stroke UI will be provided to patients. The ICIQ-UI SF and Barthel ADL Index will be used as subjective measures to investigate UI symptoms and QoL. The ICIQ-UI SF is a useful tool to assess UI with regard to the severity of symptoms and impact on QoL at baseline and at follow-up [48]. The Barthel ADL Index (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfer, mobility, and stairs) is an important predictor of stroke outcomes. Studies involving stroke survivors should include ADL assessments for better management of stroke patients [38].

In summary, we have described a protocol for a pilot RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the treatment of post-stroke UI. The results of this trial should lead to a greater understanding of promising alternative options for post-stroke UI.

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Contributors
SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript.

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Competing Interests Statement
None

Ethics approval
The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University.

Provenance and peer review
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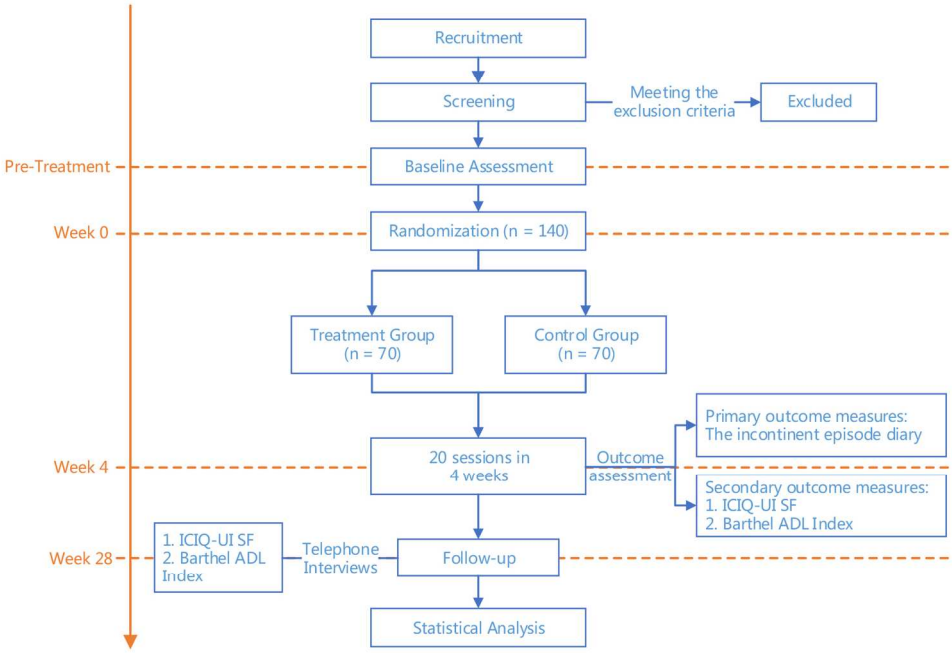
Figure legends

Figure 1 Study flowchart

Figure 2 Locations of the 'four sacral points' for electroacupuncture

Figure 3 Anatomical positions of the 'four sacral points' for electroacupuncture

Figure 4 Transverse computed tomography (CT) image of the coccygeal apex
The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN in Alcock's canal)



Study flowchart

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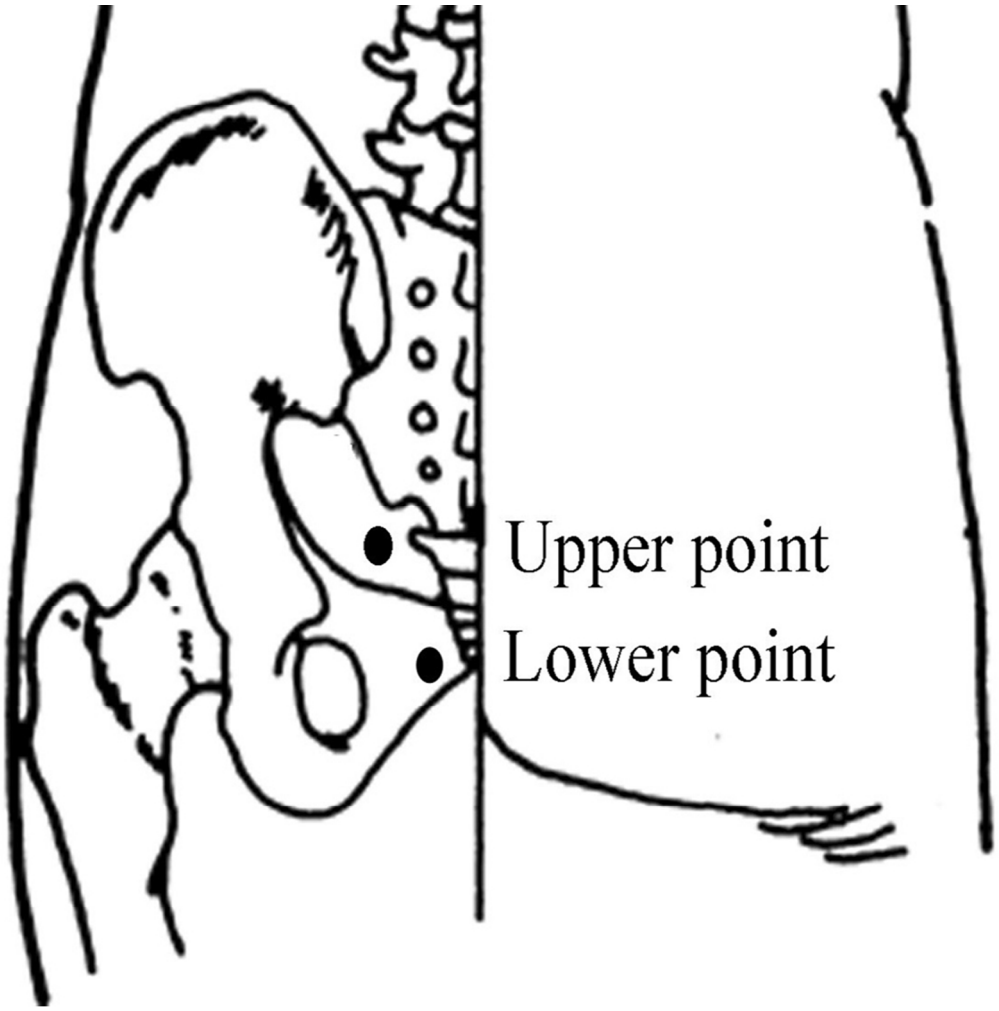

Locations of the 'four sacral points' for electroacupuncture

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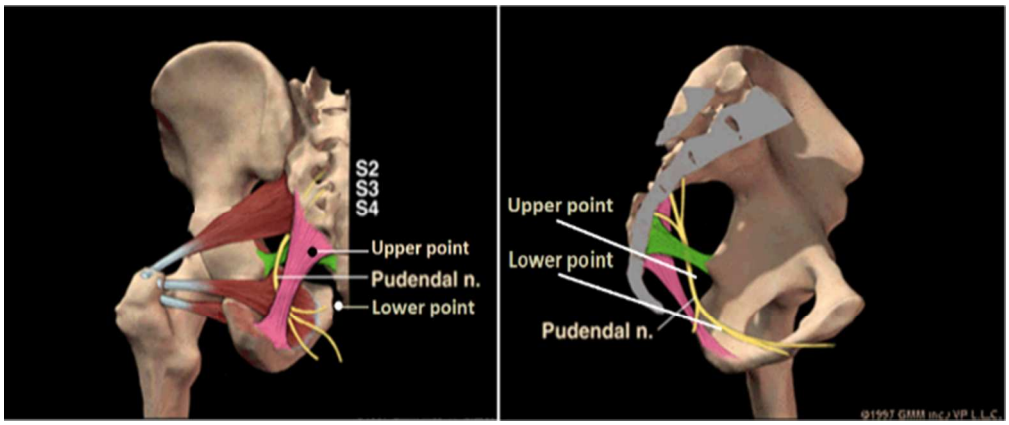

Anatomical positions of the 'four sacral points' for electroacupuncture

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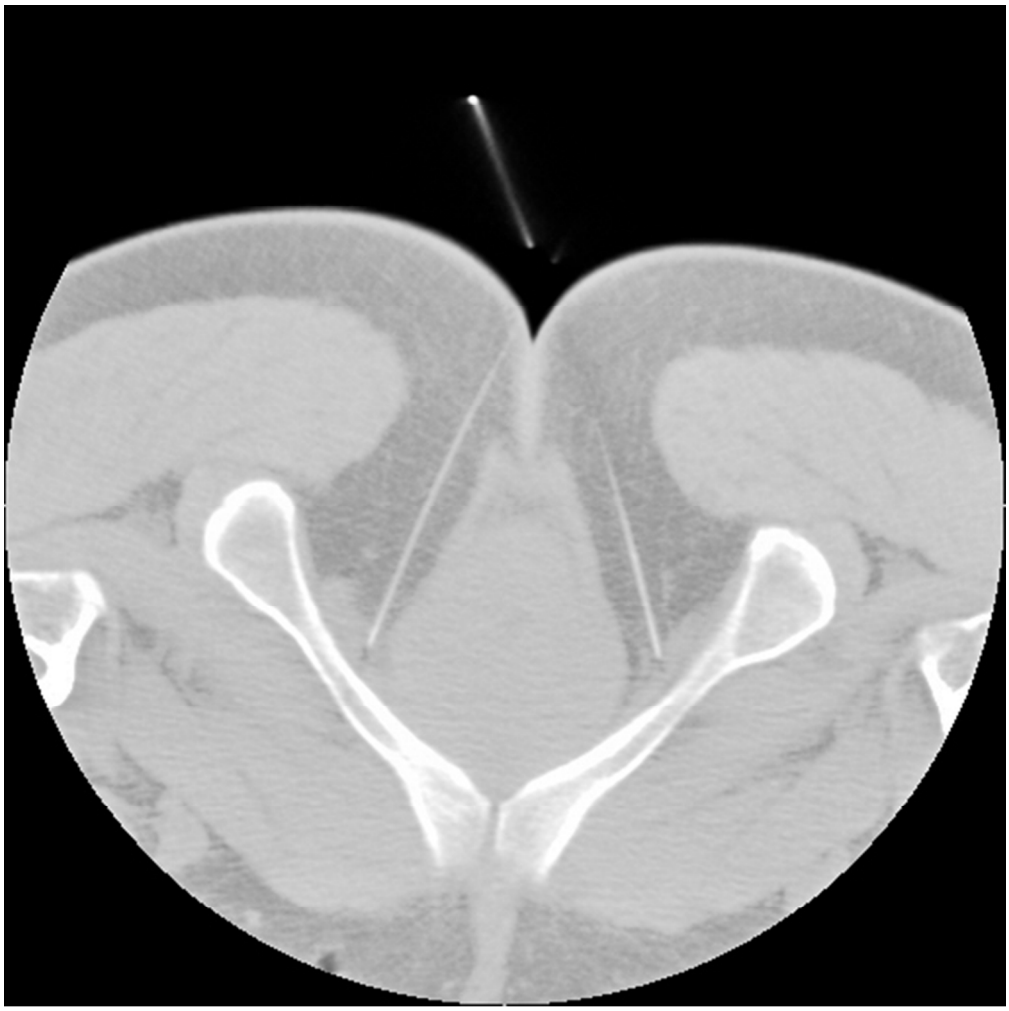


Transverse computed tomography (CT) image of the coccygeal apex
The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN in Alcock's canal)

90x90mm (300 x 300 DPI)

Section/item	ItemNo	Description	
Administrative Information			
Title	1	Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial [1]	
Trial registration	2a	ChiCTR-IOR-17012847 [2]	
	2b	Primary registry and trial identifying number	ChiCTR-IOR-17012847
		Date of registration in primary registry	30 Sep 2017
		Secondary identifying numbers	
		Source(s) of monetary or material support	Zhejiang Provincial Administration of Traditional Chinese Medicine
		Primary sponsor	Zhejiang Provincial Administration of Traditional Chinese Medicine
		Secondary sponsor(s)	
		Contact for public queries	CZ[zc985417@163.com],HFZ[zhuzhijiejie@163.com]
		Contact for scientific queries	CZ,HFZ Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China
		Public title	Electroacupuncture at 'four sacral points' for the treatment of urinary incontinence after stroke
		Scientific title	Comparison of efficacy and safety between electroacupuncture at 'four sacral points' and conventional electroacupuncture for the treatment of urinary incontinence after stroke: study protocol for a randomized controlled trial
		Countries of recruitment	China
		Health condition(s) or problem(s) studied	Acupuncture treatment; Urinary incontinence after stroke

Intervention(s)	Treatment group: electroacupuncture at ‘four sacral points’ Control group: conventional electroacupuncture
Key inclusion and exclusion criteria	Ages eligible for study: 30-85 years old; Sexes eligible for study: both; Accepts healthy volunteers: no. Inclusion criteria: Male or female patients aged 30–85 years; Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association and the International Continence Society; Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years; Stable vital signs, normal consciousness, and compliance with treatment; Refractoriness to medications (patients who have taken antimuscarinic agents with no UI improvement); Provision of written informed consent. Exclusion criteria: UI caused by other diseases such as Parkinson’s disease, multiple sclerosis, spinal injury, or Alzheimer’s disease; Pre-stroke UI, SUI or mixed UI, overflow incontinence; Urinary retention concomitant with UI; Urethral injury, lower urinary tract obstruction, acute urinary tract infection, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours; Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 ;

			Insufficiency of the heart, lungs, liver, and/or kidneys; Presence of an implantable electronic device
		Study type	Interventional Allocation: randomized; Intervention model: parallel assignment; Masking: blinded assessment and analysis. Primary purpose: treatment
		Date of first enrolment	Hasn't started
		Target sample size	140
		Recruitment status	Hasn't started
		Primary outcome(s)	The incontinent episode diary
		Key secondary outcomes	International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF); Barthel Activities of Daily Living Index (Barthel ADL Index)
Protocol version	3	Issue date: 30 Sep 2017	
		Protocol amendment number: 01	
		Authors: Chen Shan; Siyou Wang； Lihua Xuan, Hanti Lu, Zhikai Hu, Chao Zhang, Huifang Zhang [1]	
Funding	4	This work has been supported Zhejiang Provincial Administration of Traditional Chinese Medicine (grant number 2016ZA076; 2018ZA045).	
Roles and responsibilities	5a	SC[No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; SYW[No. 650 Wanpin Road, Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian, Shanghai, China]; LHX[No. 54 Youdian Road, Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; HTL[No.	

		54 Youdian Road, Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; ZKH[No. 668 Jimei Avenue, Jimei District, Department of Computer Science, Huaqiao University, Xiamen, China]; CZ[No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Rehabilitation Unit of the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China]; HFZ[No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China] Contributors: SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript. [17]
	5b	Trial sponsor: Zhejiang Provincial Administration of Traditional Chinese Medicine [18]
		Sponsor's Reference: grant number 2016ZA076;2018ZA045 [18]
		Contact name: Zhejiang Provincial Administration of Traditional Chinese Medicine
		Address: No.216 Qingchun Road
		Telephone: +86 0571 8770 9076
		Email: zjtcm@zjwst.gov.cn
	5c	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
	5d	Authors in the title page are members of the steering committee
Introduction		
Background and rationale	6a	Introduction: In a systematic review, a random-effects meta-analysis determined the prevalence of UI after stroke to be 23.6%. Physical consequences include skin dermatitis and urinary tract infections, while psychological consequences include embarrassment and low self-esteem. In addition, UI is a powerful prognostic indicator of survival and eventual functional

dependence. The most recent research on this topic demonstrated a higher mortality rate for stroke patients with UI (56.8%) than for stroke patients without UI (11.9%). Therefore, the management of UI after stroke is of great importance. Post-stroke UI may develop because of various reasons, although direct stroke-induced damage to the neuromicturition pathways is considered the most common cause. Typical symptoms include the involuntary leakage of urine accompanied or immediately preceded by urgency. Urodynamic evaluation often reveals uninhibited detrusor contraction.

Evidence-based interventions for post-stroke UI include behavioural and pharmacological interventions, as well as individually tailored structured management plans, or the aid of continence nurse specialists, in order to promote continence. Trials of behavioural and pharmacological therapies have provided insufficient evidence to guide the management of post-stroke UI in adults. Furthermore, side effect profiles and anticholinergic burden should be considered before medications are prescribed. Neuromodulation therapies, which involve the electrical stimulation of target-specific nerves, are reportedly effective for overactive bladder (OAB) or urgency UI (UUI). Neuromodulation includes transvaginal or transanal electrical stimulation (TES), posterior tibial nerve stimulation (PTNS), sacral nerve neuromodulation (SNM), and pudendal nerve (PN) neuromodulation (PNM). Although TES is an easy procedure, it is not tolerated by many patients because of discomfort, mucosal injury and high intensity stimulation for an acceptable treatment result. PTNS is a minimally invasive technique with needle electrodes but it is not direct PN stimulation and requires multiple treatments to maintain initial effect comparing with SNM. SNM requires surgical procedure with implantation of InterStim device, providing continuous stimulation by close nerve contact. It has a high success rate. Its common adverse events are pain (15-42%) and infection (3.4-6.1%) at the implant site and surgical revision that can mount up to 33%. PN afferents play a particularly important role in the inhibition of the voiding reflex. PNM as direct PN stimulation may be more effective than SNM because the latter only excites a portion of PN afferents. UUI refractory to SNM can be treated by PNM with the Interstim device or the Bion device (selective PN stimulation); however, the performance of PNM also needs surgery so its disadvantages are similar to those of SNM.

On the basis of the theory of nerve stimulation, we developed electroacupuncture at ‘four sacral points’, also known as electroacupuncture neurostimulation therapy or electrical PN stimulation therapy. This approach involves the insertion of long

		needles at 'four sacral points,' with electricity to stimulate specific nerves under the sacral region. In our previous study, this treatment has been used to treat stress UI (SUI) in women, and radiographic evidence with simultaneous records of perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure, and pelvic floor surface electromyography have shown that it causes PN excitation. It has also been used for the treatment of female urgency-frequency syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological conditions. High quality study on electroacupuncture at 'four sacral points' for post-stroke UI need to be conducted for a better management of UI after stroke.[3-4] Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks).[9]
	6b	The principle of acupuncture treatment for UI is to promote the recovery of urine control. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33 (Zhongliao), and BL 35 (Huiyang), are generally selected for the regulation of the bladder voiding function. A literature review showed that acupuncture demonstrated more favourable effects than did antimuscarinic drugs for the treatment of OAB and alleviation of symptoms in some comparative trials.[4]
Objectives	7	Here we describe a protocol for an RCT to evaluate the efficacy and safety of electroacupuncture at 'four sacral points' for the management of post-stroke UI.[5]
Trial design	8	It is designed as a blinded randomized assessment and analysis with two parallel groups over a 4-week treatment period. Randomization will be performed in a random 1:1 allocation sequence.[5]
Methods: Participants, interventions, and outcomes		
Study setting	9	Eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University [5]
Eligibility criteria	10	Inclusion Criteria 1. Male or female patients aged 30–85 years

		2. Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke Association and the International Continence Society 3. Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years 4. Stable vital signs, normal consciousness, and compliance with treatment 5. Refractoriness to medications(patients who have taken antimuscarinic agents with no UI improvement) 6. Provision of written informed consent Exclusion Criteria 1. UI caused by other diseases such as Parkinson's disease, multiple sclerosis, spinal injury, or Alzheimer's disease 2. Pre-stroke UI, SUI or mixed UI, or overflow incontinence. 3. Urinary retention concomitant with UI 4. Urethral injury, lower urinary tract obstruction, acute urinary tract infection, refractory urinary tract infection, hydronephrosis, urological calculi, or tumours 5. Severe cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score of <22 6. Insufficiency of the heart, lungs, liver, and/or kidneys 7. Presence of an implantable electronic device [6-7] Eligibility criteria for acupuncturists and training All of the study-related treatments will be provided by certified and skilled acupuncturists who will strictly follow the detailed procedures for each group.[7]
Interventions	11a	Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'. a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected. The two upper points are located on either side of the sacrococcygeal joint, approximately 1 cm from the joint. The two lower points are located on either side of the tip of the coccyx, approximately 1 cm from the coccyx. Acupuncture will be performed at LI15 (Jianyu), LI11 (Quchi), LI10 (Shousanli), SJ5

(Waiguan), and LI4 (Hegu) for participants with upper limb paralysis. For participants with lower limb paralysis, ST31 (Biguan), ST34 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia, with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang) for participants with facial paralysis and drooling.

b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong Medical Apparatus Factory, Suzhou, China) measuring 0.40 × 100 mm will be inserted perpendicularly to a depth of 80–90 mm to induce a sensation referred to the urethra or anus via stimulation of the main trunk of the PN. At the lower sacral points, a needle measuring 0.40 × 100 or 0.40 × 125 mm will be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm to induce a sensation referred to the urethra via stimulation of the perineal nerve (Figure 4). Once the sensation is induced in the respective regions, two pairs of electrodes from the G6805-A electroacupuncture device (Shantou Medical equipment factory, Shantou, China) will be connected to the two ipsilaterally inserted needles, with the anode connected to the upper needle and the cathode connected to the lower needle. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be performed for 20 min during each treatment. PFM contraction around the urethra (often comfortable) must be maintained during the entire electrostimulation procedure. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints.

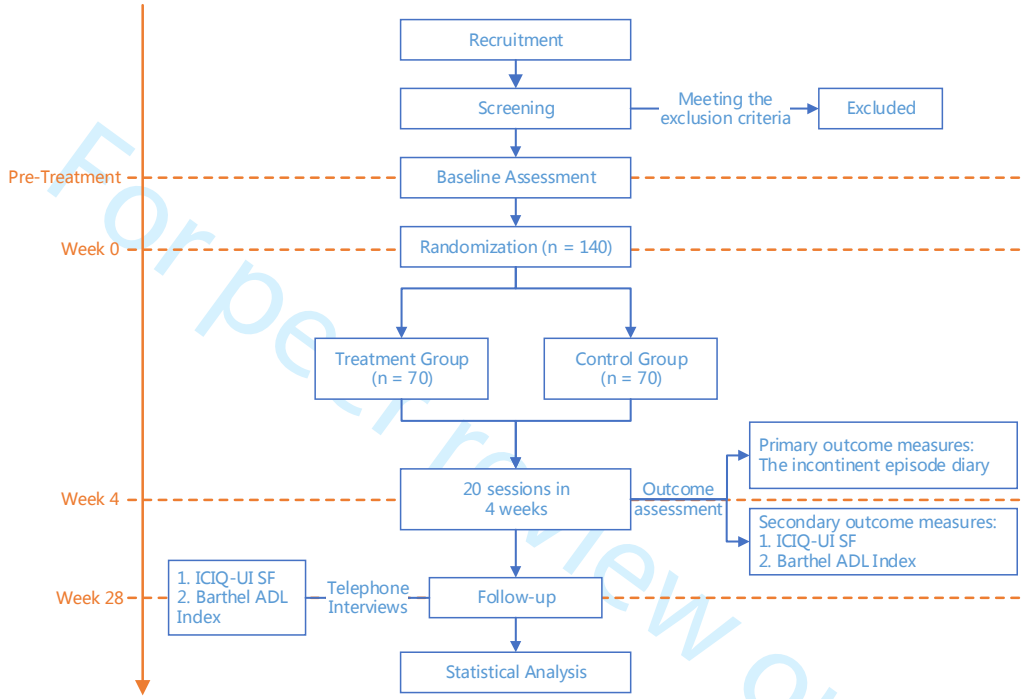
Control group: Participants in this group will receive conventional electroacupuncture.

a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao, both sides), corresponding to the conventional electroacupuncture treatment of UI. The point selection procedure for participants with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the same as that used for the treatment group.

b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao), a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the electrodes from the G6805-A electroacupuncture device will be connected to the needles at these points with the anode connected to ST28 and the cathode connected to CV6 and CV4. The device will be set to produce electrical stimulation (biphasic 2-ms pulse duration) at a

		frequency of 2.0 Hz and a moderate intensity that is tolerable by the participants. Electrostimulation will be performed for 20 min during each treatment. Conventional acupuncture without electricity will be applied for 20 min at the remaining acupoints. Treatment period: All participants will receive treatment every day from Monday to Friday. One course of treatment will comprise 10 sessions. The therapeutic effects will be evaluated after the completion of two treatment courses (4 weeks). [8-9]
	11b	Elimination criteria 1. Inclusion despite non-fulfilment of the inclusion criteria 2. Lack of exclusion despite fulfilment of the exclusion criteria 3. Eligible participants who receive no interventions Dropout criteria 1. Poor participant compliance (lack of adherence to treatment for personal reasons) 2. Serious adverse events (SAE), complications, or special physiological changes necessitating discontinuation of the intervention 3. Voluntary dropout [7]
	11c	In order to improve adherence, health education about the importance of UI management will be conducted by a special nurse and brochures on post-stroke UI will be provided to patients.[17]
	11d	All participants will receive routine medical care for stroke recovery, including the control of blood pressure, blood sugar, and blood lipids and routine rehabilitation training. During the treatment course and 24-week follow-up time, the administration of antimuscarinic agents and other drugs for neurogenic detrusor overactivity is prohibited for all the patients. They are also not permitted to receive other acupuncture treatment or physiotherapy for UI. All of the study-related treatments will be provided by certified and skilled acupuncturists who will strictly follow the detailed procedures for each group.[7]
Outcomes	12	Primary outcome measures The incontinent episode diary The incontinent episode diary (Table 1) will be used to derive the primary outcome measure. The number of incontinent episodes

		will be recorded by the participants over a period of 3 days at baseline. A template will be provided for patient use. This data will be recorded again at the end of treatment. Secondary outcome measures 1. International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) (Table 2) 2. Barthel Activities of Daily Living Index (Barthel ADL Index) (Table 3) The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and psychometrically robust patient-completed questionnaire for evaluating the frequency and severity of UI in men and women and its impact on quality of life (QoL). The ICIQ-UI SF score ranges from 0 to 21. The Barthel ADL Index is a 10-item measure of activities of daily living (ADL) that is frequently used in clinical practice and as a trial outcome measure in stroke medicine. It is used to assess baseline abilities to quantify functional changes, including UI, after rehabilitation in stroke patients. The above outcome measures will be assessed at baseline and at 4 and 28 weeks after baseline. [9-10]
Participant timeline	13	A total of 140 eligible participants will be recruited from the inpatient and outpatient departments of the First Affiliated Hospital of Zhejiang Chinese Medical University according to the inclusion and exclusion criteria. At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form. This will be followed by baseline assessment and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks will follow the recruitment procedure. [5] Figure1



Sample size	14	With reference to a similar study with 120 women (efficacy rate, 70.1%:45%), the sample size has been calculated, using PASS 11 software, as 120 patients for a power (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With consideration of the estimated dropout rate (15%), the total sample size will be 140 (70 in each group).[6]
Recruitment	15	The neurology department of the First Affiliated Hospital of Zhejiang Chinese Medical University has the major source of patients with post-stroke UI. Our reach team includes neurological physicians and special nurses who will interview potentially eligible

		patients. Advertisements will be released through health education brochures, posters, and videos displayed in the outpatient and inpatient sites of the First Affiliated Hospital of Zhejiang Chinese Medical University. Recruitment information will also be issued through media (e.g. newspapers, broadcasts, and websites) [5]
Methods: Assignment of interventions		
Administrative Information		
Allocation:		
Sequence generation	16a	The randomization scheme has been created by the Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang Chinese Medical University, where professionals used SPSS Statistics 22.0 to generate a random 1:1 allocation sequence using a computer.[5-6]
Allocation concealment mechanism	16b	Professionals involved in allocation will not be recruited in the study. The random allocation is strictly kept in an opaque envelope and is inaccessible to other research staff. After baseline assessment, the envelope will be opened by an independent staff member in the participant's presence, in order to determine the group assignment for that participant.[6]
Implementation	16c	All patients who give consent for participation and who fulfil the inclusion criteria will be assigned to a group randomly. Randomisation will be requested by the staff member responsible for recruitment and clinical interviews from the First Affiliated Hospital of Zhejiang Chinese Medical University. An independent staff member will open an envelope with printed randomisation numbers in the participant's presence. The therapists will be informed about the participant's allocation at the same time. The staff member responsible for recruitment and clinical interviews is not allowed to receive information about the group allocation.[6]
Blinding	17a	Considering the nature of acupuncture, therapists and participants cannot be blinded to the treatment allocation. Data managers and statisticians will be blinded throughout the trial. Telephone interviewers who collect follow-up information will also be blinded. Data managers, statisticians, and telephone interviewers are restricted from discussing the treatment allocations with each other. The therapists will not be permitted to communicate with any data managers, statisticians, or telephone interviewers.[6]
	17b	If an unblinding event occurs among data managers, statisticians, or telephone interviewers, the relevant work will be transferred to

		other appropriately blinded data managers, statisticians, or telephone interviewers. The Investigator must report all code breaks (with reason) as they occur on the corresponding CRF page.[6]
Methods: Data collection, management and analysis		
Data collection method	18a	A research assistant will record the baseline characteristics of all participants. Trained caregivers will record the frequency of UI at baseline and at 4 weeks after baseline. A researcher who remains blinded to treatment group allocation will collect data regarding the frequency of UI and the weight of pads from the caregivers. The participants will also complete ICIQ-UI SF and the Barthel ADL Index at baseline and at 4 weeks after baseline. A blinded telephone interviewer will interview the participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at 28 weeks after baseline. All data will be recorded on the CRFs. After the completion of the CRFs, two independent researchers blinded to the group allocation will separately input data into an Excel spreadsheet. Another independent supervisor will check the two datasets for consistency. If conflicting data entries are discovered, the supervisor will compare the datasets with the original CRFs and mark the modification on the CRFs.[14-15]
	18b	For participants who discontinue treatment early, we will use last observation carried forward analysis to handle the missing data, which means we will input outcome data of patients who lost follow-up to our analysis.[15]
Data management	19	The principal investigator of the research team will have the access to all documents and will protect the electronic documents with a password and create backups of all documents. The First Affiliated Hospital of Zhejiang Chinese Medical University will be responsible for the storage and management of all data.[15]
Statistical methods	20a	All statistical analyses will be performed by a statistician from the Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University using SPSS Statistics 22.0. A normality test will be used to determine whether the data are normally distributed. Continuous variables with a normal distribution will be expressed as means ± standard deviations (SDs). Continuous variables with a non-normal distribution or ordinal variables will be expressed as medians (with lower, upper quartiles). Categorical variables will be summarized as counts and proportions. A Student's t-test will be used if the primary and secondary outcome measures conform to normal distribution. A paired t-test will be used to compare pre-treatment and

		post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in the secondary outcome measures. The independent sample t-test will be used to compare the difference between two groups for primary and secondary outcome measures. A Wilcoxon signed rank test will be used if the primary and secondary outcome measures conform to abnormal distribution. A Wilcoxon paired test will be used to compare pre-treatment and post-treatment UI occurrence for the primary outcome measure and pre-treatment and post-treatment scores in secondary outcome measures. The inter-group rank sum test will be used to compare the difference between two groups for primary and secondary outcome measures. All reported P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A P-value of <0.05 will be considered statistically significant.[15-16]
	20b	ANCOVA (analysis of covariance) will be used if there is imbalance in the baseline characteristics and outcome measures.[15]
	20c	For participants who discontinue treatment early, we will use last observation carried forward analysis to handle the missing data, meaning that we will input outcome data of patients who are lost to follow-up in our analysis.[15]
Methods: Monitoring		
Data monitoring	21a	An independent data monitoring committee (DMC) is made up of members from Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical University. The DMC, blinded to the treatment allocations, will meet regularly to monitor the study data.[15]
	21b	The DMC will also perform interim-analysis when 50% of patients have been randomised and have completed the primary outcome measurement.[15]
Harms	22	Adverse events (AEs) An adverse event of acupuncture is defined as symptoms or diseases that are against the purpose of the treatment during or following the acupuncture treatment. The research staff will record the blood pressure, heart rate, heart rhythm, and respiration rate and observe changes in the consciousness of all participants before and after the treatment. The description of AEs, time of occurrence, location of the reaction, level of severity, corresponding management, and the necessity for patient withdrawal from the

		trial will be recorded on the Case Report Forms (CRFs). AEs of acupuncture will be classified according to their location as local and systemic reactions. Local reactions: Subcutaneous haematoma Minor bleeding on withdrawal of the needle Subcutaneous bruise Pain in the punctured region after treatment Skin allergy in the punctured region after treatment Local infection Systemic reactions: Acupuncture fainting Abdominal distention Dizziness or vertigo Leg weakness Muscle spasm Systemic allergy Systemic infection Organ injury Severe AEs are defined as symptoms or diseases that result in hospitalization or prolong hospitalization, disability, a life-threatening situation, or even death. Systemic infection and organ injury are two major AEs. Severe AEs will be reported to the Ethics Committee within 24 h. The Ethics Committee will provide medical suggestions for the research team and decide whether the patient should continue the ongoing treatment. [14]
Auditing	23	The First Affiliated Hospital of Zhejiang Chinese Medical University will audit this study mainly for participant enrolment, consent, and costs.[15]
Ethics and dissemination		
Research ethics approval	24	Research ethics approval

		The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University has reviewed and approved this protocol (approval No. 2018-K-059-01). This study will adhere to the principles of the Declaration of Helsinki.[16]
Protocol amendments	25	Modification of the protocol Any modifications to the protocol, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal application to the Zhejiang Provincial Administration of Traditional Chinese Medicine as well as the Chinese clinical trial registry.[16]
Consent or assent	26a	At the beginning of recruitment, detailed information about the study, including the research objective, study procedure, and potential benefits and risks, will be provided to all eligible patients. If the patient agrees to participate, he or she will be asked to sign a written informed consent form.[5]
	26b	There are no additional consent provisions for collection and use of participant data and biological specimens in ancillary studies.
Confidentiality	27	All study participants will be given an identification number throughout the trial to assure confidentiality. All participant information will be stored in locked cabinets with limited access. [16]
Declaration of interests	28	None.
Access to data	29	The principal investigator of the research team will have the access to all documents. [15]
Ancillary and post-trial care	30	For patients having common adverse reactions, appropriate medical care will be given to ease local bleeding, irritation, bruising, and so on. For those who have severe reactions leading to organ injury, systematic infection, systematic allergy, and so on, compensation will be given to cover their medical costs by our research team.[14]
Dissemination policy	31a	The results of this study will be published in open-access and peer-reviewed journals and presented at relevant conferences.[16]
	31b	SC conceived and wrote the protocol; SYW and LHX contributed to the study design; HTL contributed to the sample size calculation and wrote the statistical analysis plan; ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors have read and approved the final manuscript.[17]
	31c	The initial data will be accessible via Research Manager (ResMan).[16]

Appendices		
Informed consent materials	32	A model consent form have been made and provided to the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University
Biological specimens	33	We don't have biological specimens to collect.