

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021783
Article Type:	Protocol
Date Submitted by the Author:	22-Jan-2018
Complete List of Authors:	Chen, Shan; the First Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture and Moxibustion Wang, Siyou; Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian Xuan, Li; 3, Department of Acupuncture and Moxibustion Lu, Hanti; the First Affiliated Hospital of Zhejiang Chinese Medical University, Clinical Evaluation and Analysis Center Hu, Zhikai; Huaqiao University, Department of Computer Science Zhang, Chao; the First Affiliated Hospital of Zhejiang Chinese Medical University, Rehabilitation Unit Zhang, Huifang; the First Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture and Moxibustion
Keywords:	COMPLEMENTARY MEDICINE, UROLOGY, Stroke medicine < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3 **Comparison of efficacy and safety between electroacupuncture at ‘four sacral**
4 **points’ and conventional electroacupuncture for the treatment of urinary**
5 **incontinence after stroke: study protocol for a randomized controlled trial**
6
7

8 Shan Chen¹, Siyou Wang², Lihua Xuan¹, Hanti Lu³, Zhikai Hu⁴, Chao Zhang⁵,
9 Huifang Zhang¹

10 Corresponding author:

11 Shan Chen

12 Department of Acupuncture and Moxibustion, the First Affiliated Hospital of
13 Zhejiang Chinese Medical University, Hangzhou, China

14 No.9 the Ninth Street, Xiasha Economic and Technological Zone, Hangzhou,
15 Zhejiang Province 310018, China

16 breezeilly@hotmail.com

17 Phone number: +86 152 5881 3929

18 Fax number: 0571-85860230
19
20
21
22

23
24 Siyou Wang, Clinical Research Section, Shanghai Research Institute of Acupuncture
25 and Meridian, Shanghai, China

26 Lihua Xuan, Department of Acupuncture and Moxibustion, the First Affiliated
27 Hospital of Zhejiang Chinese Medical University, Hangzhou, China

28 Hanti Lu, Clinical Evaluation and Analysis Center of the First Affiliated Hospital of
29 Zhejiang Chinese Medical University, Hangzhou, China

30 Zhikai Hu, Department of Computer Science, Huaqiao University, Xiamen, China

31 Chao Zhang, Rehabilitation Unit of the First Affiliated Hospital of Zhejiang Chinese
32 Medical University, Hangzhou, China

33 Huifang Zhang, Department of Acupuncture and Moxibustion, the First Affiliated
34 Hospital of Zhejiang Chinese Medical University, Hangzhou, China
35
36
37
38
39
40
41
42

43 **Keyword:** electroacupuncture; urinary incontinence; post-stroke; electrical pudendal
44 nerve stimulation
45

46 **Word count:** 4683
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

17
18
19
20
21
22
23 Evidence-based interventions for post-stroke UI are somewhat limited, but include
24 behavioural and pharmacological interventions, as well as individually tailored
25 structured management plans, or the aid of continence nurse specialists, in order to
26 promote continence ^[3]. Trials of behavioural and pharmacological therapies have
27 provided insufficient evidence to guide the management of post-stroke UI in adults ^[7].
28 Furthermore, side effect profiles and anticholinergic burden should be considered
29 before medications are prescribed ^[8].

30
31
32
33 Neuromodulation therapies, which involve the electrical stimulation of
34 target-specific nerves, are reportedly effective for overactive bladder (OAB) or
35 urgency UI (UUI) ^[9]. Neuromodulation includes transvaginal or transanal electrical
36 stimulation (TES), percutaneous tibial nerve stimulation (PTNS), sacral nerve
37 neuromodulation (SNM), and pudendal nerve (PN) neuromodulation (PNM) ^[10].
38 Although TES is an easy procedure, it is not tolerated by several patients because of
39 discomfort, mucosal injury, and the necessity for high-intensity stimulation to achieve
40 an acceptable outcome ^[11]. SNM with the InterStim device (Medtronic, Minneapolis,
41 MN) provides continuous stimulation and close nerve contact; thus, it is different
42 from TES. The success rate is high ^[12-13]; however, at least 20% of initially tested
43 patients do not respond to the test procedure ^[14]. The disadvantages of SNM include
44 the invasiveness of the procedure, the high cost of treatment, the high rate of revision
45 surgery, the requirement for device replacement on battery exhaustion, and adverse
46 events (pain and infection) ^[15-16]. PN afferents play a particularly important role in
47 the inhibition of the voiding reflex. Because SNM only excites a portion of PN
48 afferents, direct PN stimulation may be more effective ^[10]. PNM with the Interstim
49 device or the Bion device (selective PN stimulation) can be used to treat UUI
50 refractory to SNM ^[10-17-18], although its disadvantages are similar to those of SNM

1
2
3 [10-18]. PTNS with needle electrodes is minimally invasive, effective, easy to perform,
4 and well tolerated [8]; however, its effect diminishes over time [15-17].
5

6 According to the theory of traditional Chinese medicine (TCM), UI is primarily
7 caused by kidney qi deficiency, which often causes bladder dysfunction in terms of
8 urine control. Accordingly, the principle of acupuncture treatment for UI is to
9 reinforce kidney qi and promote the recovery of bladder function [19]. Acupoints on
10 the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and ST28 (Shuidao), as
11 well as those on the sacral region, such as BL32 (Ciliao), BL33 (Zhongliao), and BL
12 35 (Huiyang), are generally selected for the reinforcement of kidney qi and regulation
13 of the bladder voiding function [20-22]. A literature review showed that acupuncture
14 demonstrated more favourable effects than did antimuscarinic drugs for the treatment
15 of OAB and alleviation of symptoms in some comparative trials [23]. In addition,
16 acupuncture reportedly improved the quality of life (QoL) and urodynamic testing
17 parameters in patients with OAB [23-24]. In a randomized, double-blind,
18 placebo-controlled study, electroacupuncture significantly increased the maximum
19 cystometric capacity and bladder compliance, decreased the detrusor leak point
20 pressure, alleviated lower urinary tract symptoms, and decreased the risk of upper
21 urinary tract damage in patients with post-stroke detrusor overactivity [22]. However,
22 high-quality clinical trials with appropriate inclusion criteria, sample size, control
23 design, acupoint selection, depth of needle insertion, and efficacy and safety
24 evaluations are necessary to properly evaluate the efficacy of acupuncture for the
25 treatment of post-stroke UI [7, 25, 26].
26
27
28
29
30
31
32
33

34 On the basis of the theory of nerve stimulation, we developed electroacupuncture at
35 'four sacral points' [27-28], also known as electroacupuncture neurostimulation
36 therapy or electrical PN stimulation therapy. This approach involves the insertion of
37 long needles at 'four sacral points,' with electricity to stimulate specific nerves under
38 the sacral region [28-29]. When it was first developed, this treatment was used to treat
39 stress UI (SUI) in women, and radiographic evidence with simultaneous records of
40 perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure,
41 and pelvic floor surface electromyography have shown that it causes PN excitation
42 [29]. In addition, it has been used for the treatment of female urgency-frequency
43 syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological
44 conditions [28, 30-31]. The mechanism of action of electroacupuncture at 'four sacral
45 points' for post-stroke UI can be explained by the modulation of reflex pathways at
46 spinal or supraspinal levels [3]. Electrical stimulation of the afferent branches of the
47 PN can induce strong inhibition of the micturition reflex and detrusor hyper-reflexia
48 [10], resulting in the effective treatment of post-stroke UI [31-32].
49
50
51
52
53
54

55 The effectiveness of post-stroke UI treatment using alternative medicine
56 approaches is worthy of investigation in a well-designed study. To the best of our
57
58
59
60

1
2
3 knowledge, no randomized controlled trials (RCT) comparing the efficacy and safety
4 of electroacupuncture at ‘four sacral points’ with those of conventional
5 electroacupuncture for the treatment of post-stroke UI have been conducted. Here we
6 describe a protocol for an RCT to evaluate the efficacy and safety of
7 electroacupuncture at ‘four sacral points’ for the management of post-stroke UI.
8
9

10 11 **METHODS AND ANALYSIS**

12 **Objectives**

13
14 This is a protocol for an RCT designed to compare the efficacy and safety of
15 electroacupuncture at ‘four sacral points’ with those of conventional
16 electroacupuncture for the treatment of post-stroke UI.
17

18 **Recruitment**

19
20 This is a pragmatic RCT comparing electroacupuncture at ‘four sacral points’ with
21 conventional electroacupuncture for the treatment of post-stroke UI. The research
22 structure is shown in Figure 1. A total of 140 eligible participants will be recruited
23 from the inpatient and outpatient departments of the First Affiliated Hospital of
24 Zhejiang Chinese Medical University according to the inclusion and exclusion criteria.
25 At the beginning of recruitment, detailed information about the study, including the
26 research objective, study procedure, and potential benefits and risks, will be provided
27 to all eligible patients. If the patient agrees to participate, he or she will be asked
28 to sign a written informed consent form. This will be followed by baseline assessment
29 and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks
30 will follow the recruitment procedure.
31
32
33
34
35

36 **Design**

37 **Randomization and allocation concealment**

38
39 The randomization scheme has been created by the Clinical Evaluation and Analysis
40 Center of The First Affiliated Hospital of Zhejiang Chinese Medical University, where
41 professionals used SPSS Statistics 22.0 to generate a random allocation sequence
42 using a computer. Professionals involved in allocation will not be recruited in the
43 study. The random allocation is strictly kept in an opaque envelope and is inaccessible
44 to other research staff. After baseline assessment, the envelope will be opened by an
45 independent staff member in the participant’s presence, in order to determine the
46 group assignment for that participant.
47
48
49
50

51 **Blinding**

52
53 Considering the nature of acupuncture, therapists and participants cannot be blinded
54 to the treatment allocation. Data managers and statisticians will be blinded throughout
55 the trial. Telephone interviewers who collect follow-up information will also be
56 blinded. Data managers, statisticians, and telephone interviewers are restricted from
57
58
59

1
2
3 discussing the treatment allocations with each other. The therapists will not be
4 permitted to communicate with any data managers, statisticians, or telephone
5 interviewers. If an unblinding event occurs among data managers, statisticians, or
6 telephone interviewers, the relevant work will be transferred to other appropriately
7 blinded data managers, statisticians, or telephone interviewers.
8
9

10 11 **Participants**

12 **Sample size**

13
14 With reference to a similar study with 120 women (efficacy rate, 70.1%:45%), the
15 sample size has been calculated, using PASS 11 software, as 120 patients for a power
16 (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With
17 consideration of the estimated dropout rate (15%), the total sample size will be 140
18 (70 in each group).
19

20 **Inclusion criteria**

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

28 **Exclusion criteria**

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

39 **Elimination criteria**

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

43 **Dropout criteria**

- 44 1. Poor participant compliance
- 45 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

1
2
3 be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm
4 to induce a sensation referred to the urethra via stimulation of the perineal
5 nerve (Figure 4 and Figure 5). Once the sensation is induced in the respective
6 regions, two pairs of electrodes from the G6805-A electroacupuncture device
7 (Shantou Medical equipment factory, Shantou, China) will be connected to
8 the two ipsilaterally inserted needles, with the anode connected to the upper
9 needle and the cathode connected to the lower needle. The device will be set
10 to produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency
11 of 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be
12 performed for 20 min during each treatment. PFM contraction around the
13 urethra (often comfortable) must be maintained during the entire
14 electrostimulation procedure. Conventional acupuncture without electricity
15 will be applied for 20 min at the remaining acupoints.
16
17
18
19
20
21

22
23 Control group: Participants in this group will receive conventional
24 electroacupuncture.

25 a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and
26 ST28 (Shuidao, both sides), corresponding to the conventional
27 electroacupuncture treatment of UI. The point selection procedure for participants
28 with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the
29 same as that used for the treatment group.
30

31 b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao),
32 a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of
33 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the
34 electrodes from the G6805-A electroacupuncture device will be connected to the
35 needles at these points. The device will be set to produce electrical stimulation
36 (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a moderate intensity
37 that is tolerable by the participants. Electrostimulation will be performed for 20
38 min during each treatment. Conventional acupuncture without electricity will be
39 applied for 20 min at the remaining acupoints.
40
41
42
43
44

- 45 5. Treatment period: All participants will receive treatment every day from Monday
46 to Friday. One course of treatment will comprise 10 sessions. The therapeutic
47 effects will be evaluated after the completion of two treatment courses (4 weeks).
48
49

50 Outcome measures

51 Primary outcome measures

- 52 1. The incontinent episode diary

53 The incontinent episode diary (table 1) will be used to derive the primary outcome
54 measure. The number of incontinent episodes will be recorded by the participants
55
56
57
58
59
60

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:	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	date month year	
2. Are you	Female <input type="checkbox"/> Male <input type="checkbox"/>	
3. How often do you leak urine? (Tick one box)		
	never	<input type="checkbox"/> 0
	about once a week or less often	<input type="checkbox"/> 1
	two or three times a week	<input type="checkbox"/> 2
	about once a day	<input type="checkbox"/> 3
	several times a day	<input type="checkbox"/> 4
	all the time	<input type="checkbox"/> 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	<input type="checkbox"/> 0
	a small amount	<input type="checkbox"/> 2
	a moderate amount	<input type="checkbox"/> 4
	a large amount	<input type="checkbox"/> 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	<input type="checkbox"/> <input type="checkbox"/>	
6. When does urine leak? (Please tick all that apply to you)		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

	never – urine does not leak	<input type="checkbox"/>
	leaks before you can get to the toilet	<input type="checkbox"/>
	leaks when you cough or sneeze	<input type="checkbox"/>
	leaks when you are asleep	<input type="checkbox"/>
	leaks when you have finished urinating and are dressed	<input type="checkbox"/>
	leaks for no obvious reason	<input type="checkbox"/>
	leaks all the time	<input type="checkbox"/>

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

1
2
3 collected and analysed.

4 After the completion of the CRFs, two independent researchers blinded to the group
5 allocation will separately input data into an Excel spreadsheet. Another independent
6 supervisor will check the two datasets for consistency. If conflicting data entries are
7 discovered, the supervisor will compare the datasets with the original CRFs and mark
8 the modification on the CRFs. The principal investigator of the research team will
9 protect the electronic documents with a password and create backups of all documents.
10 The First Affiliated Hospital of Zhejiang Chinese Medical University will be
11 responsible for the storage and management of all data.
12

13 The First Affiliated Hospital of Zhejiang Chinese Medical University will regularly
14 monitor the study data and audit this study.
15
16

17 **Statistical analysis**

18 All statistical analyses will be performed by a statistician from the Clinical Evaluation
19 and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical
20 University using SPSS Statistics 22.0. Continuous variables with a normal distribution
21 will be expressed as means \pm standard deviations (SDs). Continuous variables with a
22 non-normal distribution or ordinal variables will be expressed as medians (with lower
23 upper quartiles). Categorical variables will be summarized as counts and proportions.
24 Continuous variables will be compared using Student's t-test (normal distribution) or
25 the Wilcoxon signed rank test (abnormal distribution). Ordinal variables will be
26 compared using the Wilcoxon signed rank test. The categorical variables will be
27 compared using Fisher's exact test or the chi-square test. All reported P-values will be
28 two-sided, and confidence intervals (CI) will be at the 95% level. A P-value of <0.05
29 will be considered statistically significant.
30
31
32
33

34 **ETHICS AND DISSEMINATION**

35 **Research ethics approval**

36 The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical
37 University has reviewed and approved this protocol (approval No. 2018-K-059-01).
38 This study will adhere to the principles of the Declaration of Helsinki. This study will
39 be conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University.
40 Each participant will voluntarily sign written informed consent forms.
41
42
43
44

45 **Confidentiality**

46 All study participants will be given an identification number throughout the trial to
47 assure confidentiality.
48
49

50 **Dissemination**

51 The results of this study will be published in open-access and peer-reviewed journals
52 and presented at relevant conferences.
53
54

55 **DISCUSSION**

56 According to the present study protocol, in addition to electroacupuncture at 'four
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

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.

Author affiliations

46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

¹Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

²Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian, Shanghai, China

³Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

⁴Department of Computer Science, Huaqiao University, Xiamen, China

⁵Rehabilitation Unit of 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.

Funding Statement

This work was supported by Zhejiang Provincial Administration of Traditional Chinese Medicine (grant number 2018ZA045).

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.

References

- [1] Abrams P, Andersson KE, Birder L, *et al*. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn* 2010;29:213-240.
- [2] Ruffion A, Castro DD, Patel H, *et al*. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. *Neuroepidemiology* 2013;41:146-155.
- [3] Mehdi Z, Birns J, Bhalla A, *et al*. Post-stroke urinary incontinence. *Int J Clin Pract* 2013;67:1128-1137.
- [4] Cai W, Wang J, Wang L, *et al*. Prevalence and risk factors of urinary incontinence for post-stroke inpatients in Southern China. *Neurourol Urodyn* 2015;34:231-235.
- [5] Pizzi A, Falsini C, Martini M, *et al*. Urinary incontinence after ischemic stroke: clinical and urodynamic studies. *Neurourol Urodyn* 2014;33:420-425.
- [6] Gregor J, Steve P, Siobhan C, *et al*. Urinary incontinence and indwelling urinary catheters as predictors of death after new-onset stroke: a report of the south london stroke register. *J Stroke Cerebrovasc Dis* 2018;27:118-124.
- [7] Thomas LH, Cross S, Barrett J, *et al*. Treatment of urinary incontinence after stroke in adults. *Cochrane Database of Systematic Reviews*. 2008;23:CD004462.
- [8] Paniker JN. Urogenital symptoms in neurologic patients. *Continuum*. 2017;23:533-552.
- [9] Yamanishi T, Kaga K, Fuse M, *et al*. Neuromodulation for the treatment of lower urinary tract symptoms. *Low Urin Tract Symptoms* 2015;7:121-123.
- [10] Bosch JL. Electrical neuromodulatory therapy in female voiding dysfunction. *BJU Int* 2006;98 suppl:43-48.
- [11] van Balken MR, Vergunst H, Bemelmans BL. The use of electrical devices for the treatment of bladder dysfunction: a review of methods. *J Urol* 2004;172:846-851.
- [12] Smits MA, Oerlemans D, Marcelissen TA, *et al*. Sacral neuromodulation in patients with idiopathic overactive bladder after initial botulinum toxin therapy. *J Urol* 2013;190:2148-2152.
- [13] Siegel S, Noblett K, Mangel J, *et al*. Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. *Neurourol Urodyn* 2016;34:246-251.
- [14] Spinelli M, Sievert KD. Latest technologic and surgical developments in using InterStim Therapy for sacral neuromodulation: impact on treatment success and safety. *Eur Urol* 2008;54:1287-1296.

- 1
2
3 [15] Hijaz A, Vasavada SP, Daneshgari F, *et al.* Complications and troubleshooting of two-stage
4 sacral neuromodulation therapy: a single-institution experience. *Urology* 2006;68:533-537.
- 5 [16] Lee C, Pizarro-Berdichevsky J, Clifton MM, *et al.* Sacral neuromodulation implant infection:
6 risk factors and prevention. *Curr Urol Rep* 2017;18:16.
- 7 [17] Peters KM. Alternative approaches to sacral nerve stimulation. *Int Urogynecol J*
8 2010;21:1559-1563.
- 9 [18] Groen J, Amiel C, Bosch JL. Chronic pudendal nerve neuromodulation in women with
10 idiopathic refractory detrusor overactivity incontinence: results of a pilot study with a novel
11 minimally invasive implantable mini-stimulator. *Neurourol Urodyn* 2005;24:226-230.
- 12 [19] Sun Z, Yu N, Yue J, *et al.* Acupuncture for urinary incontinence after stroke: a protocol for
13 systematic review. *BMJ Open* 2016;6:e008062.
- 14 [20] Song F, Jiang S, Zheng L, *et al.* Electroacupuncture for post-stroke urinary incontinence: a
15 multicenter randomized controlled study. *Zhongguo Zhen Jiu* 2013;33:769-773.
- 16 [21] Paik SH, Han SR, Kwon OJ, *et al.* Acupuncture for the treatment of urinary incontinence: A
17 review of randomized controlled trials. *Exp Ther Med* 2013;6:773-780.
- 18 [22] Liu Y, Liu L, Wang X. Electroacupuncture at points Baliao and Huiyang (BL35) for
19 post-stroke detrusor overactivity. *Neural Regen Res.* 2013;8:1663-1672.
- 20 [23] Forde JC, Jaffe E, Stone BV, *et al.* The role of acupuncture in managing overactive bladder; a
21 review of the literature. *Int Urogynecol J* 2016;27:1645-1651.
- 22 [24] Olivera CK, Meriwether K, El-Nashar S, *et al.* Nonantimuscarinic treatment for overactive
23 bladder: a systematic review. *Am J Obstet Gynecol* 2016;215:34-57.
- 24 [25] Solberg M, Alræk T, Mdala I, *et al.* A pilot study on the use of acupuncture or pelvic floor
25 muscle training for mixed urinary incontinence. *Acupunct Med* 2016;34:7-13.
- 26 [26] Liu Z, Wang Y, Xu H, *et al.* Observation on therapeutic effect of electroacupuncture for
27 post-stroke urge incontinence. *Xin Zhong Yi* 2010;42:73-75.
- 28 [27] Wang S, Chen G, Li L. “Four sacral needles therapy” for female stress incontinence.
29 *Shanghai J Acup Moxib* 2006;25:15-17.
- 30 [28] Lu J. Observation on therapeutic effect of electroacupuncture neurostimulation therapy for
31 urge urinary incontinence. *Zhongguo Zhenjiu* 2012;32:691-695.
- 32 [29] Wang S, Zhang S. Simultaneous perineal ultrasound and vaginal pressure measurement prove
33 the action of electrical pudendal nerve stimulation in treating female stress incontinence. *BJU*
34 *International.* 2012;110:1338-1343.
- 35 [30] Wang S, Zhang S, Zhao L. Long-term efficacy of electrical pudendal nerve stimulation for
36 urgency–frequency syndrome in women. *Int Urogynecol J* 2014;25:397-402.
- 37 [31] Wang S, LvJ, FX *et al.* Efficacy of electrical pudendal nerve stimulation versus transvaginal
38 electrical stimulation in treating female idiopathic urgency urinary incontinence. *J Urol*
39 2017;197:1496-1501.
- 40 [32] Wang S. Electroacupuncture pudendal nerve stimulation and its application. *J Acupunct Tuina*
41 *Sci* 2013;11:117-121.
- 42 [33] Sacco RL, Kasner SE, Broderick JP, *et al.* An updated definition of stroke for the 21st
43 century: a statement for healthcare professionals from the American Heart Association/American
44 Stroke Association. *Stroke* 2013;44:2064-2089.
- 45 [34] Haylen BT, de Ridder D, Freeman RM, *et al.* Association (IUGA)/International Continence
46 Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol*
47 *Urody* 2010;29:4-20.
- 48 [35] Grut M, Fratiglioni L, Viitanen M, *et al.* Accuracy of the Mini-Mental Status Examination as
49 a screening test for dementia in a Swedish elderly population. *Acta Neurol Scand*
50 1993;87:312-317[1993-04-01].
- 51 [36] Timmermans L, Falez F, Mélot C, *et al.* Validation of use of the International Consultation on
52 Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) for impairment rating:
53 a transversal retrospective study of 120 patients. *Neurourol Urodyn* 2013;32:974-979.
- 54 [37] Duffy L, Gajree S, Langhorne P, *et al.* Reliability (inter-rater agreement) of the Barthel Index
55 for assessment of stroke survivors: systematic review and meta-analysis. *Stroke* 2013;44:462-468.
- 56 [38] Hajebrahimi S, Nourizadeh D, Hamedani R, *et al.* Validity and reliability of the International
57 Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form and its correlation
58 with urodynamic findings. *Urol J* 2012;9:685-690.
- 59 [39] Li Y, Liu Y, Zhang J, *et al.* Analysis on the situation of adverse reaction to acupuncture and
60

1
2
3 acupuncture risk. *Zhongguo Zhenjiu* 2011;31:764-768.

4 [40] Zhao L, Li Y, Zhang F, *et al.* Analysis on the occurrence of laws of adverse events from 1968
5 patients after acupuncture treatment. Symposium of seminar of the ninth national young and
6 middle-aged acupuncture and tuina of China Acupuncture and Moxibustion Association 2010;270-276.

7 [41] Yew KS, Cheng EM. Diagnosis of Acute Stroke. *Am Fam Physician* 2015;91:528-536.

8 [42] Zhang J, Wang D, Liu M. Overview of systematic reviews and meta-analyses of acupuncture
9 for stroke. *Neuroepidemiology* 2014;42:50-58.

10 [43] Mehnert U, Kessler TM. The management of urinary incontinence in the male neurological
11 patient. *Curr Opin Urol* 2014;24:586-592.

12 [44] Smith AL, Wein AJ. Urinary incontinence: pharmacotherapy options. *Ann Med*
13 2011;43:461-476.

14 [45] Robinson D, McClish DK, Wyman JF, *et al.* Comparison between urinary diaries completed
15 with and without intensive patient instructions. *Neurourol Urodyn* 1996;15:143-148.

16 [46] Gordon D, Grpouts A. Evaluation of female lower urinary tract symptoms: overview and
17 update. *Curr Opin Obstet Gynecol* 2001;13:521-527.

18 [47] Ferreira CHJ, Bø K. The Pad Test for urinary incontinence in women. *J Physiother*
19 2015;61:98.

20 [48] Nyström E, Sjöström M, Stenlund H, *et al.* ICIQ symptom and quality of life instruments
21 measure clinically relevant improvements in women with stress urinary incontinence. *Neurourol*
22 *Urodyn* 2015;34:747.

23 Figure legends:

24 Figure 1 Study flowchart

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

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

27 Figure 4 Acupuncture at the ‘four sacral points’

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

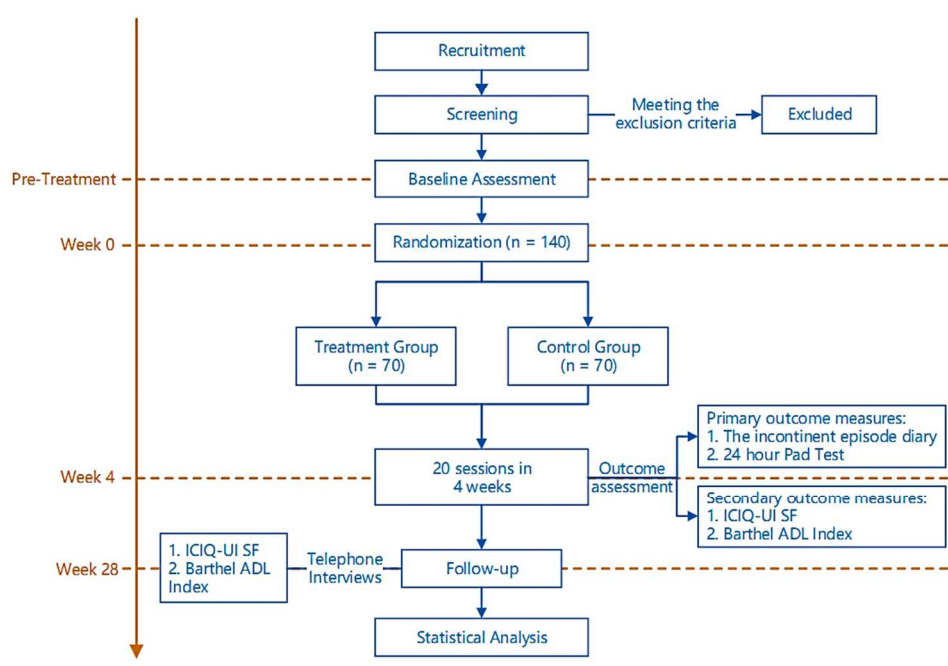


Figure 1 Study flowchart

98x70mm (300 x 300 DPI)

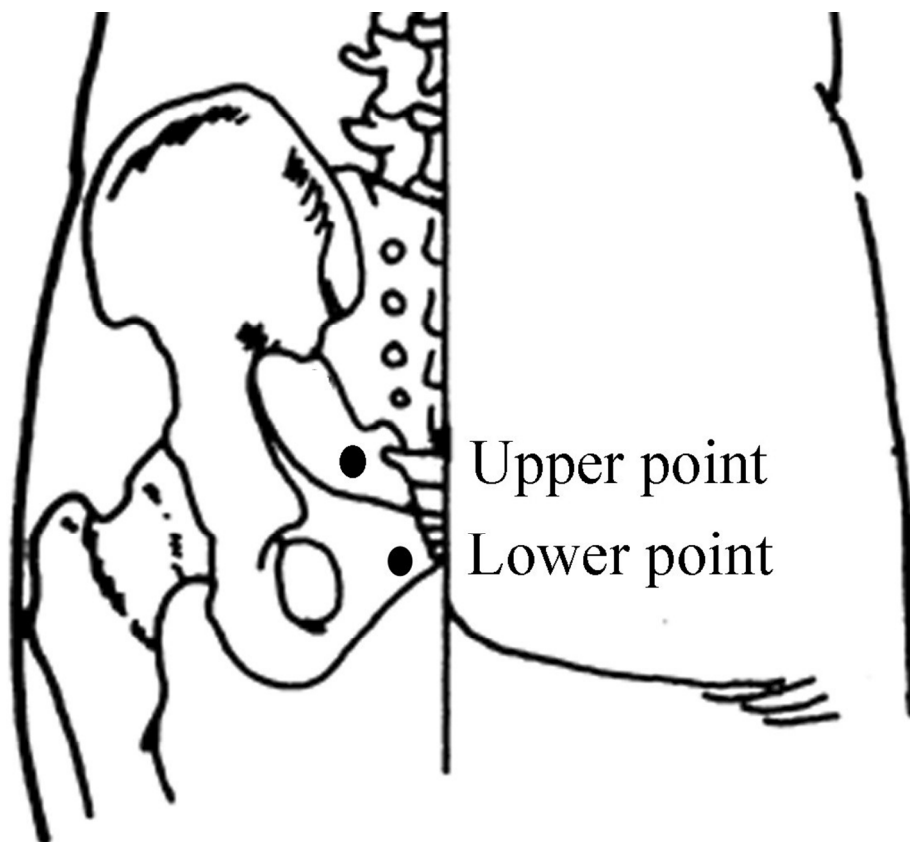


Figure 2 Locations of the 'four sacral points' for electroacupuncture

102x85mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

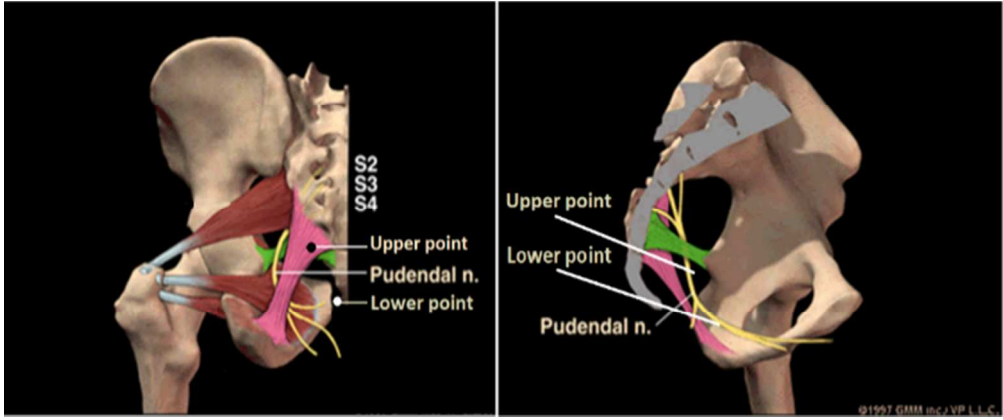


Figure 3 Anatomical positions of the 'four sacral points' for electroacupuncture

60x25mm (300 x 300 DPI)

Peer review only

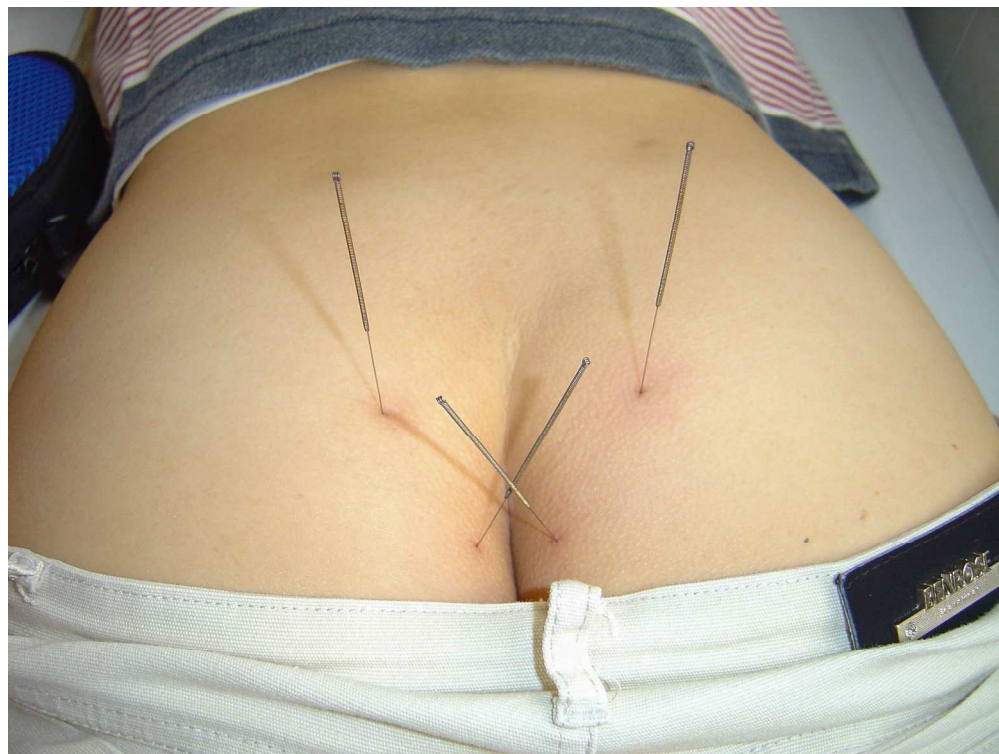


Figure 4 Acupuncture at the 'four sacral points'

219x164mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

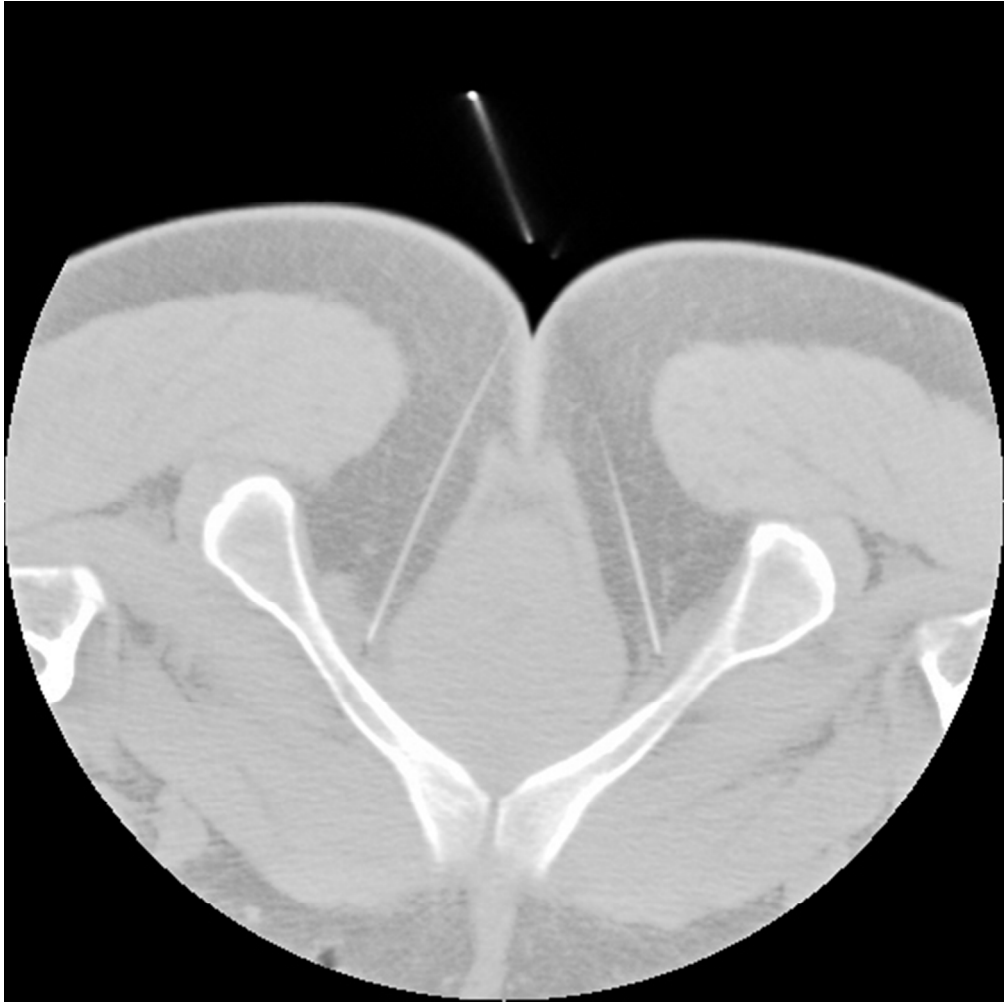


Figure 5 Transverse computed tomography (CT) image of the coccygeal apex
The tip of the needle inserted at the lower sacral point is visible in the ischiorectal fossa (adjacent to the PN
in Alcock's canal)

43x43mm (300 x 300 DPI)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021783.R1
Article Type:	Protocol
Date Submitted by the Author:	25-May-2018
Complete List of Authors:	Chen, Shan; the First Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture and Moxibustion Wang, Siyou; Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian Xuan, Li; 3, Department of Acupuncture and Moxibustion Lu, Hanti; the First Affiliated Hospital of Zhejiang Chinese Medical University, Clinical Evaluation and Analysis Center Hu, Zhikai; Huaqiao University, Department of Computer Science Zhang, Chao; the First Affiliated Hospital of Zhejiang Chinese Medical University, Rehabilitation Unit Zhang, Huifang; the First Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture and Moxibustion
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Urology
Keywords:	COMPLEMENTARY MEDICINE, UROLOGY, Stroke medicine < INTERNAL MEDICINE, Stroke < NEUROLOGY, STROKE MEDICINE

SCHOLARONE™
Manuscripts

1
2
3 **Comparison of efficacy and safety between electroacupuncture at ‘four sacral**
4 **points’ and conventional electroacupuncture for the treatment of urinary**
5 **incontinence after stroke: study protocol for a randomized controlled trial**
6
7

8 Shan Chen¹, Siyou Wang², Lihua Xuan¹, Hanti Lu³, Zhikai Hu⁴, Chao Zhang⁵,
9 Huifang Zhang¹

10
11 Corresponding author:

12 Shan Chen

13
14 Department of Acupuncture and Moxibustion, the First Affiliated Hospital of
15 Zhejiang Chinese Medical University, Hangzhou, China

16
17 No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Hangzhou,
18 Zhejiang Province 310018, China

19
20 E-mail: breezehilly@hotmail.com

21
22 Phone number: +86 152 5881 3929

23
24 Fax number: 0571-85860230

25
26 Siyou Wang, Clinical Research Section, Shanghai Research Institute of Acupuncture
27 and Meridian, Shanghai, China

28
29 Lihua Xuan, Department of Acupuncture and Moxibustion, the First Affiliated
30 Hospital of Zhejiang Chinese Medical University, Hangzhou, China

31
32 Hanti Lu, Clinical Evaluation and Analysis Center of the First Affiliated Hospital of
33 Zhejiang Chinese Medical University, Hangzhou, China

34
35 Zhikai Hu, Department of Computer Science, Huaqiao University, Xiamen, China

36
37 Chao Zhang, Rehabilitation Unit of the First Affiliated Hospital of Zhejiang Chinese
38 Medical University, Hangzhou, China

39
40 Huifang Zhang, Department of Acupuncture and Moxibustion, the First Affiliated
41 Hospital of Zhejiang Chinese Medical University, Hangzhou, China

42
43
44 **Keyword:** electroacupuncture; urinary incontinence; post-stroke; electrical pudendal
45 nerve stimulation

46
47
48 **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

1 refractory to SNM [10· 17· 18], although its disadvantages are similar to those of SNM
2 [10· 18]. PTNS with needle electrodes is minimally invasive, effective, easy to perform,
3 and well tolerated [8]; however, its effect diminishes over time [15· 17].
4
5

6 According to the theory of traditional Chinese medicine (TCM), UI is primarily
7 caused by kidney and bladder dysfunction in terms of urine control. Accordingly, the
8 principle of acupuncture treatment for UI is to promote the recovery of urine control
9 [19]. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and
10 ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33
11 (Zhongliao), and BL 35 (Huiyang), are generally selected for the regulation of the
12 bladder voiding function [20-22]. A literature review showed that acupuncture
13 demonstrated more favourable effects than did antimuscarinic drugs for the treatment
14 of OAB and alleviation of symptoms in some comparative trials [23]. In addition,
15 acupuncture reportedly improved the quality of life (QoL) and urodynamic testing
16 parameters in patients with OAB [23· 24]. In a randomized, double-blind,
17 placebo-controlled study, electroacupuncture significantly increased the maximum
18 cystometric capacity and bladder compliance, decreased the detrusor leak point
19 pressure, alleviated lower urinary tract symptoms, and decreased the risk of upper
20 urinary tract damage in patients with post-stroke detrusor overactivity [22]. However,
21 high-quality clinical trials with appropriate inclusion criteria, sample size, control
22 design, acupoint selection, depth of needle insertion, and efficacy and safety
23 evaluations are necessary to properly evaluate the efficacy of acupuncture for the
24 treatment of post-stroke UI [7· 25· 26].
25
26
27
28
29
30
31
32
33

34 On the basis of the theory of nerve stimulation, we developed electroacupuncture at
35 ‘four sacral points’ [27· 28], also known as electroacupuncture neurostimulation
36 therapy or electrical PN stimulation therapy. This approach involves the insertion of
37 long needles at ‘four sacral points’, with electricity to stimulate specific nerves under
38 the sacral region [28· 29]. When it was first developed, this treatment was used to treat
39 stress UI (SUI) in women, and radiographic evidence with simultaneous records of
40 perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure,
41 and pelvic floor surface electromyography have shown that it causes PN excitation
42 [29]. In addition, it has been used for the treatment of female urgency-frequency
43 syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological
44 conditions [28· 30· 31]. The mechanism of action of electroacupuncture at ‘four sacral
45 points’ for post-stroke UI can be explained by the modulation of reflex pathways at
46 spinal or supraspinal levels [3]. Electrical stimulation of the afferent branches of the
47 PN can induce strong inhibition of the micturition reflex and detrusor hyper-reflexia
48 [10], resulting in the effective treatment of post-stroke UI [31· 32].
49
50
51
52
53
54

55 The effectiveness of post-stroke UI treatment using alternative medicine
56 approaches is worthy of investigation in a well-designed study. To the best of our
57
58
59
60

1
2
3 knowledge, no randomized controlled trials (RCT) comparing the efficacy and safety
4 of electroacupuncture at ‘four sacral points’ with those of conventional
5 electroacupuncture for the treatment of post-stroke UI have been conducted. Here we
6 describe a protocol for an RCT to evaluate the efficacy and safety of
7 electroacupuncture at ‘four sacral points’ for the management of post-stroke UI.
8
9

11 **METHODS AND ANALYSIS**

13 **Objectives**

14 This is a protocol comparing the efficacy and safety of electroacupuncture at ‘four
15 sacral points’ with those of conventional electroacupuncture for the treatment of
16 post-stroke UI. It is designed as a blinded randomized assessment and analysis with
17 two parallel groups over a 4-week treatment period. Randomization will be performed
18 in a random 1:1 allocation sequence.
19

21 **Recruitment**

22 This is a pragmatic RCT comparing electroacupuncture at ‘four sacral points’ with
23 conventional electroacupuncture for the treatment of post-stroke UI. The research
24 structure is shown in Figure 1. A total of 140 eligible participants will be recruited
25 from the inpatient and outpatient departments of the First Affiliated Hospital of
26 Zhejiang Chinese Medical University according to the inclusion and exclusion criteria.
27 At the beginning of recruitment, detailed information about the study, including the
28 research objective, study procedure, and potential benefits and risks, will be provided
29 to all eligible patients. If the patient agrees to participate, he or she will be asked to
30 sign a written informed consent form. This will be followed by baseline assessment
31 and randomization. A treatment period of 4 weeks and a follow-up period of 24 weeks
32 will follow the recruitment procedure. The neurology department of the First
33 Affiliated Hospital of Zhejiang Chinese Medical University has the major source of
34 patients with post-stroke UI. Our reach team includes neurological physicians and
35 special nurses who will interview potentially eligible patients. Advertisements will be
36 released through health education brochures, posters, and videos displayed in the
37 outpatient and inpatient sites of the First Affiliated Hospital of Zhejiang Chinese
38 Medical University. Recruitment information will also be issued through media (e.g.
39 newspapers, broadcasts, and websites).
40
41
42
43
44
45
46
47
48

49 **Design**

51 *Randomization and allocation concealment*

52 The randomization scheme has been created by the Clinical Evaluation and Analysis
53 Center of The First Affiliated Hospital of Zhejiang Chinese Medical University, where
54 professionals used SPSS Statistics 22.0 to generate a random 1:1 allocation sequence
55 using a computer. Professionals involved in allocation will not be recruited in the
56
57
58
59
60

1
2
3 study. The random allocation is strictly kept in an opaque envelope and is inaccessible
4 to other research staff. After baseline assessment, the envelope will be opened by an
5 independent staff member in the participant's presence, in order to determine the
6 group assignment for that participant. All patients who give consent for participation
7 and who fulfil the inclusion criteria will be assigned to a group randomly.
8 Randomisation will be requested by the staff member responsible for recruitment and
9 clinical interviews from the First Affiliated Hospital of Zhejiang Chinese Medical
10 University. An independent staff member will open an envelope with printed
11 randomisation numbers in the participant's presence. The therapists will be informed
12 about the participant's allocation at the same time. The staff member responsible for
13 recruitment and clinical interviews is not allowed to receive information about the
14 group allocation.

15 *Blinding*

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

26 **Participants**

27 *Sample size*

28 With reference to a similar study^[33] with 120 women (efficacy rate, 70.1%:45%), the
29 sample size has been calculated, using PASS 11 software, as 120 patients for a power
30 (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With
31 consideration of the estimated dropout rate (15%), the total sample size will be 140
32 (70 in each group).

33 *Inclusion criteria*

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

1
2
3 6. Provision of written informed consent

4 *Exclusion criteria*

- 5 1. UI caused by other diseases such as Parkinson's disease, multiple sclerosis, spinal
6 injury, or Alzheimer's disease
7
8 2. Pre-stroke UI, SUI or mixed UI, or overflow incontinence
9
10 3. Urinary retention concomitant with UI
11
12 4. Urethral injury, lower urinary tract obstruction, acute urinary tract infection,
13 refractory urinary tract infection, hydronephrosis, urological calculi, or tumours
14
15 5. Severe cognitive impairment, as defined by a Mini-Mental State Examination
16 (MMSE) score of <22 [36]
17
18 6. Insufficiency of the heart, lungs, liver, and/or kidneys
19
20 7. Presence of an implantable electronic device

21 *Elimination criteria*

- 22 1. Inclusion despite non-fulfilment of the inclusion criteria
23
24 2. Lack of exclusion despite fulfilment of the exclusion criteria
25
26 3. Eligible participants who receive no interventions

27 *Dropout criteria*

- 28 1. Poor participant compliance (lack of adherence to treatment for personal reasons)
29
30 2. Serious adverse events (SAE), complications, or special physiological changes
31 necessitating discontinuation of the intervention
32
33 3. Voluntary dropout

34 **Intervention**

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

44 **Standard operating procedure**

- 45 1. Needle requirements
46 Disposable sterile acupuncture needles in accordance with national standards
47 within the validity period will be used.
48
49 2. Hand hygiene of the operator
50 The operator is required to sterilize his or her hands with a sanitizer before the
51 acupuncture procedure.
52
53 3. Sterilization of the acupuncture points
54
55
56
57
58
59
60

1
2
3 Within a 5-cm diameter with the acupoint as the centre, sterilize the skin over the
4 acupoints using a cotton swab dipped in 0.45%–0.55% povidone iodine or 75%
5 ethanol.
6

7 4. Procedure

8 Treatment group: Participants in this group will receive electroacupuncture at
9 ‘four sacral points’.

10 a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected.

11 The two upper points are located on either side of the sacrococcygeal joint,
12 approximately 1 cm from the joint. The two lower points are located on either
13 side of the tip of the coccyx, approximately 1 cm from the coccyx.
14 Acupuncture will be performed at LI15(Jianyu), LI11 (Quchi), LI10
15 (Shousanli), SJ5 (Waiguan), and LI4 (Hegu) for participants with upper limb
16 paralysis. For participants with lower limb paralysis, ST31 (Biguan), ST34
17 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40
18 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17
19 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia,
20 with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang)
21 for participants with facial paralysis and drooling.
22

23 b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong 24 Medical Apparatus Factory, Suzhou, China) measuring 0.40×100 mm will be 25 inserted perpendicularly to a depth of 80–90 mm to induce a sensation 26 referred to the urethra or anus via stimulation of the main trunk of the PN. At 27 the lower sacral points, a needle measuring 0.40×100 or 0.40×125 mm will 28 be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm 29 to induce a sensation referred to the urethra via stimulation of the perineal 30 nerve (Figure 4). Once the sensation is induced in the respective regions, two 31 pairs of electrodes from the G6805-A electroacupuncture device (Shantou 32 Medical equipment factory, Shantou, China) will be connected to the two 33 ipsilaterally inserted needles, with the anode connected to the upper needle 34 and the cathode connected to the lower needle. The device will be set to 35 produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 36 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be 37 performed for 20 min during each treatment. PFM contraction around the 38 urethra (often comfortable) must be maintained during the entire 39 electrostimulation procedure. Conventional acupuncture without electricity 40 will be applied for 20 min at the remaining acupoints. 41 42 43 44 45 46 47 48 49 50 51 52 53

54 Control group: Participants in this group will receive conventional
55 electroacupuncture.
56
57

- 1
2
3 a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and
4 ST28 (Shuidao, both sides), corresponding to the conventional
5 electroacupuncture treatment of UI. The point selection procedure for participants
6 with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the
7 same as that used for the treatment group.
8
9 b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao),
10 a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of
11 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the
12 electrodes from the G6805-A electroacupuncture device will be connected to the
13 needles at these points, with the anode connected to ST28 and the cathode
14 connected to CV6 and CV4. The device will be set to produce electrical
15 stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a
16 moderate intensity that is tolerable by the participants. Electrostimulation will be
17 performed for 20 min during each treatment. Conventional acupuncture without
18 electricity will be applied for 20 min at the remaining acupoints.
19
20 5. Treatment period: All participants will receive treatment every day from Monday
21 to Friday. One course of treatment will comprise 10 sessions. The therapeutic
22 effects will be evaluated after the completion of two treatment courses (4 weeks).
23
24
25
26
27
28
29

30 Outcome measures

31 Primary outcome measures

32 The incontinent episode diary

33 The incontinent episode diary (Table 1) will be used to derive the primary outcome
34 measure. The number of incontinent episodes will be recorded by the participants
35 over a period of 3 days at baseline. A template will be provided for patient use. This
36 data will be recorded again at the end of treatment.
37
38
39
40

41 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					

1
2
3 *Secondary outcome measures*

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

6
7 2. Barthel Activities of Daily Living Index (Barthel ADL Index) [38] (Table 3)

8 The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and
9 psychometrically robust patient-completed questionnaire for evaluating the frequency
10 and severity of UI in men and women and its impact on quality of life (QoL). The
11 ICIQ-UI SF score ranges from 0 to 21 [39]. The Barthel ADL Index is a 10-item
12 measure of activities of daily living (ADL) that is frequently used in clinical practice
13 and as a trial outcome measure in stroke medicine [38]. It is used to assess baseline
14 abilities to quantify functional changes, including UI, after rehabilitation in stroke
15 patients.
16

17 The above outcome measures will be assessed at baseline and at 4 and 28 weeks after
18 baseline.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1. Please write in your date of birth:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
	date month year	
2. Are you	Female <input type="checkbox"/> Male <input type="checkbox"/>	
3. How often do you leak urine? (Tick one box)		
	never	<input type="checkbox"/> 0
	about once a week or less often	<input type="checkbox"/> 1
	two or three times a week	<input type="checkbox"/> 2
	about once a day	<input type="checkbox"/> 3
	several times a day	<input type="checkbox"/> 4
	all the time	<input type="checkbox"/> 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	<input type="checkbox"/> 0
	a small amount	<input type="checkbox"/> 2
	a moderate amount	<input type="checkbox"/> 4
	a large amount	<input type="checkbox"/> 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

	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

1
2
3 at 4 weeks after baseline. A blinded telephone interviewer will interview the
4 participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at
5 28 weeks after baseline. All data will be recorded on the CRFs. For participants who
6 discontinue treatment early, we will use last observation carried forward analysis to
7 handle the missing data, meaning that we will input outcome data of patients who are
8 lost to follow-up in our analysis.
9

10 After the completion of the CRFs, two independent researchers blinded to the group
11 allocation will separately input data into an Excel spreadsheet. Another independent
12 supervisor will check the two datasets for consistency. If conflicting data entries are
13 discovered, the supervisor will compare the datasets with the original CRFs and mark
14 the modification on the CRFs. The principal investigator of the research team will
15 have the access to all documents and will protect the electronic documents with a
16 password and create backups of all documents. The First Affiliated Hospital of
17 Zhejiang Chinese Medical University will be responsible for the storage and
18 management of all data.
19

20 An independent data monitoring committee (DMC) is made up of members from
21 Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang
22 Chinese Medical University. The DMC, blinded to the treatment allocations, will meet
23 regularly to monitor the study data. The DMC will also perform interim-analysis
24 when 50% of patients have been randomised and have completed the primary
25 outcome measurement.
26
27
28

29 The First Affiliated Hospital of Zhejiang Chinese Medical University will audit this
30 study mainly for participant enrolment, consent, and costs.
31
32

33 **Statistical analysis**

34 All statistical analyses will be performed by a statistician from the Clinical Evaluation
35 and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical
36 University using SPSS Statistics 22.0. A normality test will be used to determine
37 whether the data are normally distributed. ANCOVA (analysis of covariance) will be
38 used if there is imbalance in the baseline characteristics and outcome measures.
39 Continuous variables with a normal distribution will be expressed as means \pm
40 standard deviations (SDs). Continuous variables with a non-normal distribution or
41 ordinal variables will be expressed as medians (with lower, upper quartiles).
42 Categorical variables will be summarized as counts and proportions. A Student's t-test
43 will be used if the primary and secondary outcome measures conform to normal
44 distribution. A paired t-test will be used to compare pre-treatment and post-treatment
45 UI occurrence for the primary outcome measure and pre-treatment and post-treatment
46 scores in the secondary outcome measures. The independent sample t-test will be used
47 to compare the difference between two groups for primary and secondary outcome
48 measures. A Wilcoxon signed rank test will be used if the primary and secondary
49 outcome measures conform to abnormal distribution. A Wilcoxon paired test will be
50 used to compare pre-treatment and post-treatment UI occurrence for the primary
51 outcome measure and pre-treatment and post-treatment scores in secondary outcome
52 measures. The inter-group rank sum test will be used to compare the difference
53
54
55
56
57
58
59
60

1
2
3 between two groups for primary and secondary outcome measures. All reported
4 P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A
5 P-value of <0.05 will be considered statistically significant.
6
7

8 **Patient and Public Involvement**

9 Patients and the public were not directly involved in the design, recruitment or
10 conduct of this pilot study. Since the participants in our study are under chronic
11 conditions, the outcome measures valued in this study was influenced by patients'
12 priorities, experience and preferences. As most stroke patients are in great need of
13 acupuncture treatment in China, we did not view the intervention as burdensome and
14 the burden of the intervention was not assessed by the patients themselves. The results
15 of this study will be disseminated in peer-reviewed journals and at academic
16 conferences. A summary of the study report will be written for patients through online
17 website (<https://sandyshen.haodf.com/>) and WeChat (a free messaging and
18 calling application) account or group.
19
20
21
22

23 **ETHICS AND DISSEMINATION**

24 **Research ethics approval**

25 The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical
26 University has reviewed and approved this protocol (approval No. 2018-K-059-01).
27 This study will adhere to the principles of the Declaration of Helsinki. This study will
28 be conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University.
29 Each participant will voluntarily sign written informed consent forms.
30
31
32

33 **Modification of the protocol**

34 Any modifications to the protocol, including changes of study objectives, study design,
35 patient population, sample sizes, study procedures, or significant administrative
36 aspects, will require a formal application to the Zhejiang Provincial Administration of
37 Traditional Chinese Medicine as well as the Chinese clinical trial registry.
38
39

40 **Confidentiality**

41 All study participants will be given an identification number throughout the trial to
42 assure confidentiality. All participants' information will be stored in locked cabinets
43 with limited access.
44
45

46 **Dissemination**

47 The initial data will be accessible via Research Manager (ResMan). The results of this
48 study will be published in open-access and peer-reviewed journals and presented at
49 relevant conferences.
50
51
52

53 **DISCUSSION**

54 According to the present study protocol, in addition to electroacupuncture at 'four
55 sacral points' in the treatment group and conventional electroacupuncture in the
56
57
58
59
60

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.

Author affiliations

¹Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

²Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian, Shanghai, China

³Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

⁴Department of Computer Science, Huaqiao University, Xiamen, China

⁵Rehabilitation Unit of 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.

Funding Statement

This work was supported by Zhejiang Provincial Administration of Traditional Chinese Medicine (grant number 2018ZA045).

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.

REFERENCES

- 1 Abrams P, Andersson KE, Birder L, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn* 2010;29:213-40.
- 2 Ruffion A, Castro DD, Patel H, et al. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. *Neuroepidemiology* 2013;41:146-55.
- 3 Mehdi Z, Birns J, Bhalla A, et al. Post-stroke urinary incontinence. *Int J Clin Pract* 2013;67:1128-37.
- 4 Cai W, Wang J, Wang L, et al. Prevalence and risk factors of urinary incontinence for post-stroke inpatients in Southern China. *Neurourol Urodyn* 2015;34:231-5.
- 5 Pizzi A, Falsini C, Martini M, et al. Urinary incontinence after ischemic stroke: clinical and urodynamic studies. *Neurourol Urodyn* 2014;33:420-5.
- 6 Gregor J, Steve P, Siobhan C, et al. Urinary incontinence and indwelling urinary catheters as predictors of death after new-onset stroke: a report of the south london stroke register. *J Stroke Cerebrovasc Dis* 2018;27:118-24.
- 7 Thomas LH, Cross S, Barrett J, et al. Treatment of urinary incontinence after stroke in adults. *Cochrane Database of Systematic Reviews* 2008;23:CD004462.
- 8 Paniker JN. Urogenital symptoms in neurologic patients. *Continuum*. 2017;23:533-52.
- 9 Amundsen CL, Komesu YM, Chermansky C, et al. Two-Year outcomes of sacral neuromodulation versus onabotulinumtoxinA for refractory urgency urinary incontinence: a randomized trial. *Eur Urol* Published Online First: 23 February 2018. doi:10.1016/j.eururo.2018.02.011
- 10 Bosch JL. Electrical neuromodulatory therapy in female voiding dysfunction. *BJU Int* 2006;98 suppl:43-8.
- 11 van Balken MR, Vergunst H, Bemelmans BL. The use of electrical devices for the treatment of bladder dysfunction: a review of methods. *J Urol* 2004;172:846-51.

- 1
2
3 12 Smits MA, Oerlemans D, Marcelissen TA, et al. Sacral neuromodulation in
4 patients with idiopathic overactive bladder after initial botulinum toxin therapy. *J*
5 *Urol* 2013;190:2148-52.
- 6 13 Siegel S, Noblett K, Mangel J, et al. Results of a prospective, multicenter study
7 evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve
8 months in subjects with symptoms of overactive bladder. *Neurourol Urodyn*
9 2016;34:246-51.
- 10 14 Spinelli M, Sievert KD. Latest technologic and surgical developments in using
11 InterStim Therapy for sacral neuromodulation: impact on treatment success and safety.
12 *Eur Urol* 2008;54:1287-96.
- 13 15 Hijaz A, Vasavada SP, Daneshgari F, et al. Complications and troubleshooting of
14 two-stage sacral neuromodulation therapy: a single-institution experience. *Urology*
15 2006;68:533-7.
- 16 16 Lee C, Pizarro-Berdichevsky J, Clifton MM, et al. Sacral neuromodulation
17 implant infection: risk factors and prevention. *Curr Urol Rep* 2017;18:16.
- 18 17 Peters KM. Alternative approaches to sacral nerve stimulation. *Int Urogynecol J*
19 2010;21:1559-63.
- 20 18 Groen J, Amiel C, Bosch JL. Chronic pudendal nerve neuromodulation in women
21 with idiopathic refractory detrusor overactivity incontinence: results of a pilot study
22 with a novel minimally invasive implantable mini-stimulator. *Neurourol Urodyn*
23 2005;24:226-30.
- 24 19 Sun Z, Yu N, Yue J, et al. Acupuncture for urinary incontinence after stroke: a
25 protocol for systematic review. *BMJ Open* 2016;6:e008062.
- 26 20 Song F, Jiang S, Zheng L, et al. Electroacupuncture for post-stroke urinary
27 incontinence: a multicenter randomized controlled study. *Zhongguo Zhen Jiu*
28 2013;33:769-73.
- 29 21 Paik SH, Han SR, Kwon OJ, et al. Acupuncture for the treatment of urinary
30 incontinence: A review of randomized controlled trials. *Exp Ther Med* 2013;6:773-80.
- 31 22 Liu Y, Liu L, Wang X. Electroacupuncture at points Baliao and Huiyang (BL35)
32 for post-stroke detrusor overactivity. *Neural Regen Res* 2013;8:1663-72.
- 33 23 Forde JC, Jaffe E, Stone BV, et al. The role of acupuncture in managing
34 overactive bladder; a review of the literature. *Int Urogynecol J* 2016;27:1645-51.
- 35 24 Olivera CK, Meriwether K, El-Nashar S, et al. Nonantimuscarinic treatment for
36 overactive bladder: a systematic review. *Am J Obstet Gynecol* 2016;215:34-57.
- 37 25 Solberg M, Alræk T, Mdala I, et al. A pilot study on the use of acupuncture or
38 pelvic floor muscle training for mixed urinary incontinence. *Acupunct Med*
39 2016;34:7-13.
- 40 26 Liu Z, Wang Y, Xu H, et al. Observation on therapeutic effect of
41 electroacupuncture for post-stroke urge incontinence. *Xin Zhong Yi* 2010;42:73-5.
- 42 27 Wang S, Chen G, Li L. "Four sacral needles therapy" for female stress
43 incontinence. *Shanghai J Acup Moxib* 2006;25:15-7.
- 44 28 Lu J. Observation on therapeutic effect of electroacupuncture neurostimulation
45 therapy for urge urinary incontinence. *Zhongguo Zhenjiu* 2012;32:691-5.
- 46 29 Wang S, Zhang S. Simultaneous perineal ultrasound and vaginal pressure
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 measurement prove the action of electrical pudendal nerve stimulation in treating
4 female stress incontinence. *BJU International* 2012;110:1338-1343.
- 5 30 Wang S, Zhang S, Zhao L. Long-term efficacy of electrical pudendal nerve
6 stimulation for urgency–frequency syndrome in women. *Int Urogynecol J*
7 2014;25:397-402.
- 8 31 Wang S, LvJ, FX et al. Efficacy of electrical pudendal nerve stimulation versus
9 transvaginal electrical stimulation in treating female idiopathic urgency urinary
10 incontinence. *J Urol* 2017;197:1496-501.
- 11 32 Wang S. Electroacupuncture pudendal nerve stimulation and its application. *J*
12 *Acupunt Tuina Sci* 2013;11:117-21.
- 13 33 Wang S, Lv J, Feng X, et al. Efficacy of Electrical Pudendal Nerve Stimulation
14 versus Transvaginal Electrical Stimulation in Treating Female Idiopathic Urgency
15 Urinary Incontinence. *J Urol* 2017;6:1496-501.
- 16 34 Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the
17 21st century: a statement for healthcare professionals from the American Heart
18 Association/American Stroke Association. *Stroke* 2013;44:2064-89.
- 19 35 Haylen BT, de Ridder D, Freeman RM, et al. Association (IUGA)/International
20 Continence Society (ICS) joint report on the terminology for female pelvic floor
21 dysfunction. *Neurourol Urodyn* 2010;29:4-20.
- 22 36 Grut M, Fratiglioni L, Viitanen M, et al. Accuracy of the Mini-Mental Status
23 Examination as a screening test for dementia in a Swedish elderly population. *Acta*
24 *Neurol Scand* 1993;87:312-71993-04-01.
- 25 37 Timmermans L, Falez F, Mélot C, et al. Validation of use of the International
26 Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form
27 (ICIQ-UI-SF) for impairment rating: a transversal retrospective study of 120 patients.
28 *Neurourol Urodyn* 2013;32:974-9.
- 29 38 Duffy L, Gajree S, Langhorne P, et al. Reliability (inter-rater agreement) of the
30 Barthel Index for assessment of stroke survivors: systematic review and meta-analysis.
31 *Stroke* 2013;44:462-8.
- 32 39 Hajebrahimi S, Nourizadeh D, Hamedani R, et al. Validity and reliability of the
33 International Consultation on Incontinence Questionnaire-Urinary Incontinence Short
34 Form and its correlation with urodynamic findings. *Urol J* 2012;9:685-90.
- 35 40 Li Y, Liu Y, Zhang J, et al. Analysis on the situation of adverse reaction to
36 acupuncture and acupuncture risk. *Zhongguo Zhenjiu* 2011;31:764-8.
- 37 41 Zhao L, Li Y, Zhang F, et al. Analysis on the occurrence of laws of adverse
38 events from 1968 patients after acupuncture treatment. Symposium of seminar of the
39 Ninth National Young and Middle-aged Acupuncture and Tuina of China
40 Acupuncture and Moxibustion Association 2010;270-6.
- 41 42 Yew KS, Cheng EM. Diagnosis of Acute Stroke. *Am Fam Physician*
42 2015;91:528-36.
- 43 43 Zhang J, Wang D, Liu M. Overview of systematic reviews and meta-analyses of
44 acupuncture for stroke. *Neuroepidemiology* 2014;42:50-8.
- 45 44 Mehnert U, Kessler TM. The management of urinary incontinence in the male
46 neurological patient. *Curr Opin Urol* 2014;24:586-92.
- 47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 45 Smith AL, Wein AJ. Urinary incontinence: pharmacotherapy options. *Ann Med*
4 2011;43:461-76.

5 46 Robinson D, McClish DK, Wyman JF, et al. Comparison between urinary diaries
6 completed with and without intensive patient instructions. *Neurol Urodyn*
7 1996;15:143-8.

8
9 47 Gordon D, Grpouts A. Evaluation of female lower urinary tract symptoms:
10 overview and update. *Curr Opin Obstet Gynecol* 2001;13:521-7.

11 48 Nyström E, Sjöström M, Stenlund H, et al. ICIQ symptom and quality of life
12 instruments measure clinically relevant improvements in women with stress urinary
13 incontinence. *Neurol Urodyn* 2015;34:747.
14
15

16 17 **Figure legends**

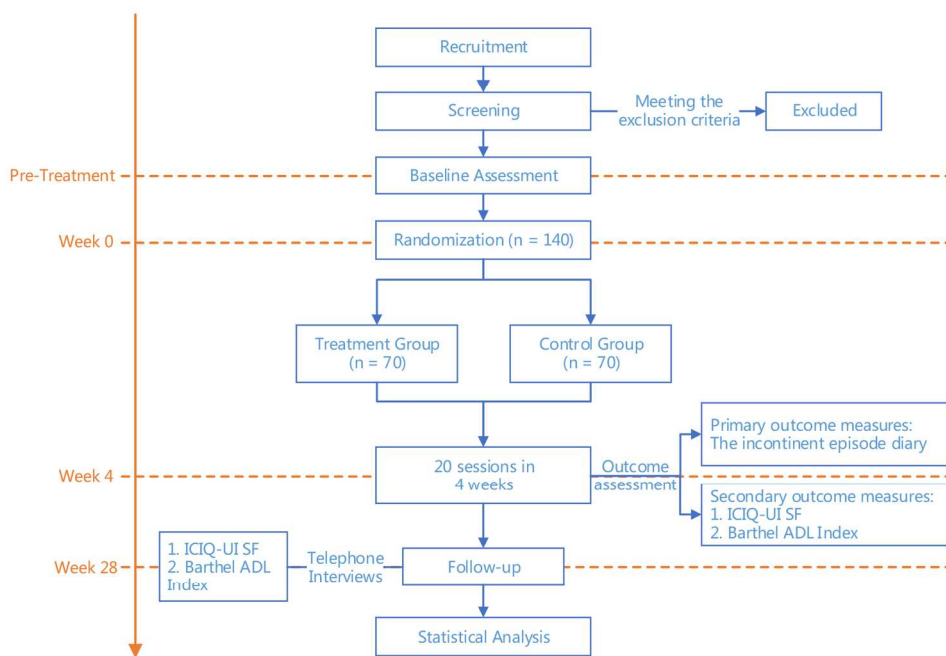
18
19
20 Figure 1 Study flowchart

21
22 Figure 2 Locations of the 'four sacral points' for electroacupuncture

23
24 Figure 3 Anatomical positions of the 'four sacral points' for electroacupuncture

25
26 Figure 4 Transverse computed tomography (CT) image of the coccygeal apex

27
28 The tip of the needle inserted at the lower sacral point is visible in the
29 ischiorectal fossa (adjacent to the PN in Alcock's canal)
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

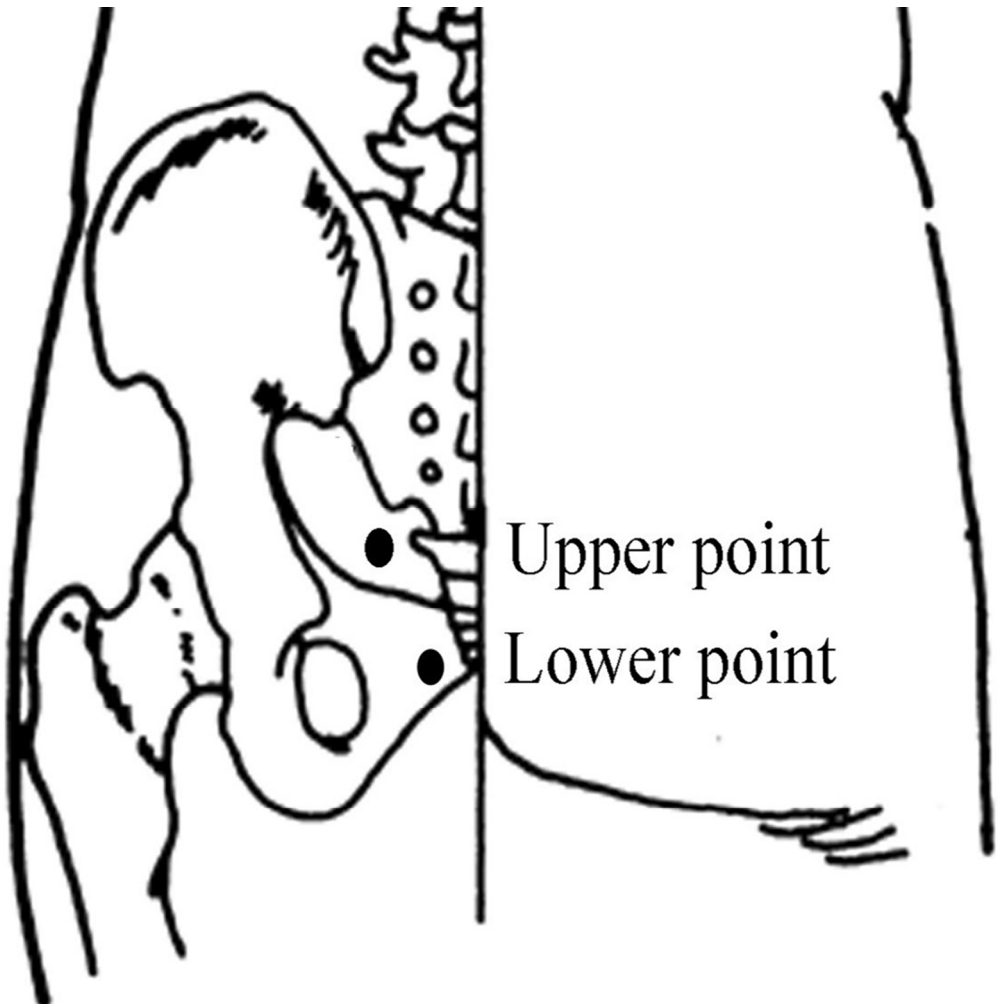


Study flowchart

151x105mm (300 x 300 DPI)

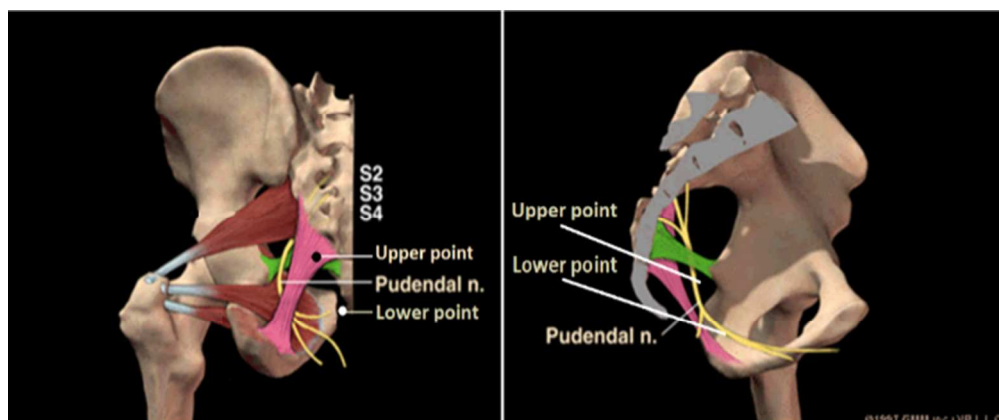
View only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Locations of the 'four sacral points' for electroacupuncture

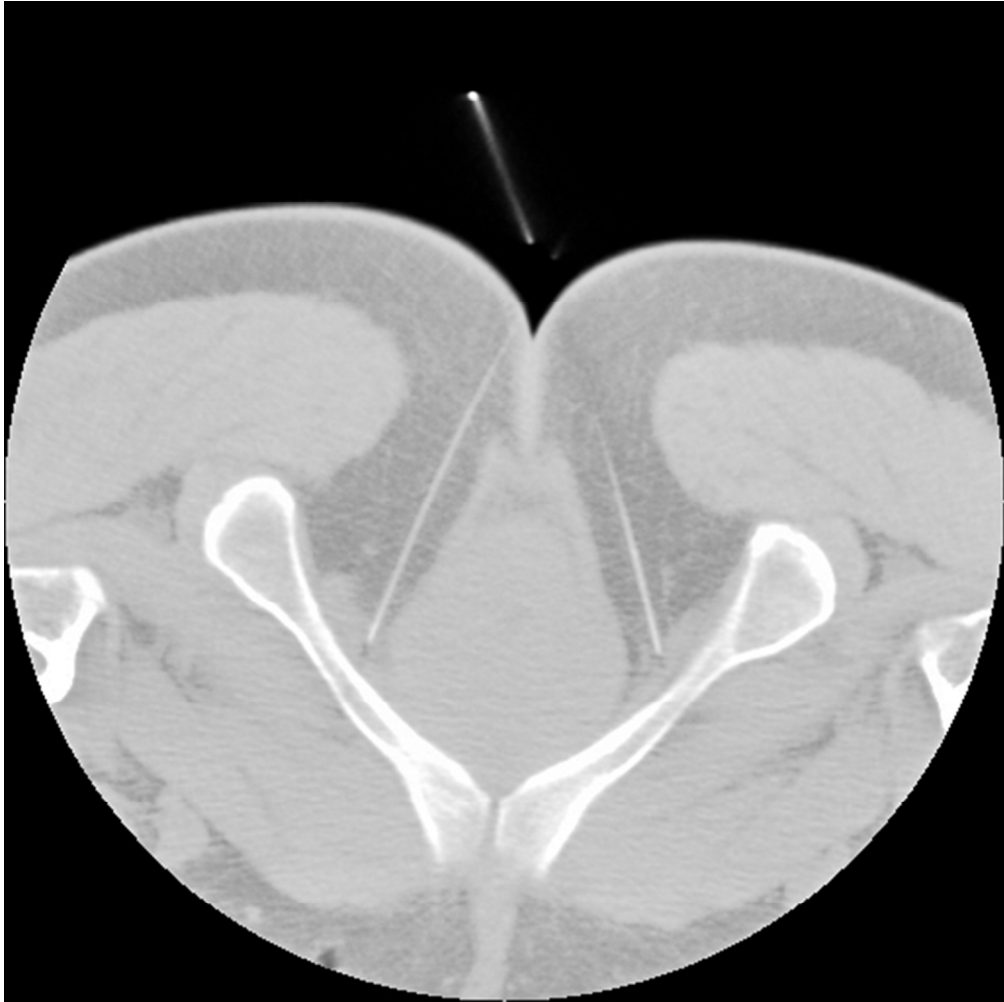
90x90mm (300 x 300 DPI)



Anatomical positions of the 'four sacral points' for electroacupuncture

216x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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	<table border="1"> <tr> <td>Primary registry and trial identifying number</td> <td>ChiCTR-IOR-17012847</td> </tr> <tr> <td>Date of registration in primary registry</td> <td>30 Sep 2017</td> </tr> <tr> <td>Secondary identifying numbers</td> <td></td> </tr> <tr> <td>Source(s) of monetary or material support</td> <td>Zhejiang Provincial Administration of Traditional Chinese Medicine</td> </tr> <tr> <td>Primary sponsor</td> <td>Zhejiang Provincial Administration of Traditional Chinese Medicine</td> </tr> <tr> <td>Secondary sponsor(s)</td> <td></td> </tr> <tr> <td>Contact for public queries</td> <td>CZ[z985417@163.com],HFZ[zhuzhijie@163.com]</td> </tr> <tr> <td>Contact for scientific queries</td> <td>CZ,HFZ Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China</td> </tr> <tr> <td>Public title</td> <td>Electroacupuncture at ‘four sacral points’ for the treatment of urinary incontinence after stroke</td> </tr> <tr> <td>Scientific title</td> <td>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</td> </tr> <tr> <td>Countries of recruitment</td> <td>China</td> </tr> <tr> <td>Health condition(s) or problem(s) studied</td> <td>Acupuncture treatment; Urinary incontinence after stroke</td> </tr> </table>	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[z985417@163.com],HFZ[zhuzhijie@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
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[z985417@163.com],HFZ[zhuzhijie@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																									

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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 Medicine¹⁸

Sponsor’s Reference: grant number 2018ZA045¹⁸

Contact name: Zhejiang Provincial Administration of Traditional Chinese Medicine

Address: No.216 Qingchun Road

Telephone: +86 0571 8770 9076

Email: zjtcn@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

1
2
3
4
5
6
7 for stroke patients without UI (11.9%). Therefore, the management of UI after stroke is of great importance.
8 Post-stroke UI may develop because of various reasons, although direct stroke-induced damage to the neuromicturition pathways is
9 considered the most common cause. Typical symptoms include the involuntary leakage of urine accompanied or immediately
10 preceded by urgency. Urodynamic evaluation often reveals uninhibited detrusor contraction.

11
12 Evidence-based interventions for post-stroke UI include behavioural and pharmacological interventions, as well as individually
13 tailored structured management plans, or the aid of continence nurse specialists, in order to promote continence. Trials of
14 behavioural and pharmacological therapies have provided insufficient evidence to guide the management of post-stroke UI in
15 adults. Furthermore, side effect profiles and anticholinergic burden should be considered before medications are prescribed.
16 Neuromodulation therapies, which involve the electrical stimulation of target-specific nerves, are reportedly effective for overactive
17 bladder (OAB) or urgency UI (UUI). Neuromodulation includes transvaginal or transanal electrical stimulation (TES),
18 percutaneous tibial nerve stimulation (PTNS), sacral nerve neuromodulation (SNM), and pudendal nerve (PN) neuromodulation
19 (PNM). TES is an easy procedure, but it is not tolerated by several patients because of discomfort, mucosal injury, and the necessity
20 for high-intensity stimulation to achieve an acceptable outcome. SNM with the InterStim device provides continuous stimulation
21 and close nerve contact; however, at least 20% of initially tested patients do not respond to the test procedure. The disadvantages of
22 SNM include the invasiveness of the procedure, the high cost of treatment, the high rate of revision surgery, the requirement for
23 device replacement on battery exhaustion, and adverse events (pain and infection). PNM with the Interstim device or the Bion
24 device (selective PN stimulation) can be used to treat UUI refractory to SNM, although its disadvantages are similar to those of
25 SNM. PTNS with needle electrodes is minimally invasive, effective, easy to perform, and well tolerated; however, its effect
26 diminishes over time.

27
28 On the basis of the theory of nerve stimulation, we developed electroacupuncture at ‘four sacral points’, also known as
29 electroacupuncture neurostimulation therapy or electrical PN stimulation therapy. This approach involves the insertion of long
30 needles at ‘four sacral points,’ with electricity to stimulate specific nerves under the sacral region. In our previous study, this
31 treatment has been used to treat stress UI (SUI) in women, and radiographic evidence with simultaneous records of perineal
32
33
34
35
36
37
38

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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 University⁵

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 device⁶⁻⁷

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	<p>Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'.</p> <p>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),</p>
---------------	-----	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

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	<p>Elimination criteria</p> <ol style="list-style-type: none"> 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 <p>Dropout criteria</p> <ol style="list-style-type: none"> 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 dropout⁷
	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	<p>Primary outcome measures</p> <p>The incontinent episode diary</p> <p>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</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

be recorded again at the end of treatment.

Secondary outcome measures

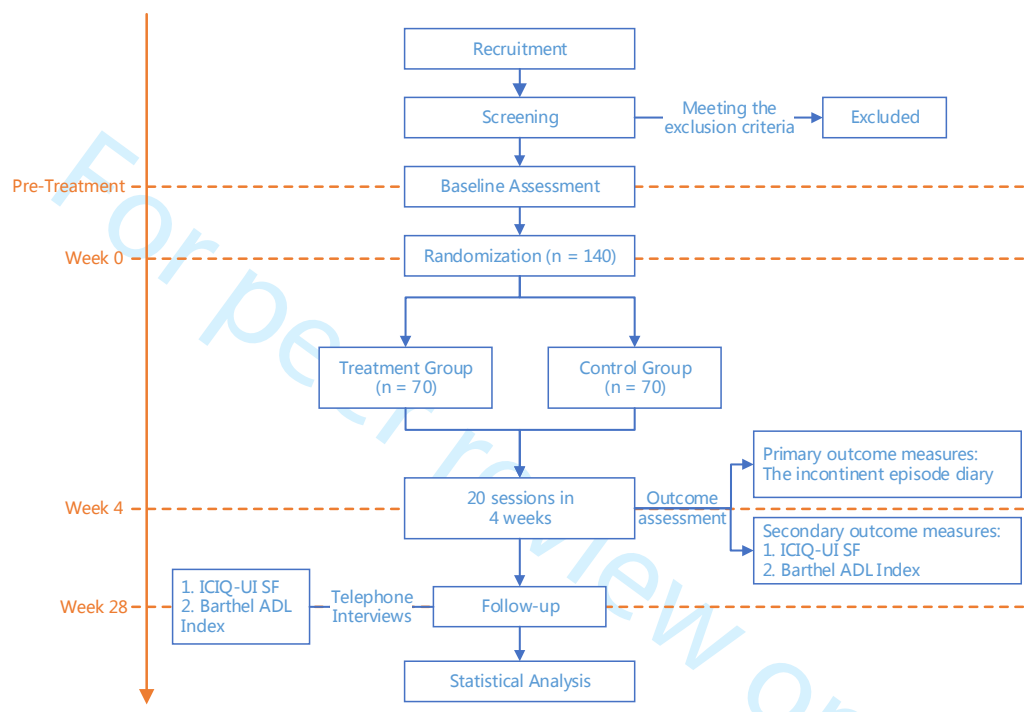
- 1. International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-UI SF) (Table 2)
- 2. Barthel Activities of Daily Living Index (Barthel ADL Index) (Table 3)

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 \pm 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021783.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Jul-2018
Complete List of Authors:	Chen, Shan; the First Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture and Moxibustion Wang, Siyou; Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian Xuan, Li; 3, Department of Acupuncture and Moxibustion Lu, Hanti; the First Affiliated Hospital of Zhejiang Chinese Medical University, Clinical Evaluation and Analysis Center Hu, Zhikai; Huaqiao University, Department of Computer Science Zhang, Chao; the First Affiliated Hospital of Zhejiang Chinese Medical University, Rehabilitation Unit Zhang, Huifang; the First Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture and Moxibustion
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Urology
Keywords:	COMPLEMENTARY MEDICINE, UROLOGY, Stroke medicine < INTERNAL MEDICINE, Stroke < NEUROLOGY, STROKE MEDICINE

SCHOLARONE™
Manuscripts

1
2
3 **Comparison of efficacy and safety between electroacupuncture at ‘four sacral**
4 **points’ and conventional electroacupuncture for the treatment of urinary**
5 **incontinence after stroke: study protocol for a randomized controlled trial**
6
7

8 Shan Chen¹, Siyou Wang², Lihua Xuan¹, Hanti Lu³, Zhikai Hu⁴, Chao Zhang⁵,
9 Huifang Zhang¹

10
11 Corresponding author:

12 Shan Chen

13
14 Department of Acupuncture and Moxibustion, the First Affiliated Hospital of
15 Zhejiang Chinese Medical University, Hangzhou, China

16
17 No. 9 the Ninth Street, Xiasha Economic and Technological Zone, Hangzhou,
18 Zhejiang Province 310018, China

19
20 E-mail: breezehilly@hotmail.com

21
22 Phone number: +86 152 5881 3929

23
24 Fax number: 0571-85860230

25
26 Siyou Wang, Clinical Research Section, Shanghai Research Institute of Acupuncture
27 and Meridian, Shanghai, China

28
29 Lihua Xuan, Department of Acupuncture and Moxibustion, the First Affiliated
30 Hospital of Zhejiang Chinese Medical University, Hangzhou, China

31
32 Hanti Lu, Clinical Evaluation and Analysis Center of the First Affiliated Hospital of
33 Zhejiang Chinese Medical University, Hangzhou, China

34
35 Zhikai Hu, Department of Computer Science, Huaqiao University, Xiamen, China

36
37 Chao Zhang, Rehabilitation Unit of the First Affiliated Hospital of Zhejiang Chinese
38 Medical University, Hangzhou, China

39
40 Huifang Zhang, Department of Acupuncture and Moxibustion, the First Affiliated
41 Hospital of Zhejiang Chinese Medical University, Hangzhou, China

42
43
44 **Keyword:** electroacupuncture; urinary incontinence; post-stroke; electrical pudendal
45 nerve stimulation

46
47
48 **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];

1
2
3 however, the performance of PNM also needs surgery so its disadvantages are similar
4 to those of SNM [10, 18].

5
6 According to the theory of traditional Chinese medicine (TCM), UI is primarily
7 caused by kidney and bladder dysfunction in terms of urine control. Accordingly, the
8 principle of acupuncture treatment for UI is to promote the recovery of urine control
9 [19]. Acupoints on the lower abdomen, such as CV4 (Guanyuan), CV6 (Qihai), and
10 ST28 (Shuidao), as well as those on the sacral region, such as BL32 (Ciliao), BL33
11 (Zhongliao), and BL 35 (Huiyang), are generally selected for the regulation of the
12 bladder voiding function [20-22]. A literature review showed that acupuncture
13 demonstrated more favourable effects than did antimuscarinic drugs for the treatment
14 of OAB and alleviation of symptoms in some comparative trials [23]. In addition,
15 acupuncture reportedly improved the quality of life (QoL) and urodynamic testing
16 parameters in patients with OAB [23, 24]. In a randomized, double-blind,
17 placebo-controlled study, electroacupuncture significantly increased the maximum
18 cystometric capacity and bladder compliance, decreased the detrusor leak point
19 pressure, alleviated lower urinary tract symptoms, and decreased the risk of upper
20 urinary tract damage in patients with post-stroke detrusor overactivity [22]. However,
21 high-quality clinical trials with appropriate inclusion criteria, sample size, control
22 design, acupoint selection, depth of needle insertion, and efficacy and safety
23 evaluations are necessary to properly evaluate the efficacy of acupuncture for the
24 treatment of post-stroke UI [7, 25, 26].

25
26 On the basis of the theory of nerve stimulation, we developed electroacupuncture at
27 'four sacral points' [27, 28], also known as electroacupuncture neurostimulation
28 therapy or electrical PN stimulation therapy. This approach involves the insertion of
29 long needles at 'four sacral points', with electricity to stimulate specific nerves under
30 the sacral region [28, 29]. When it was first developed, this treatment was used to treat
31 stress UI (SUI) in women, and radiographic evidence with simultaneous records of
32 perineal ultrasonographic pelvic floor muscle (PFM) contraction, vaginal pressure,
33 and pelvic floor surface electromyography have shown that it causes PN excitation
34 [29]. In addition, it has been used for the treatment of female urgency-frequency
35 syndrome, idiopathic urgency UI, and UI caused by neurological or non-neurological
36 conditions [28, 30, 31]. The mechanism of electroacupuncture at 'four sacral points' for
37 the treatment of post-stroke UI is that as this therapy can stimulate PN directly, it is
38 speculated that it is able to inhibit central hyperactivity through the vicerosomatic
39 convergence at S2-S4 common spinal neurons of PNs and bladder nerves to relieve the
40 symptoms post-stroke UI [32, 33].

41
42 The effectiveness of post-stroke UI treatment using alternative medicine
43 approaches is worthy of investigation in a well-designed study. To the best of our
44 knowledge, no randomized controlled trials (RCT) comparing the efficacy and safety
45
46
47
48
49
50
51
52
53

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

1
2
3 study. The random allocation is strictly kept in an opaque envelope and is inaccessible
4 to other research staff. After baseline assessment, the envelope will be opened by an
5 independent staff member in the participant's presence, in order to determine the
6 group assignment for that participant. All patients who give consent for participation
7 and who fulfil the inclusion criteria will be assigned to a group randomly.
8 Randomisation will be requested by the staff member responsible for recruitment and
9 clinical interviews from the First Affiliated Hospital of Zhejiang Chinese Medical
10 University. An independent staff member will open an envelope with printed
11 randomisation numbers in the participant's presence. The therapists will be informed
12 about the participant's allocation at the same time. The staff member responsible for
13 recruitment and clinical interviews is not allowed to receive information about the
14 group allocation.

15 *Blinding*

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

26 **Participants**

27 *Sample size*

28 With reference to a similar study^[33] with 120 women (efficacy rate, 70.1%:45%), the
29 sample size has been calculated, using PASS 11 software, as 120 patients for a power
30 (1-beta) of 0.80, an alpha (significance level) of 0.05, and a ratio of 1:1. With
31 consideration of the estimated dropout rate (15%), the total sample size will be 140
32 (70 in each group).

33 *Inclusion criteria*

- 34 1. Male or female patients aged 30–85 years
- 35 2. Diagnosis of post-stroke UI in accordance with the criteria of the American Stroke
36 Association^[34] and the International Continence Society^[35]
- 37 3. Inpatients or outpatients with a post-stroke interval of 4 weeks to 2 years
- 38 4. Stable vital signs, normal consciousness, and compliance with treatment
- 39 5. Refractoriness to medications (patients who have taken antimuscarinic agents with
40 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

1
2
3 Within a 5-cm diameter with the acupoint as the centre, sterilize the skin over the
4 acupoints using a cotton swab dipped in 0.45%–0.55% povidone iodine or 75%
5 ethanol.
6

7 4. Procedure

8 Treatment group: Participants in this group will receive electroacupuncture at
9 ‘four sacral points’.

10 a. Selection of points: Four sacral points (Figure 2 and Figure 3) are selected.

11 The two upper points are located on either side of the sacrococcygeal joint,
12 approximately 1 cm from the joint. The two lower points are located on either
13 side of the tip of the coccyx, approximately 1 cm from the coccyx.
14 Acupuncture will be performed at LI15 (Jianyu), LI11 (Quchi), LI10
15 (Shousanli), SJ5 (Waiguan), and LI4 (Hegu) for participants with upper limb
16 paralysis. For participants with lower limb paralysis, ST31 (Biguan), ST34
17 (Liangqiu), SP10 (Xuehai), SP9 (Yinlingquan), GB39 (Xuanzhong), GB40
18 (Qiuxu), and LR3 (Taichong) will also be used. GB20 (Fengchi), SJ17
19 (Yifeng), and GB12 (Wangu) will be used for participants with dysphagia,
20 with the additional use of ST4 (Dicang), ST6 (Jiache), and LI20 (Yingxiang)
21 for participants with facial paralysis and drooling.
22

23 b. Detailed procedure: At the upper sacral points, a needle (Suzhou Shenlong 24 Medical Apparatus Factory, Suzhou, China) measuring 0.40×100 mm will be 25 inserted perpendicularly to a depth of 80–90 mm to induce a sensation 26 referred to the urethra or anus via stimulation of the main trunk of the PN. At 27 the lower sacral points, a needle measuring 0.40×100 or 0.40×125 mm will 28 be inserted obliquely toward the ischiorectal fossa to a depth of 90–110 mm 29 to induce a sensation referred to the urethra via stimulation of the perineal 30 nerve (Figure 4). Once the sensation is induced in the respective regions, two 31 pairs of electrodes from the G6805-A electroacupuncture device (Shantou 32 Medical equipment factory, Shantou, China) will be connected to the two 33 ipsilaterally inserted needles, with the anode connected to the upper needle 34 and the cathode connected to the lower needle. The device will be set to 35 produce electrical stimulation (biphasic 2-ms pulse duration) at a frequency of 36 2.0 Hz and a moderate intensity of 25–35 mA. Electrostimulation will be 37 performed for 20 min during each treatment. PFM contraction around the 38 urethra (often comfortable) must be maintained during the entire 39 electrostimulation procedure. Conventional acupuncture without electricity 40 will be applied for 20 min at the remaining acupoints. 41 42 43 44 45 46 47 48 49 50 51 52 53

54 Control group: Participants in this group will receive conventional
55 electroacupuncture.
56
57

- 1
2
3 a. Selection of points: Abdominal points CV6 (Qihai), CV4 (Guanyuan), and
4 ST28 (Shuidao, both sides), corresponding to the conventional
5 electroacupuncture treatment of UI. The point selection procedure for participants
6 with upper or lower limb paralysis, facial paralysis, and/or dysphagia will be the
7 same as that used for the treatment group.
8
9 b. Detailed procedure: At CV6 (Qihai), CV4 (Guanyuan), and ST28 (Shuidao),
10 a needle measuring 0.25 × 40 mm will be inserted perpendicularly to a depth of
11 25–40 mm to induce a local sensation (distention or sourness). Subsequently, the
12 electrodes from the G6805-A electroacupuncture device will be connected to the
13 needles at these points, with the anode connected to ST28 and the cathode
14 connected to CV6 and CV4. The device will be set to produce electrical
15 stimulation (biphasic 2-ms pulse duration) at a frequency of 2.0 Hz and a
16 moderate intensity that is tolerable by the participants. Electrostimulation will be
17 performed for 20 min during each treatment. Conventional acupuncture without
18 electricity will be applied for 20 min at the remaining acupoints.
19
20 5. Treatment period: All participants will receive treatment every day from Monday
21 to Friday. One course of treatment will comprise 10 sessions. The therapeutic
22 effects will be evaluated after the completion of two treatment courses (4 weeks).
23
24
25
26
27
28
29

30 Outcome measures

31 Primary outcome measures

32 The incontinent episode diary

33 The incontinent episode diary (Table 1) will be used to derive the primary outcome
34 measure. The number of incontinent episodes will be recorded by the participants
35 over a period of 3 days at baseline. A template will be provided for patient use. This
36 data will be recorded again at the end of treatment.
37
38
39
40

41 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					

1
2
3 *Secondary outcome measures*

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

6
7 2. Barthel Activities of Daily Living Index (Barthel ADL Index) [38] (Table 3)

8 The ICIQ-UI SF is used in research and clinical practice worldwide. It is a brief and
9 psychometrically robust patient-completed questionnaire for evaluating the frequency
10 and severity of UI in men and women and its impact on quality of life (QoL). The
11 ICIQ-UI SF score ranges from 0 to 21 [39]. The Barthel ADL Index is a 10-item
12 measure of activities of daily living (ADL) that is frequently used in clinical practice
13 and as a trial outcome measure in stroke medicine [38]. It is used to assess baseline
14 abilities to quantify functional changes, including UI, after rehabilitation in stroke
15 patients.
16

17 The above outcome measures will be assessed at baseline and at 4 and 28 weeks after
18 baseline.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1. Please write in your date of birth:	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	date month year	
2. Are you	Female <input type="checkbox"/>	Male <input type="checkbox"/>
3. How often do you leak urine? (Tick one box)	never	<input type="checkbox"/> 0
	about once a week or less often	<input type="checkbox"/> 1
	two or three times a week	<input type="checkbox"/> 2
	about once a day	<input type="checkbox"/> 3
	several times a day	<input type="checkbox"/> 4
	all the time	<input type="checkbox"/> 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	<input type="checkbox"/> 0
	a small amount	<input type="checkbox"/> 2
	a moderate amount	<input type="checkbox"/> 4
	a large amount	<input type="checkbox"/> 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

	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

1
2
3 at 4 weeks after baseline. A blinded telephone interviewer will interview the
4 participants and collect data pertaining to ICIQ-UI SF and the Barthel ADL Index at
5 28 weeks after baseline. All data will be recorded on the CRFs. For participants who
6 discontinue treatment early, we will use last observation carried forward analysis to
7 handle the missing data, meaning that we will input outcome data of patients who are
8 lost to follow-up in our analysis.
9

10 After the completion of the CRFs, two independent researchers blinded to the group
11 allocation will separately input data into an Excel spreadsheet. Another independent
12 supervisor will check the two datasets for consistency. If conflicting data entries are
13 discovered, the supervisor will compare the datasets with the original CRFs and mark
14 the modification on the CRFs. The principal investigator of the research team will
15 have the access to all documents and will protect the electronic documents with a
16 password and create backups of all documents. The First Affiliated Hospital of
17 Zhejiang Chinese Medical University will be responsible for the storage and
18 management of all data.
19

20 An independent data monitoring committee (DMC) is made up of members from
21 Clinical Evaluation and Analysis Center of The First Affiliated Hospital of Zhejiang
22 Chinese Medical University. The DMC, blinded to the treatment allocations, will meet
23 regularly to monitor the study data. The DMC will also perform interim-analysis
24 when 50% of patients have been randomised and have completed the primary
25 outcome measurement.
26
27
28

29 The First Affiliated Hospital of Zhejiang Chinese Medical University will audit this
30 study mainly for participant enrolment, consent, and costs.
31
32

33 **Statistical analysis**

34 All statistical analyses will be performed by a statistician from the Clinical Evaluation
35 and Analysis Center of The First Affiliated Hospital of Zhejiang Chinese Medical
36 University using SPSS Statistics 22.0. A normality test will be used to determine
37 whether the data are normally distributed. ANCOVA (analysis of covariance) will be
38 used if there is imbalance in the baseline characteristics and outcome measures.
39 Continuous variables with a normal distribution will be expressed as means \pm
40 standard deviations (SDs). Continuous variables with a non-normal distribution or
41 ordinal variables will be expressed as medians (with lower, upper quartiles).
42 Categorical variables will be summarized as counts and proportions. A Student's t-test
43 will be used if the primary and secondary outcome measures conform to normal
44 distribution. A paired t-test will be used to compare pre-treatment and post-treatment
45 UI occurrence for the primary outcome measure and pre-treatment and post-treatment
46 scores in the secondary outcome measures. The independent sample t-test will be used
47 to compare the difference between two groups for primary and secondary outcome
48 measures. A Wilcoxon signed rank test will be used if the primary and secondary
49 outcome measures conform to abnormal distribution. A Wilcoxon paired test will be
50 used to compare pre-treatment and post-treatment UI occurrence for the primary
51 outcome measure and pre-treatment and post-treatment scores in secondary outcome
52 measures. The inter-group rank sum test will be used to compare the difference
53
54
55
56
57
58
59
60

1
2
3 between two groups for primary and secondary outcome measures. All reported
4 P-values will be two-sided, and confidence intervals (CI) will be at the 95% level. A
5 P-value of <0.05 will be considered statistically significant.
6
7

8 **Patient and Public Involvement**

9 Patients and the public were not directly involved in the design, recruitment or
10 conduct of this pilot study. Since the participants in our study are under chronic
11 conditions, the outcome measures valued in this study was influenced by patients'
12 priorities, experience and preferences. As most stroke patients are in great need of
13 acupuncture treatment in China, we did not view the intervention as burdensome and
14 the burden of the intervention was not assessed by the patients themselves. The results
15 of this study will be disseminated in peer-reviewed journals and at academic
16 conferences. A summary of the study report will be written for patients through online
17 website (<https://sandychenshan.haodf.com/>) and WeChat (a free messaging and
18 calling application) account or group.
19
20
21
22

23 **ETHICS AND DISSEMINATION**

24 **Research ethics approval**

25 The Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical
26 University has reviewed and approved this protocol (approval No. 2018-K-059-01).
27 This study will adhere to the principles of the Declaration of Helsinki. This study will
28 be conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University.
29 Each participant will voluntarily sign written informed consent forms.
30
31
32

33 **Modification of the protocol**

34 Any modifications to the protocol, including changes of study objectives, study design,
35 patient population, sample sizes, study procedures, or significant administrative
36 aspects, will require a formal application to the Zhejiang Provincial Administration of
37 Traditional Chinese Medicine as well as the Chinese clinical trial registry.
38
39

40 **Confidentiality**

41 All study participants will be given an identification number throughout the trial to
42 assure confidentiality. All participants' information will be stored in locked cabinets
43 with limited access.
44
45

46 **Dissemination**

47 The initial data will be accessible via Research Manager (ResMan). The results of this
48 study will be published in open-access and peer-reviewed journals and presented at
49 relevant conferences.
50
51
52

53 **DISCUSSION**

54 According to the present study protocol, in addition to electroacupuncture at 'four
55 sacral points' in the treatment group and conventional electroacupuncture in the
56
57
58
59
60

1
2
3 control group, the same acupoints for other stroke symptoms will also be selected for
4 both groups. Other stroke symptoms include unilateral limb weakness, facial paresis,
5 dysphasia, and dysphagia [42]. In China, acupuncture has been a primary medical
6 intervention for stroke [43]. In fact, not providing acupuncture therapy to a stroke
7 patient is considered impractical.
8

9 Antimuscarinic agents are considered first-line drugs for neurogenic detrusor
10 overactivity (NDO) [44]. However, because of their moderate efficacy and
11 troublesome side effects, quite a few patients exhibit refractory disease [45].
12 According to the eligibility criteria, participants who are refractory to medication will
13 be included in this RCT.
14

15 With regard to the outcome measures, the incontinent episode diary will be used as
16 objective measure to record the frequency of incontinence. Patients will record their
17 findings in the incontinent diary for only 3 days, because a longer recording period
18 can lead to decreased patient compliance [46-47]. In order to improve adherence,
19 health education about the importance of UI management will be conducted by a
20 special nurse and brochures on post-stroke UI will be provided to patients. The
21 ICIQ-UI SF and Barthel ADL Index will be used as subjective measures to investigate
22 UI symptoms and QoL. The ICIQ-UI SF is a useful tool to assess UI with regard to
23 the severity of symptoms and impact on QoL at baseline and at follow-up [48]. The
24 Barthel ADL Index (feeding, bathing, grooming, dressing, bowels, bladder, toilet use,
25 transfer, mobility, and stairs) is an important predictor of stroke outcomes. Studies
26 involving stroke survivors should include ADL assessments for better management of
27 stroke patients [38].
28

29 In summary, we have described a protocol for a pilot RCT to evaluate the efficacy
30 and safety of electroacupuncture at ‘four sacral points’ for the treatment of post-stroke
31 UI. The results of this trial should lead to a greater understanding of promising
32 alternative options for post-stroke UI.
33
34
35
36
37

38 **Author affiliations**

39 ¹Department of Acupuncture and Moxibustion, the First Affiliated Hospital of
40 Zhejiang Chinese Medical University, Hangzhou, China

41 ²Clinical Research Section, Shanghai Research Institute of Acupuncture and Meridian,
42 Shanghai, China

43 ³Clinical Evaluation and Analysis Center of the First Affiliated Hospital of Zhejiang
44 Chinese Medical University, Hangzhou, China

45 ⁴Department of Computer Science, Huaqiao University, Xiamen, China

46 ⁵Rehabilitation Unit of the First Affiliated Hospital of Zhejiang Chinese Medical
47 University, Hangzhou, China
48
49
50

51 **Contributors**

52 SC conceived and wrote the protocol; SYW and LHX contributed to the study design;
53 HTL contributed to the sample size calculation and wrote the statistical analysis plan;
54 ZKH drew the flow charts; CZ and HFZ prepared the figures and tables. All authors
55 have read and approved the final manuscript.
56
57
58
59
60

Funding Statement

This work was supported by Zhejiang Provincial Administration of Traditional Chinese Medicine (grant number 2016ZA076; 2018ZA045).

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.

REFERENCES

- 1 Abrams P, Andersson KE, Birder L, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn* 2010;29:213-40.
- 2 Ruffion A, Castro DD, Patel H, et al. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. *Neuroepidemiology* 2013;41:146-55.
- 3 Mehdi Z, Birns J, Bhalla A, et al. Post-stroke urinary incontinence. *Int J Clin Pract* 2013;67:1128-37.
- 4 Cai W, Wang J, Wang L, et al. Prevalence and risk factors of urinary incontinence for post-stroke inpatients in Southern China. *Neurourol Urodyn* 2015;34:231-5.
- 5 Pizzi A, Falsini C, Martini M, et al. Urinary incontinence after ischemic stroke: clinical and urodynamic studies. *Neurourol Urodyn* 2014;33:420-5.
- 6 Gregor J, Steve P, Siobhan C, et al. Urinary incontinence and indwelling urinary catheters as predictors of death after new-onset stroke: a report of the south london stroke register. *J Stroke Cerebrovasc Dis* 2018;27:118-24.
- 7 Thomas LH, Cross S, Barrett J, et al. Treatment of urinary incontinence after stroke in adults. *Cochrane Database of Systematic Reviews* 2008;23:CD004462.
- 8 Paniker JN. Urogenital symptoms in neurologic patients. *Continuum*. 2017;23:533-52.
- 9 Amundsen CL, Komesu YM, Chermansky C, et al. Two-Year outcomes of sacral neuromodulation versus onabotulinumtoxinA for refractory urgency urinary incontinence: a randomized trial. *Eur Urol* Published Online First: 23 February 2018. doi:10.1016/j.eururo.2018.02.011
- 10 Bosch JL. Electrical neuromodulatory therapy in female voiding dysfunction. *BJU Int* 2006;98 suppl:43-8.
- 11 van Balken MR, Vergunst H, Bemelmans BL. The use of electrical devices for the treatment of bladder dysfunction: a review of methods. *J Urol* 2004;172:846-51.

- 1
2
3 12 Tahereh E, Nastaran T, Elahe, et al. Posterior Tibial Nerve Stimulation for
4 Treating Neurologic Bladder in Women: a Randomized Clinical Trial. *Acta Medica*
5 *Iranica* 2014;52:817-21.
6
7 13 Manuela T, Enrico A, Frank VA. What Is New in Neuromodulation for
8 Overactive Bladder? *Eur Urol Focus* 2018; 4:49-53.
9
10 14 Smits MA, Oerlemans D, Marcelissen TA, et al. Sacral neuromodulation in
11 patients with idiopathic overactive bladder after initial botulinum toxin therapy. *J*
12 *Urol* 2013;190:2148-52.
13
14 15 Siegel S, Noblett K, Mangel J, et al. Results of a prospective, multicenter study
15 evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve
16 months in subjects with symptoms of overactive bladder. *Neurourol Urodyn*
17 2016;34:246-51.
18
19 16 Lee C, Pizarro-Berdichevsky J, Clifton MM, et al. Sacral neuromodulation
20 implant infection: risk factors and prevention. *Curr Urol Rep* 2017;18:16.
21
22 17 Peters KM. Alternative approaches to sacral nerve stimulation. *Int Urogynecol J*
23 2010;21:1559-63.
24
25 18 Groen J, Amiel C, Bosch JL. Chronic pudendal nerve neuromodulation in women
26 with idiopathic refractory detrusor overactivity incontinence: results of a pilot study
27 with a novel minimally invasive implantable mini-stimulator. *Neurourol Urodyn*
28 2005;24:226-30.
29
30 19 Sun Z, Yu N, Yue J, et al. Acupuncture for urinary incontinence after stroke: a
31 protocol for systematic review. *BMJ Open* 2016;6:e008062.
32
33 20 Song F, Jiang S, Zheng L, et al. Electroacupuncture for post-stroke urinary
34 incontinence: a multicenter randomized controlled study. *Zhongguo Zhen Jiu*
35 2013;33:769-73.
36
37 21 Paik SH, Han SR, Kwon OJ, et al. Acupuncture for the treatment of urinary
38 incontinence: A review of randomized controlled trials. *Exp Ther Med* 2013;6:773-80.
39
40 22 Liu Y, Liu L, Wang X. Electroacupuncture at points Baliao and Huiyang (BL35)
41 for post-stroke detrusor overactivity. *Neural Regen Res* 2013;8:1663-72.
42
43 23 Forde JC, Jaffe E, Stone BV, et al. The role of acupuncture in managing
44 overactive bladder; a review of the literature. *Int Urogynecol J* 2016;27:1645-51.
45
46 24 Olivera CK, Meriwether K, El-Nashar S, et al. Nonantimuscarinic treatment for
47 overactive bladder: a systematic review. *Am J Obstet Gynecol* 2016;215:34-57.
48
49 25 Solberg M, Alræk T, Mdala I, et al. A pilot study on the use of acupuncture or
50 pelvic floor muscle training for mixed urinary incontinence. *Acupunct Med*
51 2016;34:7-13.
52
53 26 Liu Z, Wang Y, Xu H, et al. Observation on therapeutic effect of
54 electroacupuncture for post-stroke urge incontinence. *Xin Zhong Yi* 2010;42:73-5.
55
56 27 Wang S, Chen G, Li L. "Four sacral needles therapy" for female stress
57 incontinence. *Shanghai J Acup Moxib* 2006;25:15-7.
58
59 28 Lu J. Observation on therapeutic effect of electroacupuncture neurostimulation
60 therapy for urge urinary incontinence. *Zhongguo Zhenjiu* 2012;32:691-5.
29 Wang S, Zhang S. Simultaneous perineal ultrasound and vaginal pressure
measurement prove the action of electrical pudendal nerve stimulation in treating

- 1
2
3 female stress incontinence. *BJU International* 2012;110:1338-1343.
- 4 30 Wang S, Zhang S, Zhao L. Long-term efficacy of electrical pudendal nerve
5 stimulation for urgency–frequency syndrome in women. *Int Urogynecol J*
6 2014;25:397-402.
- 7
8 31 Wang S, LvJ, FX et al. Efficacy of electrical pudendal nerve stimulation versus
9 transvaginal electrical stimulation in treating female idiopathic urgency urinary
10 incontinence. *J Urol* 2017;197:1496-501.
- 11
12 32 Wang S. Electroacupuncture pudendal nerve stimulation and its application. *J*
13 *Acupunt Tuina Sci* 2013;11:117-21.
- 14
15 33 Wang S, Lv J, Feng X, et al. Efficacy of Electrical Pudendal Nerve Stimulation
16 versus Transvaginal Electrical Stimulation in Treating Female Idiopathic Urgency
17 Urinary Incontinence. *J Urol* 2017;6:1496-501.
- 18
19 34 Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the
20 21st century: a statement for healthcare professionals from the American Heart
21 Association/American Stroke Association. *Stroke* 2013;44:2064-89.
- 22
23 35 Haylen BT, de Ridder D, Freeman RM, et al. Association (IUGA)/International
24 Continence Society (ICS) joint report on the terminology for female pelvic floor
25 dysfunction. *Neurourol Urodyn* 2010;29:4-20.
- 26
27 36 Grut M, Fratiglioni L, Viitanen M, et al. Accuracy of the Mini-Mental Status
28 Examination as a screening test for dementia in a Swedish elderly population. *Acta*
29 *Neurol Scand* 1993;87:312-71993-04-01.
- 30
31 37 Timmermans L, Falez F, Mélot C, et al. Validation of use of the International
32 Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form
33 (ICIQ-UI-SF) for impairment rating: a transversal retrospective study of 120 patients.
34 *Neurourol Urodyn* 2013;32:974-9.
- 35
36 38 Duffy L, Gajree S, Langhorne P, et al. Reliability (inter-rater agreement) of the
37 Barthel Index for assessment of stroke survivors: systematic review and meta-analysis.
38 *Stroke* 2013;44:462-8.
- 39
40 39 Hajebrahimi S, Nourizadeh D, Hamedani R, et al. Validity and reliability of the
41 International Consultation on Incontinence Questionnaire-Urinary Incontinence Short
42 Form and its correlation with urodynamic findings. *Urol J* 2012;9:685-90.
- 43
44 40 Li Y, Liu Y, Zhang J, et al. Analysis on the situation of adverse reaction to
45 acupuncture and acupuncture risk. *Zhongguo Zhenjiu* 2011;31:764-8.
- 46
47 41 Zhao L, Li Y, Zhang F, et al. Analysis on the occurrence of laws of adverse
48 events from 1968 patients after acupuncture treatment. Symposium of seminar of the
49 Ninth National Young and Middle-aged Acupuncture and Tuina of China
50 Acupuncture and Moxibustion Association 2010;270-6.
- 51
52 42 Yew KS, Cheng EM. Diagnosis of Acute Stroke. *Am Fam Physician*
53 2015;91:528-36.
- 54
55 43 Zhang J, Wang D, Liu M. Overview of systematic reviews and meta-analyses of
56 acupuncture for stroke. *Neuroepidemiology* 2014;42:50-8.
- 57
58 44 Mehnert U, Kessler TM. The management of urinary incontinence in the male
59 neurological patient. *Curr Opin Urol* 2014;24:586-92.
- 60
45 Smith AL, Wein AJ. Urinary incontinence: pharmacotherapy options. *Ann Med*

2011;43:461-76.

46 Robinson D, McClish DK, Wyman JF, et al. Comparison between urinary diaries completed with and without intensive patient instructions. *Neurourol Urodyn* 1996;15:143-8.

47 Gordon D, Grpouts A. Evaluation of female lower urinary tract symptoms: overview and update. *Curr Opin Obstet Gynecol* 2001;13:521-7.

48 Nyström E, Sjöström M, Stenlund H, et al. ICIQ symptom and quality of life instruments measure clinically relevant improvements in women with stress urinary incontinence. *Neurourol Urodyn* 2015;34:747.

Figure legends

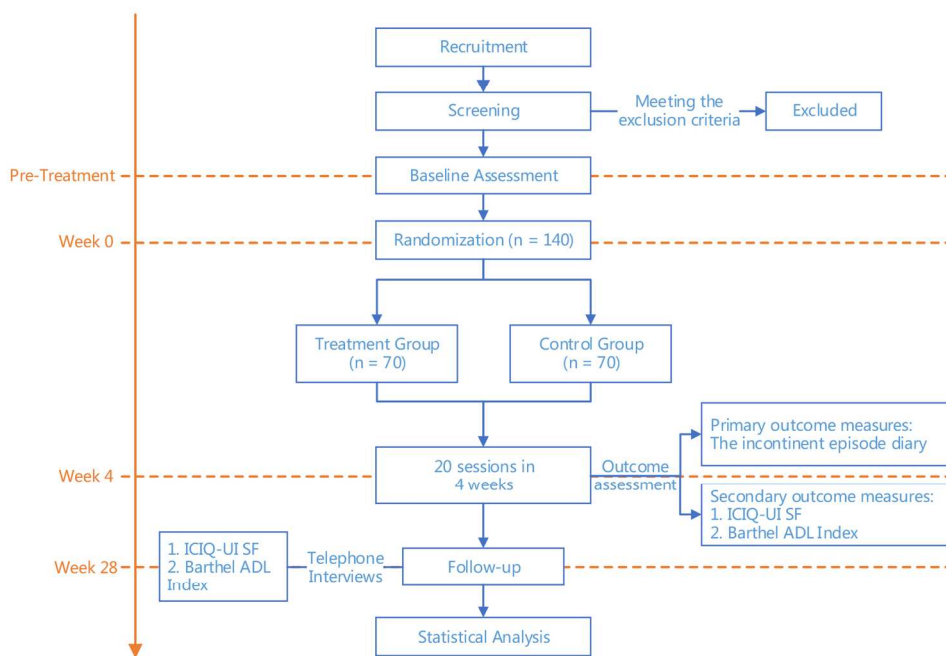
Figure 1 Study flowchart

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)

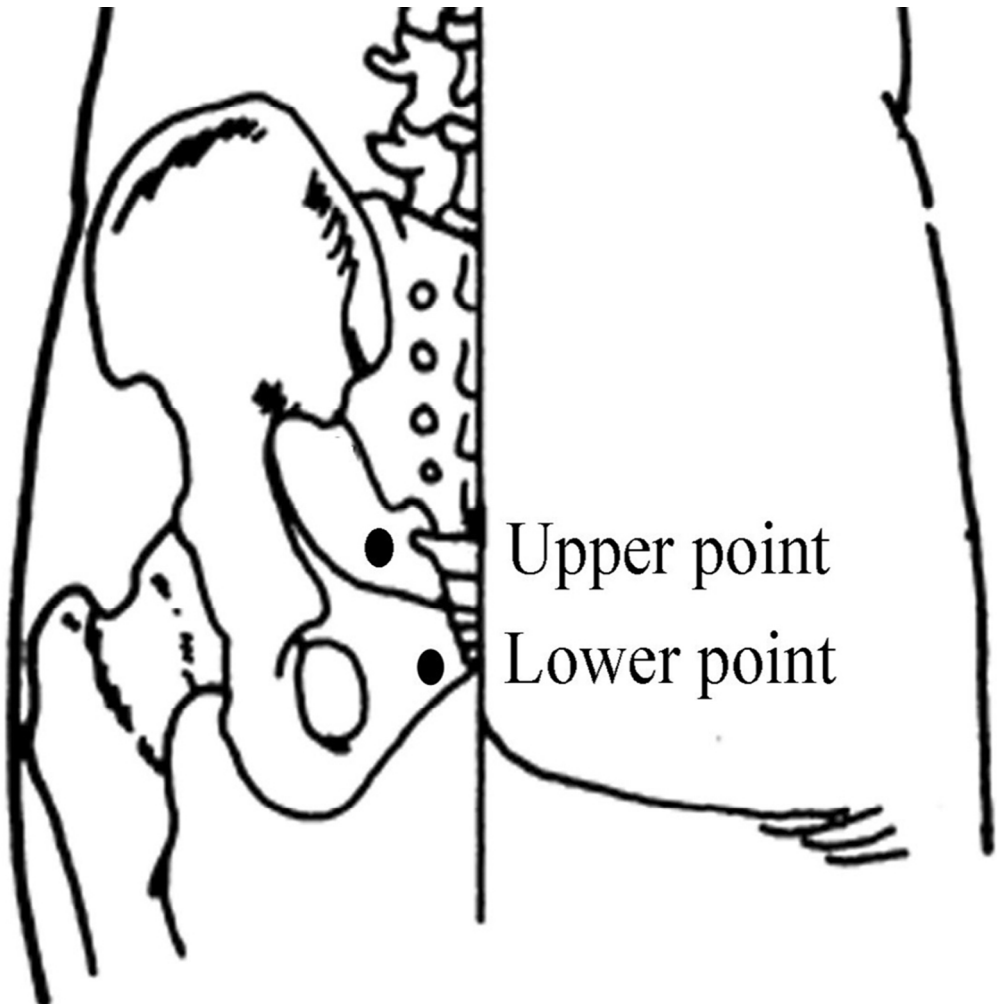


Study flowchart

151x105mm (300 x 300 DPI)

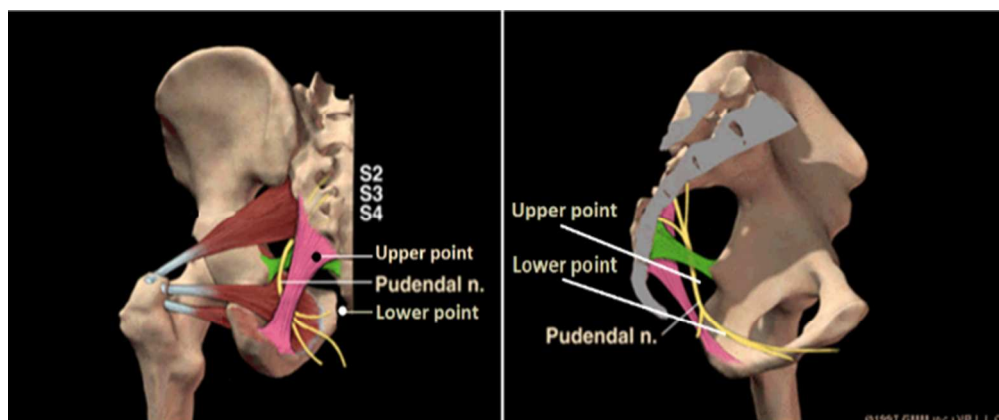
View only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Locations of the 'four sacral points' for electroacupuncture

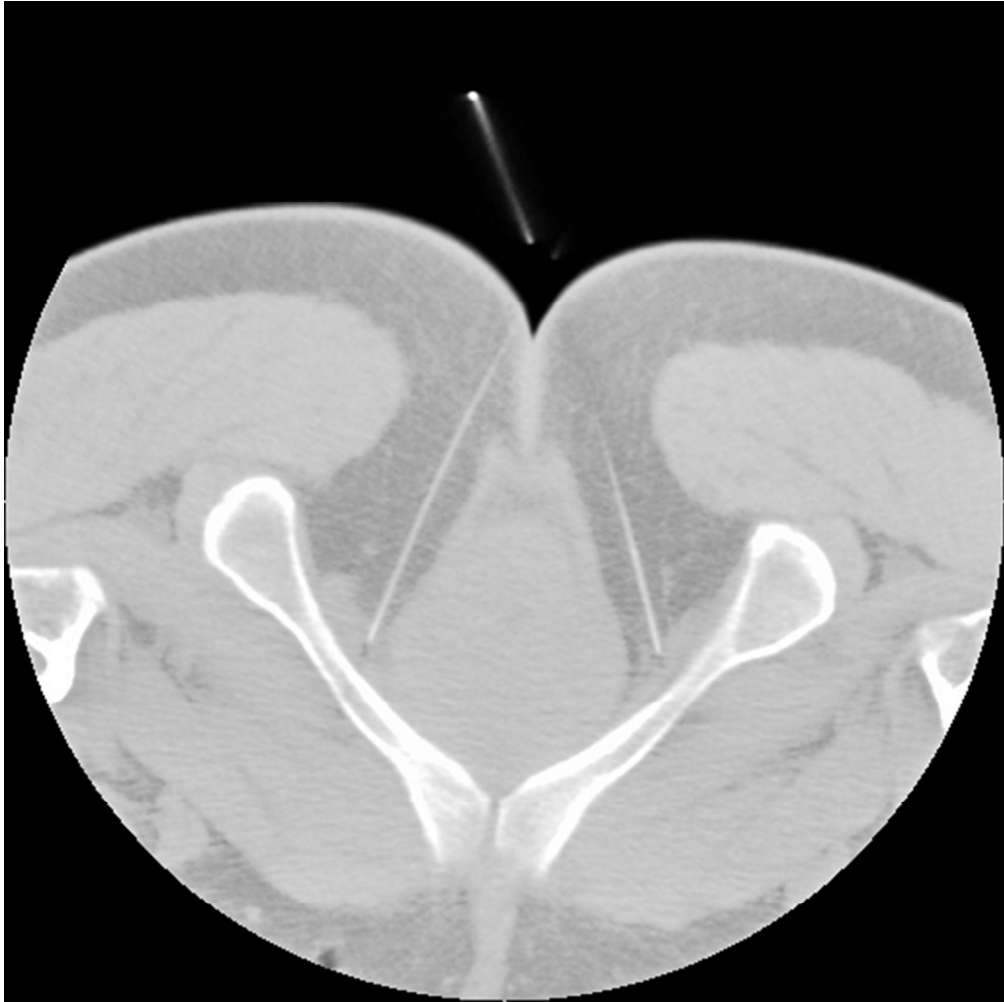
90x90mm (300 x 300 DPI)



Anatomical positions of the 'four sacral points' for electroacupuncture

216x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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	<table border="1"> <tr> <td>Primary registry and trial identifying number</td> <td>ChiCTR-IOR-17012847</td> </tr> <tr> <td>Date of registration in primary registry</td> <td>30 Sep 2017</td> </tr> <tr> <td>Secondary identifying numbers</td> <td></td> </tr> <tr> <td>Source(s) of monetary or material support</td> <td>Zhejiang Provincial Administration of Traditional Chinese Medicine</td> </tr> <tr> <td>Primary sponsor</td> <td>Zhejiang Provincial Administration of Traditional Chinese Medicine</td> </tr> <tr> <td>Secondary sponsor(s)</td> <td></td> </tr> <tr> <td>Contact for public queries</td> <td>CZ[zc985417@163.com],HFZ[zhuzhijie@163.com]</td> </tr> <tr> <td>Contact for scientific queries</td> <td>CZ,HFZ Department of Acupuncture and Moxibustion, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China</td> </tr> <tr> <td>Public title</td> <td>Electroacupuncture at ‘four sacral points’ for the treatment of urinary incontinence after stroke</td> </tr> <tr> <td>Scientific title</td> <td>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</td> </tr> <tr> <td>Countries of recruitment</td> <td>China</td> </tr> <tr> <td>Health condition(s) or problem(s) studied</td> <td>Acupuncture treatment; Urinary incontinence after stroke</td> </tr> </table>	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[zhuzhijie@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
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[zhuzhijie@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																									

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Intervention(s)	Treatment group: electroacupuncture at ‘four sacral points’ Control group: conventional electroacupuncture
Key inclusion and exclusion criteria	<p>Ages eligible for study: 30-85 years old; Sexes eligible for study: both; Accepts healthy volunteers: no.</p> <p>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.</p> <p>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 ;</p>

		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 Medicine¹⁸

Sponsor's Reference: grant number 2016ZA076;2018ZA045¹⁸

Contact name: Zhejiang Provincial Administration of Traditional Chinese Medicine

Address: No.216 Qingchun Road

Telephone: +86 0571 8770 9076

Email: zjtcn@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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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 device⁶⁻⁷

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	<p>Treatment group: Participants in this group will receive electroacupuncture at 'four sacral points'.</p> <p>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</p>
---------------	-----	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

(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

		<p>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.</p> <p>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</p>
	11b	<p>Elimination criteria</p> <ol style="list-style-type: none"> 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 <p>Dropout criteria</p> <ol style="list-style-type: none"> 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 dropout⁷
	11c	<p>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</p>
	11d	<p>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.</p> <p>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</p>
Outcomes	12	<p>Primary outcome measures</p> <p>The incontinent episode diary</p> <p>The incontinent episode diary (Table 1) will be used to derive the primary outcome measure. The number of incontinent episodes</p>

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)

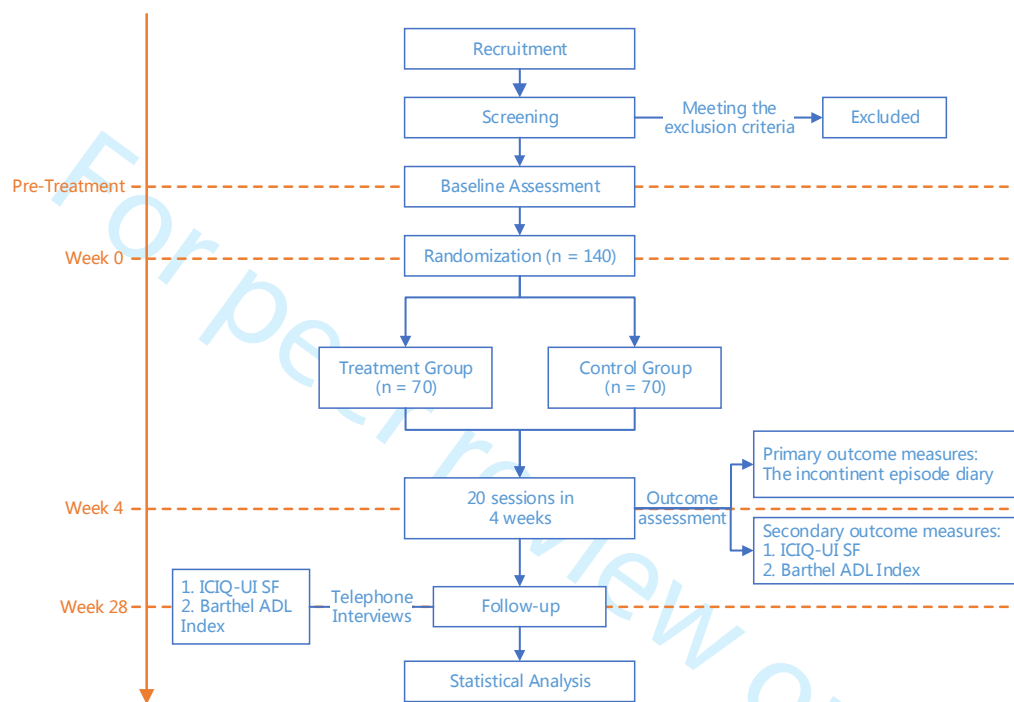
2. Barthel Activities of Daily Living Index (Barthel ADL Index) (Table 3)

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 \pm 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.

For peer review only