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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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ABSTRACT

Introduction: Ginger-salt-indirect moxibustion is widely applied to treat urge urinary incontinence after stroke, which is a common complication in stroke survivors. Moxa cone moxibustion and moxa box moxibustion are main patterns of ginger-salt-indirect moxibustion. Our previous study had shown that ginger-salt-indirect moxibustion using moxa cones was feasible and effective to treat urination disorders post-stroke. This pilot study aims to assess the feasibility of a research that evaluate the efficacy and safety of ginger-salt-indirect moxibustion for patients with post-stroke urge urinary incontinence.

Methods and analysis: This is a multicenter, prospective, single-blinded, pilot randomized controlled trial. 120 eligible patients with urge urinary incontinence after stroke will be randomly allocated to three groups. Treatment group A (n = 40) will receive moxa cone moxibustion and routine care; treatment group B (n = 40) will receive moxa box moxibustion and routine care; control group (n = 40) will only receive routine care for stroke recovery. The entire moxibustion treatment course will consist of 28 sessions in 4 weeks. Primary outcome measure is increase of mean volume per void at week 4 from the baseline, basing on the data of a 72-hour frequency-volume chart. Secondary outcome measures include mean frequency of urination per day and quality of life assessments measured by completion of Incontinence Quality of Life Questionnaire and Barthel Index. All outcome measures will be assessed before the first moxibustion session, at 4 weeks and 16 weeks after the first moxibustion session. Adverse events in both groups will be recorded to assess safety of moxibustion.

Ethics and dissemination: Research ethics was approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). Written informed consent will be achieved from all participants. Study results will be published in peer-reviewed journals.

Trial Registration number: ISRCTN 44706974.

Strengths and limitations of this study

- First pilot study to evaluate the feasibility of a research that assess the efficacy and safety of ginger-salt-indirect moxibustion for UUI after stroke
- Multicentre, randomised controlled trial with pragmatic design
- Interventions conducted by certified acupuncturists according to the STRICTOM and GCP.
- Lack of blinding of acupuncturists and participants due to the nature of moxibustion

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary leakage of urine that causes hygienic or social problems by International Continence Society (ICS)[1]. Prevalence of UI after stroke varies from 32–79% at admission[2-4], 25% at hospital discharge and 15% after one year[4]. As a common type of UI[5], urge urinary incontinence (UUI) after stroke is characterized by involuntary loss accompanied or preceded by urgency[1], which arises from acute cerebral accident onset.

Stroke causes deficiency of inhibitory neurons and leads to neurogenic detrusor overactivity[6]. This seems to be the primary mechanism of UUI after stroke[1, 7-9]. Detrusor overactivity is characterized by involuntary detrusor contractions during filling and storage phase[1, 6, 10]. When intra-detrusor pressure generated by abnormal detrusor contractions exceeds sphincter pressure, urinary incontinence occurs[6]. UI is a strong prognostic indicator for stroke recovery, which is associated with high rates of mortality [11, 12], disability[13] and increasing admission to institutional care[14]. Micturition disorders may result in urinary infection, nephritis, fungal dermatitis[15], even bedsore. Typical symptoms, including frequent micturition, nocturia and urgency (compelling desire to void which is difficult to defer), could lead to impaired quality of life[16] and heavy economic burdens[17, 18].

Initial treatments for UUI after stroke recommended by ICS are behavioral therapy and pharmacotherapy[1]. Behavioral therapies, including healthy bladder habits and training techniques, aim at changing patients' lifestyle and at teaching patients to control urgency and enhance continence ability[19]. For habit modification, patients are guided to re-establish a healthy voiding schedule, eliminate bladder irritants from the diet, manage fluid intake and bowel regularity, control weight and give up smoking[20-26]. Training techniques consist of bladder training, urgency control techniques, pelvic muscle exercises, delayed voiding and multicomponent behavioral training[19]. Behavioral interventions could be applied in the primary care setting, with or without pharmacotherapy[27-29]. Among these strategies, behavioral training and bladder training have the strongest evidences for the treatment of UUI[30-33]. Antimuscarinic drugs can reduce urgency and improve bladder function with the mechanism of controlling detrusor muscle overactivity by inhibiting M2 and M3 muscarinic receptors on bladder[34-36]. Several meta-analyses have shown that the most widely used antimuscarinic drugs have significant clinical benefits on UUI[37-40].

Nevertheless, application of antimuscarinic agents is influenced by dosing convenience, drug contraindication and financial consideration[41]. A recent cochrane systematic review concluded that no rigorously studies designed to manage urinary incontinence after stroke in secondary care had been conducted by far[42]. Evidences from relevant trials were insufficient to guide clinical practices[43]. More available therapies and well-designed studies are required to provide further evidences for management of UUI after stroke.

Moxibustion is a therapy using ignited materials (usually moxa) to heat certain points of skin surface. This technique has been widely used as a treatment for cold syndrome and chronic deficiency diseases[44] and UUI was regarded as one of common indications[45]. Despite uncertain modern mechanisms, it is generally identified that action of moxibustion is produced by the meridian system combining with thermal, radiation and pharmacological effects of the materials used[46]. In China, ginger-salt-indirect moxibustion on CV8 (Shenque) is frequently applied to treat UUI after stroke. Moxa cone moxibustion and moxa box moxibustion are primary forms of ginger-salt-indirect moxibustion in clinical practices. Moxa cone moxibustion involves a moxa cone burning directly on the ginger slice and provides thermal stimulus to the skin surface (see Figure 2). Moxa box moxibustion facilitates manipulations and reduces adverse reactions by using the device of moxa box with moxa sticks inside over the ginger slice (see Figure 3). Results of our previous study[47] showed that ginger-salt-partitioned moxibustion with moxa cone could reduce mean daytime and nighttime voiding frequency in the treatment of urination disorders poststroke. Besides, we also observed that ginger-salt-indirect moxibustion with moxa cones could increase mean volume per void of UUI after stroke in an unpublished study. A recent cochrane review concluded that ginger-salt-indirect moxibustion may be effective for UI after stroke and worth further research[47, 48].

METHODS

Objectives

This pilot study is to evaluate the feasibility of a research that assess the efficacy and safety of ginger-salt-indirect moxibustion for UUI after stroke.

Recruitment

This is a multicenter, single-blinded, pilot randomized controlled trial. The research consists of three sequential parts (see Figure 1): a recruitment period before randomization, a treatment period for 4 weeks, and a follow-up period for 12 weeks. 120 eligible subjects will be recruited from acupuncture wards of three hospitals according to the inclusion and exclusion criteria. During the first visit, potentially qualified patients will be provided with detail information about this study, including the research objective, study procedure, potential benefits and risks. If patient shows a willingness to participate in, they will be required to sign a written informed consent. Baseline assessment and randomization will be conduct afterwards.

Design

Randomization and allocation concealment

The randomization scheme is provided by Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical experts will adopt block randomization method (block size of 6) of the SAS package (Version 9.1.3; SAS institute Inc., Cary, NC, USA) to form the random allocation sequence. Then computer-generated opaque sealed envelopes with serial number outside and group number inside will be produced. The envelopes will be kept in a secure locked drawer making it inaccessible to all study personnel. After baseline assessments, the

envelopes should be opened sequentially by an independent researcher in front of the participants to ensure adequate concealment. Participants will be allocated to the three groups according to the group number printed inside the envelopes.

Blinding

Due to the feature of the moxibustion, it is difficult to make the therapists or participants blinded to the allocation. Data managers and statisticians will be blinded throughout the trial. During the intervention, therapists and data managers are requested not to communicate with each other about the allocation. Blinded telephone interviewers will collect the follow-up materials to evaluate long term effect of moxibustion at 16 weeks after the first moxibustion session.

Participants

Sample size

Because this is a pilot study, a power calculation to determine sample size was not conducted. Sample size calculation will be performed basing on estimates of the number of participants we would expect to recruit within 24 months. We therefore plan to recruit five participants per month, according to our previous trial of ginger-salt-partitioned moxibustion for urination disorders after stroke[47]. A sample size of 40 per group and a total number of 120 will be included, which is larger than the minimum of 12 per group suggested for pilot studies[49]. Outcomes of this pilot study will help calculate appropriate sample size for future randomized clinical trials.

Inclusion criteria

1. Male or female, aged 40- 75 years;
2. In-patients with UUI after stroke, according to the diagnosis criteria of the American Stroke Association (ASA) and the International Continence Society (ICS);
3. 4th to 48th week after stroke onset;
4. Normal consciousness, communication ability and recognition;
5. Written informed consent.

Exclusion criteria

1. UUI caused by spinal injury, multiple sclerosis or hyperplasia of prostate gland;
2. Chronic urinary retention or UI before stroke onset;
3. Stress urinary incontinence, mixed urinary incontinence and chronic urinary tract infection;
4. Insufficiency of heart, liver, kidney organs;
5. Participants in another clinical trial.

Intervention

Ginger-Salt-Indirect Moxibustion is formulated on the basis of description in ancient literature and our previous research[47]. Moxibustion will be manipulated by certified acupuncturists with at least 20 years of clinical experiences. All treatment details will be standardized between practitioners by guiding videos and relative trainings before the first acupuncture session. Interventions will be performed in accordance with the STRICTOM[50] and good clinical practice guidelines (GCP).

Treatment group A

Subjects of treatment group A will receive moxa cone moxibustion and routine care once a day for 4 weeks. The procedure of each session is described as follow (see figure 2). Participants are asked to lie on a bed in a supine position and remove clothing to fully expose the navel in a room with 25 to 30□ temperature. A certain amount of salt is put on the navel to cover the CV-8 (Shenque) and covered by a piece of fresh ginger slice (30mm in diameter and 4-5 mm in thickness). Then a moxa cone (pure wormwood fiber in material; 15 mm in diameter and 30 mm

in length; Tongrentang Inc., China.) is placed on the fresh ginger slice and lit by the therapist. Once the moxa cone is burnt out, therapist removes the whole moxa cone and replaces it with another one. The technique requires a sensation of heat but no painful burning for participants. If subjects feel insufferable pain or burning sensation, the ginger slice with burning moxa cone will be removed immediately and reset after several minutes. Each session requires three units of moxa cone. Therapist is required to observe the situation of patient and whisk away the burning ash to avoid burning injury. This study is designed to evaluate moxibustion treatment as it is used in normal practice. So moxibustion group will also receive the usual care provided to the control group.

Treatment group B

Subjects of treatment group B will receive moxa box moxibustion and routine care once a day for 4 weeks. The manipulatiocns are generally similar to treatment group A. The only difference is that a double-holes moxa box (13 x 8 x 8.5 cm in volume) with two moxa sticks (pure wormwood fiber; 15 mm in diameter and 70 mm in length; Tongrentang Inc., China.) in the holes will be placed on the fresh ginger slice (see figure 3). The moxa sticks will be ignited from the bottom. If patients feel pain, therapist will remove the lid with moxa sticks for several minutes. Each session requires three units of moxa sticks.

Control group

According to pragmatic design, the control group will receive routine therapies for stroke recovery. Routine therapies include control of blood pressure, inhibition of platelet aggregation, routine physiotherapy, occupational therapy, glucose control treatment. Subjects in this group will be encouraged to maintain their normal lifestyle, including diet, exercise and workload. Moreover, participants will be suggested to inform the researchers of any new treatments performed after entry into the trial.

Outcome measures

Primary outcome measures

Increase of mean volume per void at week 4 from the baseline, basing on the data of 72-hour frequency-volume chart.

Mean volume per void is one of main quantitative indicators recorded in bladder dairies or frequency volume charts[19, 33, 51-53]. It is defined by dividing total volume of voluntary urination by total frequency of voluntary urination in 72 hours in this study. Increase of mean volume per void objectively reflects improvement of bladder capacity and detrusor stability in the urine filling and storage period. In previous study, we observed that mean volume per void increased in ginger-salt-indirect moxibustion group, comparing with control group with a statistical difference. Consequently, we select increase of mean volume per void at week 4 from the baseline as primary outcome to estimate efficacy of ginger-salt-indirect moxibustion on urination function of participants. We assess increase of mean volume per at week 16 from the baseline to evaluate long-term efficacy as well.

Secondary outcome measures

1. The mean frequency of urination per day, including voluntary and incontinence urination.
2. Quality of life assessments measured by completion of the Incontinence Quality of Life Questionnaire (I-QOL)[54] and the Barthel Index (BI)[55] in Chinese version.

The average frequency of urination per day is composed of mean frequency of voluntary and incontinent urination, which represents reduction in frequent micturition and urinary incontinence.

This outcome measure is strongly linked to stability of bladder and detrusor. Questionnaires for quality of life assessment will be completed basing on objective condition and subjective sensation of participants.

All outcome measures will be assessed at before the first moxibustion session, at 4 weeks and 16 weeks after the first moxibustion session.

Adverse events

Adverse events are defined as negative or unintended clinical manifestation following the treatments. Common adverse events such as allergy, burn and infection are reported by a systematic review[56]. Adverse reactions should be reported by patients or caregivers and solved by the therapists.

Data management

Before recruitment, the whole research group, including therapists, data administrators and outcome assessors, will participate in a training seminar about research contents and data management. Baseline characteristics of participants will be recorded on Case Report Forms (CRFs) by a research assistant. Data collection of urination and questionnaires will be conducted by a researcher who remains blinded to the group allocation at the baseline, 4 and 16 weeks after first moxibustion session. Occupational caregivers will be trained to identify urinary incontinence and voluntary urination. Caregivers will collect urine of voluntary urination and measure it with a pot-shaped urine collector with scales. They will be required to record accurate voiding time, voluntary urinary volume and urinary incontinence episodes on a 72-hour frequency-volume chart (see Figure 4). The record should be started at 8AM and last for 72 hours. If caregivers failed to collect urine in time, they will note voiding time and specific reasons on the chart. The blinded researcher will complete the urination section on CRFs according to the 72-hour frequency-volume charts handed in by caregivers.

Two independent researchers blinded to the group allocation will enter the data into Excel spreadsheet after the completion of the CRFs separately. Another independent researcher will compare the two data sets to check up errors. If different data entry is discovered, data will be compared with the original CRF to verify inconsistency. All modification will be marked on the CRFs. Research data will be gathered and saved abiding by the Data Protection Act 1998. Paper files will be kept in a locked filing cabinet and electronic documents will be stored in a password protected computer, with access restricted to primary research personnel. All research documents will be preserved for at least 5 years after publication.

Statistical analysis

Data analysis will be performed in a blinded pattern by statisticians of Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical analyses will be conducted on an intention-to-treat basis using the SPSS statistical package program (ver.18.0). Missing data will be replaced in accordance with the principle of the last observation carried forward. A P value < 0.05 is considered statistically significant with two-sided test. Baseline characteristics including gender, age and previous duration are described as n (%) for categorical data and mean ± SD (standard deviation) for continuous data. To compare the differences among groups, we will perform analysis of variance (ANOVA) for normally distributed data, Kruskal-Wallis test for abnormally distributed data and chi-squared test for categorical data. Comparisons between two groups will be conducted using bonferroni method of post hoc multiple comparisons.

Ethical considerations

This study adheres to the principles of the Declaration of Helsinki and has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). We will conduct the research in the following hospitals: Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, Beijing Huguosi Hospital of Traditional Chinese Medicine and China Rehabilitation Research Center. Each participant will sign written informed consents voluntarily.

DISCUSSION

Exploration of UI dates back to the era of Yellow Emperor's Inner Canon in China. The term of UI after stroke was first recorded in "JingYueQuanShu", a Chinese ancient book by Zhang Jiebin. Ancient physicians began to realize that apoplexy was one of the causes of UI since then. In the theory of traditional Chinese medicine (TCM), kidney qi could regulate voiding function and ensure voluntary urination. Deficiency of kidney qi was known to be the primary pathogenesis referring to "ZhuBingYuanHouLun", a famous ancient TCM literature. Ginger and salt are able to warm and tonify the kidney Qi in TCM theory. Shenque (CV8) is applied as a principal acupoint for nourishing kidney Qi, which is only allowed to be used with moxibustion. Owing to the features of materials and usage, ginger-salt-indirect moxibustion is likely to warm and nourish kidney Qi, thereby controlling bladder and regulating voiding function.

Placebo or sham control is encouraged in clinical trials to avoid bias[57]. To our knowledge, no consensus has been established to recommend valid placebo or sham methods of moxibustion by far. Sham moxibustion is impractical to achieve blinding because of the common cognition of moxibustion in Chinese patients. Because of preference for moxibustion, incompliance of Chinese patients will make it difficult to use standard therapies as control treatment. With the pragmatic purpose, we set a usual care group as a blank control group, rather than a certain effective therapy or a sham device.

Concerning evaluation instruments, we select 72-hour frequency-volume chart to record urination details and I-QOL together with Barthel Index to assess quality of life. The frequency volume chart and bladder diary is highly recommended in clinical trials by ICS[1]. Frequency-volume chart records the time and volume of each voiding, as well as incontinence episodes. ICS suggested that frequency-volume chart should be recorded for at least 24 hours[1]. Recent literatures[51, 58-61] considered that a minimum of 72 hours is required to ensure reliability for diary parameters. Thus, we use a 72-hour frequency-volume chart to alleviate burdens of patients and improve compliance[62, 63].

As for the assessment of quality of life, I-QOL is strongly recommended to assess the effect of urinary incontinence on patients' status[64]. A recent research[54] has affirmed the reliability and validity of I-QOL as an incontinence-related QOL instrument in neurogenic UI patients. The items of I-QOL focus on three dimensions, namely social embarrassment, avoidance behaviors and psychosocial impacts, without physical mobility and self-care ability. Barthel Index is added to evaluate patients' activities of daily living, which is recognized as a valid and reliable outcome measurement for stroke survivors[55].

One limitation of this pilot study is that we fail to prevent therapists and participants from knowing the group allocation because of the characteristics of moxibustion. To minimize the bias, acupuncturists will receive professional training and strict quality control. In order to homogenize the psychological effects, participants are informed that effects of two moxibustion techniques are

uncertain. The words 'placebo' or 'control' will be avoided. Similar strategies have been applied in previous trials[65, 66]. Noncompliance of the control group is another deficiency of this pilot trial and may lead to a high drop-out rate. We will solve this problem by providing participants with financial compensations and free moxibustion therapies after the completion of the entire trial.

This study is the major sub-project focusing on stroke recovery, which is sponsored and funded by National Administration of Traditional Chinese Medicine of China. This protocol describes the first pilot randomized controlled trial evaluating the feasibility of a research that assess the curative effects and safety of ginger-salt-indirect moxibustion on UUI after stroke. Results of this preliminary study will provide essential information for the design of subsequent large-scale trials.

Trial status

The trial is currently in the recruitment phase.

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Contributors LPW and HLL conceived this study and prepared the initial protocol. LLW drafted the manuscript and participated in design of the study. GXS, YY, LZ, TZ participated in revising the protocol. LZ plans for the statistical analysis. LPW and HLL made amendments of the trial protocol. All authors read and approved the final manuscript.

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Competing interests None.

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Figure 1 Trial profile

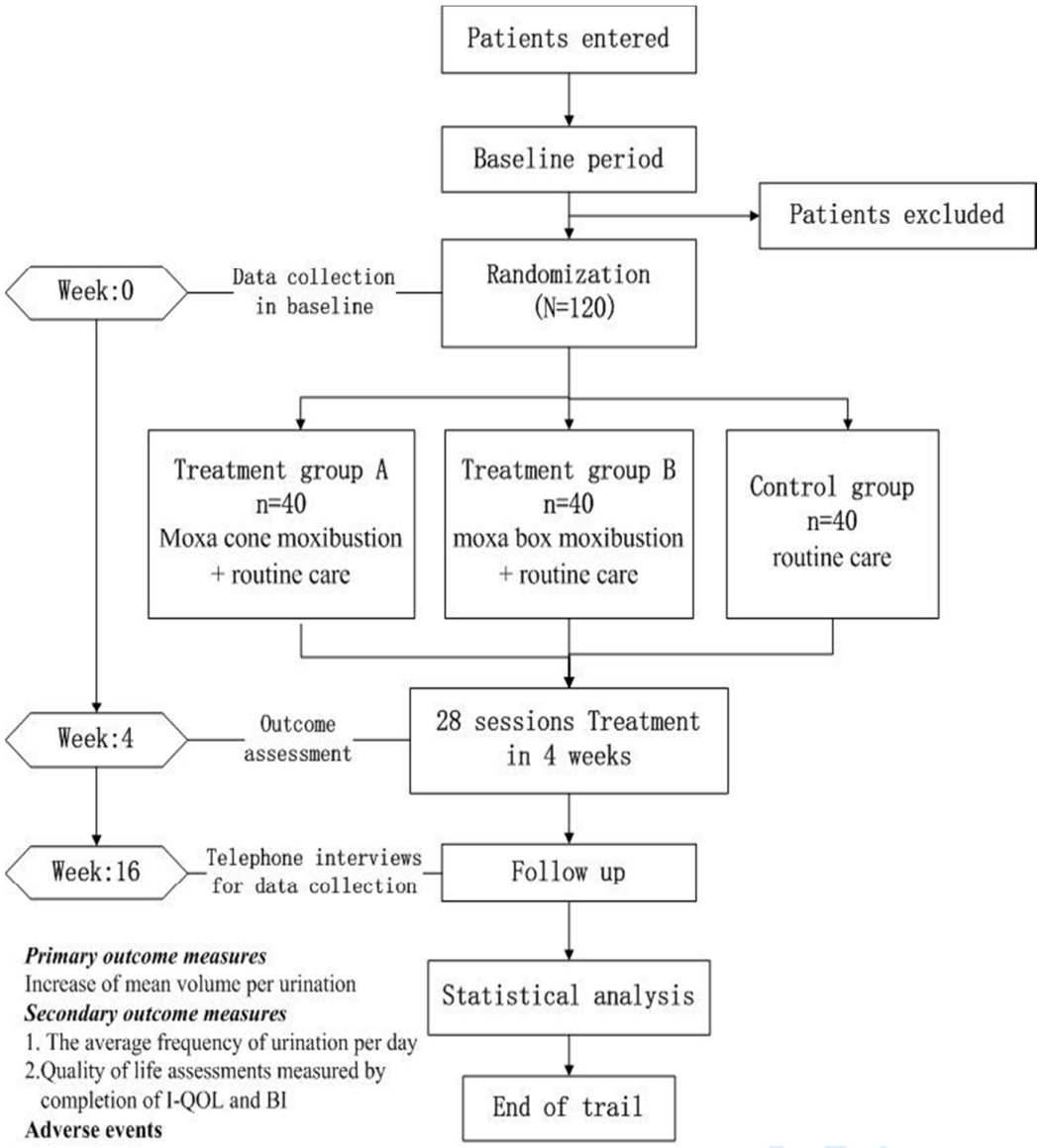


Figure 2. Moxa cone moxibustion

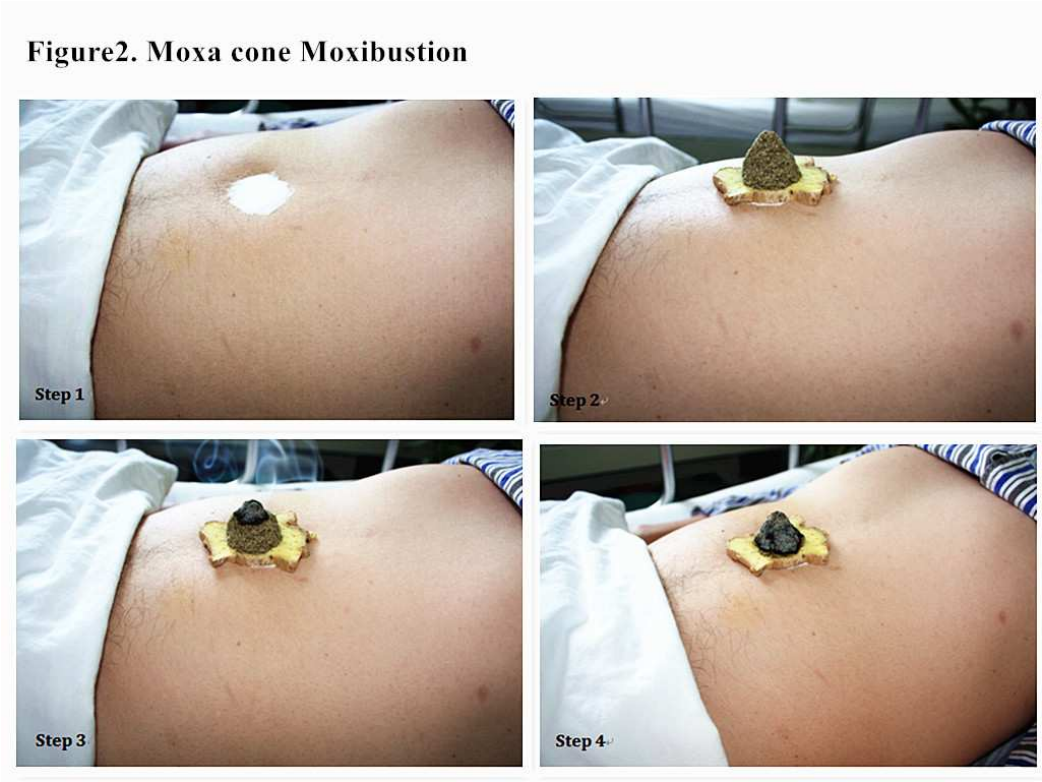
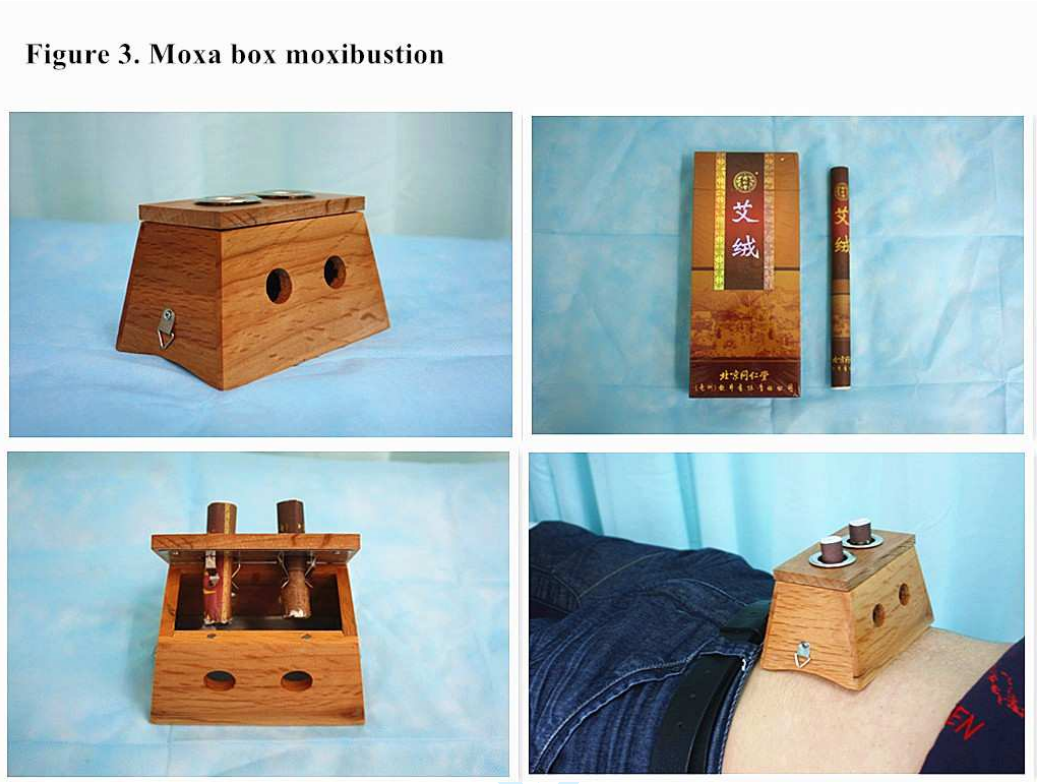


Figure 3. Moxa box moxibustion



72-hour frequency-volume chart

Date	Time (a.m/p.m)	Volume voided (ml)	urinary incontinence (tick in the blank)	notes

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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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ABSTRACT

Introduction: Ginger-salt-indirect moxibustion is widely applied to treat urge urinary incontinence after stroke, which is a common complication in stroke survivors. Moxa cone moxibustion and moxa box moxibustion are main techniques of ginger-salt-indirect moxibustion. Our previous study had shown that ginger-salt-indirect moxibustion using moxa cones was feasible and effective for urination disorders post-stroke. This pilot study aims to assess the feasibility of conducting research to evaluate the efficacy and safety of ginger-salt-indirect moxibustion for patients with post-stroke urge urinary incontinence.

Methods and analysis: This is a multicenter, prospective, single-blinded, pilot randomized controlled trial. 120 eligible patients will be randomly allocated to three groups. Treatment group A (n = 40) will receive moxa cone moxibustion and routine care; treatment group B (n = 40) will receive moxa box moxibustion and routine care; control group (n = 40) will only receive routine care for stroke recovery. The entire moxibustion treatment will consist of a total of 28 sessions during the course of 4 weeks. Primary outcome measure will be increase of mean volume per void assessed at week 4 from the baseline, based on the data of a 72-hour frequency-volume chart. Secondary outcome measures will include mean frequency of urination per day and quality of life assessments measured by completion of Incontinence Quality of Life Questionnaire and Barthel Index. All outcome measures will be assessed before the first moxibustion session (baseline) , at 4 weeks and 16 weeks from baseline. Adverse events in three groups will be recorded to assess safety of moxibustion.

Ethics and dissemination: Research ethics was approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). Written informed consent will be obtained from all participants. Study results will be published in peer-reviewed journals.

Trial Registration number: ISRCTN 44706974.

Strengths and limitations of this study

- First pilot study to evaluate the feasibility of conducting research to assess the efficacy and safety of ginger-salt-indirect moxibustion as treatment for urge urinary incontinence after stroke
- Multicentre, randomised controlled trial with pragmatic design
- Interventions conducted by certified acupuncturists according to the STRICTOM and GCP.
- Lack of blinding of acupuncturists and participants

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary leakage of urine that causes hygienic or social problems by International Continence Society (ICS) [1]. Prevalence of UI after stroke varies from 32–79% at admission[2-4], 25% at hospital discharge and 15% after one year[4]. Urge urinary incontinence (UUI) is a common type of UI[5] after stroke. It is characterized by involuntary leakage of urine accompanied or preceded by urgency[1].

Results of previous review[6] suggested that there were three major causes of urinary incontinence after stroke: detrusor hyperreflexia caused by infarction; stroke-related cognitive or language deficits; bladder hyporeflexia with resultant overflow incontinence. UUI can be caused by detrusor overactivity due to the loss of inhibitory neurons after stroke[7]. Detrusor overactivity is characterized by involuntary detrusor contractions during the filling and storage phase[1, 7, 8]. When intra-detrusor pressure generated by abnormal detrusor contractions exceeds sphincter pressure, urinary incontinence occurs[7]. UI is a strong prognostic indicator for stroke recovery, which is associated with high rates of mortality [9, 10], disability[11] and increasing admission to institutional care[12]. Micturition disorders may result in urinary infection, nephritis, fungal dermatitis[13], and even bedsore. Typical symptoms, including frequent micturition, nocturia and urgency, could lead to impaired quality of life[14] and heavy economic burdens[15, 16].

Initial treatments for UUI after stroke recommended by ICS are behavioral therapy and pharmacotherapy[1]. Behavioral therapies, including healthy bladder habits and training techniques, aim at changing patients' lifestyle and at teaching patients to control urgency and enhance continence ability[17]. For habit modification, patients are guided to re-establish a healthy voiding schedule, eliminate bladder irritants from the diet, manage fluid intake and bowel regularity, control weight and give up smoking[18-24]. Training techniques consist of bladder training, urgency control techniques, pelvic muscle exercises, delayed voiding and multicomponent behavioral training[17]. Behavioral interventions are applied in the primary care setting, with or without pharmacotherapy[25-27]. Among these strategies, behavioral training and bladder training have the strongest efficacy evidence for the treatment of UUI[28-31]. Antimuscarinic drugs can reduce urgency and improve bladder function by controlling detrusor muscle overactivity through inhibition of M2 and M3 muscarinic bladder receptors on bladder[32-34]. Several meta-analyses

have shown that the most widely used antimuscarinic drugs have significant clinical benefits on UUI[35-38]. However, use of antimuscarinic agents is complicated by dose convenience, drug contraindication and financial concerns[39]. A Cochrane systematic review[40] concluded that no studies designed to manage urinary incontinence after stroke in secondary care had been rigorously conducted by far. Although there is clinical guideline for the management of urinary incontinence after stroke[1], to date there is insufficient good quality evidence to support the current clinical practices[41].. More available therapies and well-designed studies are required to provide further evidences for management of UUI after stroke.

Moxibustion is a therapy using ignited materials (usually moxa) to heat selected points of the skin surface. This therapy is widely used for chronic deficiency diseases[42] and is commonly indicated for UUI [43]. The mechanism of action of moxibustion combines thermal, radiation and pharmacological effects of the materials used, acting on the meridian system [44]. Following the theory of Traditional Chinese Medicine (TCM), kidney *qi* regulates voiding function and ensures voluntary urination. Deficiency of kidney *qi* is known to be the primary pathogenesis of UI according to "ZhuBingYuanHouLun" (a famous ancient TCM literature). Ginger and salt are typically used on *Shenque* (CV8) acupoint to warm, tonify and nourish the kidney *qi* thereby controlling bladder and regulating voiding function.

Moxa cone moxibustion and moxa box moxibustion are primary techniques of ginger-salt-indirect moxibustion commonly used in clinical practices in China. Moxa cone moxibustion involves a moxa cone burning directly on the ginger slice and providing thermal stimulus to the skin surface (see Figure 2). Moxa box moxibustion facilitates manipulations and reduces adverse reactions by using the device of moxa box with moxa sticks inside over the ginger slice (see Figure 3). Results of our previous study[45] showed that ginger-salt-partitioned moxibustion with moxa cone could reduce mean daytime and nighttime voiding frequency in the treatment of urination disorders poststroke. In addition, we also observed that ginger-salt-indirect moxibustion with moxa cones could increase mean volume per void of UI after stroke in an unpublished study. Our previous studies, together with results from an earlier Cochrane review[40, 45] suggest ginger-salt-indirect moxibustion may be worth investigating with a more rigorous study design.

METHODS

Objectives

This pilot study is to evaluate the feasibility of a research to assess the efficacy and safety of ginger-salt-indirect moxibustion for the treatment of UUI after stroke.

Recruitment

This is a multicenter, single-blinded, pilot randomized controlled trial. The research consists of three sequential parts (see Figure 1): a recruitment period before randomization, a treatment period of 4 weeks, and a follow-up period of 12 weeks. 120 eligible participants will be recruited from acupuncture wards of three hospitals according to the inclusion and exclusion criteria. During the first visit, potentially qualified patients will be provided with detailed information about this study, including the research objective, study procedure, potential benefits and risks. If a patient shows willingness to participate, they will be required to sign a written informed consent. This will be followed by baseline assessment and randomization.

Design

Randomization and allocation concealment

The randomization scheme is provided by the Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical experts will use the block randomization method (block size of 6) of the SAS package (Version 9.1.3; SAS institute Inc., Cary, NC, USA) to form the random allocation sequence. Then computer-generated opaque sealed envelopes with serial number outside and group number inside will be produced. The envelopes will be kept in a secure locked drawer making it inaccessible to all study personnel. After baseline assessments, the envelopes will be opened sequentially by an independent researcher in front of the participants to ensure adequate concealment. Participants will be allocated to the three groups according to the group number printed inside the envelopes.

Blinding

Due to the feature of the moxibustion, it is difficult to make the therapists or participants blinded to the allocation. Data managers and statisticians will be blinded throughout the trial. During the intervention, therapists and data managers are requested not to communicate with each other about the allocation. Blinded telephone interviewers will collect the follow-up materials to evaluate long term effect of moxibustion at 16 weeks after the baseline.

Participants

Sample size

Because this is a pilot study, a power calculation to determine sample size was not conducted. Sample size calculation was performed based on estimates of the number of participants we would expect to recruit within 24 months. We therefore plan to recruit five participants per month, according to our previous trial. A sample size of 40 per group and a total number of 120 will be included, which is larger than the minimum of 12 per group suggested for pilot studies[46]. Outcomes of this pilot study will help calculate appropriate sample size for further randomized clinical trials.

Inclusion criteria

1. Male or female, aged 40- 75 years;
2. In-patients with UUI after stroke, according to the diagnosis criteria of the American Stroke Association (ASA) and the International Continence Society (ICS);
3. 4th to 48th week after stroke onset;
4. Normal consciousness, communication ability and recognition;
5. Written informed consent.

Exclusion criteria

1. UUI caused by spinal injury, multiple sclerosis or hyperplasia of prostate gland;
2. Chronic urinary retention or UI before stroke onset;
3. Stress urinary incontinence, mixed urinary incontinence and chronic urinary tract infection;
4. Insufficiency of heart, liver, kidney organs;
5. Participants in another clinical trial.

Discontinuation criteria

Reasons for discontinuation of treatment may include, but are not limited to, the following:

1. Participants' decision of discontinuation of treatment at any time for any reason;
2. Investigators' determination to discontinue the treatment for patient's safety and best interests at any time;
3. Non-compliance of participants with the study procedure (eg, study visits);

4. Concomitant therapy that could affect the study results during the trial;
5. Detection of protocol violations at any time.

Intervention

Ginger-Salt-Indirect Moxibustion is formulated on the basis of description in ancient literature and our clinical experience. Moxibustion will be manipulated by certified acupuncturists with at least 20 years of clinical experience. All treatment details will be standardized between practitioners by guiding videos and relative trainings before the first acupuncture session. Interventions will be performed in accordance with the STRICTOM[47] and good clinical practice guidelines (GCP).

Treatment group A

Participants in treatment group A will receive moxa cone moxibustion and routine care once a day for 4 weeks. The procedure of each session as it is used in normal practices is described as follows (see figure 2). Participants are asked to lie on a bed in a supine position and remove clothing to fully expose the navel in a temperature controlled room (25 to 30°C). A certain amount of salt is put on the navel to cover *Shenque* (CV8) acupoint and covered by a piece of fresh ginger slice (30mm in diameter and 4-5 mm in thickness). Then a moxa cone (pure wormwood fiber in material; 15 mm in diameter and 30 mm in length; Tongrentang Inc., China.) is placed on the fresh ginger slice and lit by the therapist. Once the moxa cone is burnt out, the therapist removes the whole moxa cone and replaces it with another one. The technique requires a sensation of heat but no painful burning sensation for participants. If participants feel pain or a burning sensation, the ginger slice with burning moxa cone will be removed immediately and reset after several minutes. Each session requires three units of moxa cone. The therapist is required to carefully observe the patient and whisk away the burning ash to avoid burning injury. This study is designed to evaluate moxibustion treatment as it is used in normal practice. The moxibustion group will also receive the usual care provided to the control group.

Treatment group B

Participants in treatment group B will receive moxa box moxibustion and routine care once a day for 4 weeks. The manipulations are generally similar to those in treatment group A. The only difference is that the double-holes moxa box (13 x 8 x 8.5 cm in volume) with two moxa sticks (pure wormwood fiber; 15 mm in diameter and 70 mm in length; Tongrentang Inc., China.) in the holes will be placed on the fresh ginger slice (see figure 3). The moxa sticks will be ignited from the bottom. If patients feel pain, the therapist will remove the lid with the moxa sticks for several minutes. Each session requires three units of moxa sticks.

Control group

According to pragmatic design, the control group will receive routine therapies for stroke recovery. These include control of blood pressure, inhibition of platelet aggregation, routine physiotherapy, occupational therapy and glucose control treatment. Participants in this group will be suggested to maintain their normal lifestyle, including diet, exercise and workload. Moreover, participants will be encouraged to inform the researchers of any new treatments performed after entry into the trial.

Outcome measures

Primary outcome measures

Increase of mean volume per void at week 4 from baseline, based on 72-hour frequency-volume chart data.

Mean volume per void is one of the main quantitative indicators recorded in bladder dairies or frequency volume charts[17, 31, 48-50]. It is calculated by dividing total volume of voluntary urination

by total frequency of voluntary urination in 72 hours. Increase of mean volume per void objectively reflects improvement of bladder capacity and detrusor stability in the urine filling and storage period. In a previous study, we observed that mean volume per void increased in the ginger-salt-indirect moxibustion group, compared to the control group with a statistical difference. Consequently, we selected increase of mean volume per void at week 4 from the baseline as primary outcome. We will assess increase of mean volume per void at week 16 from the baseline to evaluate long-term efficacy as well.

Secondary outcome measures

1. The mean frequency of urination per day, including voluntary and incontinence urination.
2. Quality of life assessments measured by completion of the Incontinence Quality of Life Questionnaire (I-QOL)[51] and the Barthel Index (BI)[52].

The average frequency of urination per day is composed of mean frequency of voluntary and incontinent urination, which represents the severity of frequent micturition and urinary incontinence respectively. This is strongly linked to stability of bladder and detrusor. Questionnaires for quality of life assessment will be completed based on objective condition and subjective sensation of participants.

All outcome measures will be assessed before the baseline, at 4 weeks and 16 weeks from the baseline.

Adverse events

Adverse events (AEs) are defined as negative or unintended clinical manifestation following the treatments. Participants will be instructed to report any abnormal reactions to the clinical research team at any time. In addition, study investigators will collect information about abnormal reactions weekly by visiting the participants. All details of related and unexpected AEs, such as time of occurrence, degree and suspected causes, will be recorded on Case Report Forms (CRFs). The common AEs related to moxibustion include allergy, burn and infection[53]. AEs will be classified into 5 grades: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); Moderate (minimal, local or noninvasive intervention indicated); Severe (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated); Very severe (life-threatening consequences; urgent intervention indicated); Death related to adverse events. Participants with mild and moderate AEs will receive symptomatic treatment and will be closely followed up by the research team. Severe AEs will be reported to the Research Ethics Committee within 48 hours. The Research Ethics Committee will offer medical advice to the research team and determine whether the patient is eligible for further treatment.

Data management

Before recruitment, the whole research group, including therapists, data administrators and outcome assessors, will participate in a training seminar about research contents and data management. Baseline characteristics of participants will be recorded on CRFs by a research assistant. Data collection of urination and questionnaires will be conducted by a researcher who remains blinded to the group allocation at the baseline, 4 and 16 weeks after the baseline. Occupational caregivers will be trained to identify urinary incontinence and voluntary urination. Caregivers will collect urine of voluntary urination and measure it with a pot-shaped urine collector with scales. They will be trained to record accurate voiding time, voluntary urinary volume and urinary incontinence episodes on a 72-hour frequency-volume chart (see Figure 4).

The record will be started at 8AM and last for 72 hours. If caregivers failed to collect urine in time, they will note voiding time and specific reasons on the chart. The blinded researcher will complete the urination section on CRFs according to the 72-hour frequency-volume charts handed in by caregivers.

Two independent researchers blinded to the group allocation will enter the data on Excel spreadsheet after the completion of the CRFs separately. Another independent researcher will compare the two data sets for check-up. If different data entry is discovered, data will be compared with the original CRFs to verify inconsistency. All modification will be marked on the CRFs. Research data will be gathered and saved abiding by the Data Protection Act 1998. Paper files will be kept in a locked filing cabinet and electronic documents will be stored in a password protected computer, with access restricted to the principal investigator. All research documents will be preserved for at least 5 years after publication.

Statistical analysis

Data analysis will be performed in a blinded pattern by statisticians of Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical analyses will be conducted on an intention-to-treat basis using the SPSS statistical package program (ver.18.0). Missing data will be replaced in accordance with the principle of the last observation carried forward. A P value < 0.05 will be considered statistically significant with two-sided test. Baseline characteristics including gender, age and previous duration are described as n (%) for categorical data and mean ± SD (standard deviation) for continuous data. To compare the differences among groups, we will perform analysis of variance (ANOVA) for normally distributed data, Kruskal-Wallis test for abnormally distributed data and chi-squared test for categorical data. Comparisons between two groups will be conducted using Bonferroni method of post hoc multiple comparisons.

Ethical considerations

This study adheres to the principles of the Declaration of Helsinki and has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). We will conduct the research in the following hospitals: Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, Beijing Huguosi Hospital of Traditional Chinese Medicine and China Rehabilitation Research Center. Each participant will sign written informed consents voluntarily.

DISCUSSION

Placebo or sham control is encouraged in clinical trials to avoid bias[54]. To our knowledge, no consensus has been established to recommend valid placebo or sham methods of moxibustion by far. Sham moxibustion is impractical to achieve blinding because of the common knowledge of moxibustion in Chinese patients. Because of preference for moxibustion, incompliance of Chinese patients will make it difficult to use standard therapies as control treatment. Following pragmatic purpose, we set a usual care group as a blank control group, rather than a certain effective therapy or a sham device.

Concerning evaluation instruments, we selected 72-hour frequency-volume chart to record urination details and I-QOL together with Barthel Index to assess quality of life. The frequency volume chart and bladder diary is highly recommended in clinical trials by ICS[1]. Frequency-volume charts record the time and volume of each voiding, as well as incontinence

episodes. ICS suggested that frequency-volume charts should be recorded for at least 24 hours[1]. A minimum of 72 hours was required to ensure reliability for diary parameters[48, 55-58]. Thus, we will use a 72-hour frequency-volume chart to alleviate burdens for patients and improve compliance[59, 60].

As for the assessment of quality of life, I-QOL is strongly recommended to assess the effect of urinary incontinence on patients' quality of life[61]. Previous research[51] has affirmed the reliability and validity of I-QOL as an incontinence-related QOL instrument in neurogenic UI patients. The items of I-QOL focus on three dimensions, namely social embarrassment, avoidance behaviors and psychosocial impacts, without physical mobility and self-care ability. Barthel Index is added to evaluate patients' activities of daily living, which is recognized as a valid and reliable outcome measurement for stroke survivors[52].

One limitation of this pilot study is that we will be unable to prevent therapists and participants from knowing the group allocation because of the characteristics of moxibustion. To minimize the bias, acupuncturists will receive professional training and strict quality control. In order to homogenize the psychological effects, participants are informed that effects of the two moxibustion techniques are uncertain. The words 'placebo' or 'control' will be avoided. Similar strategies have been applied in previous trials[62, 63]. Noncompliance of the control group is another limitation of this pilot trial and may lead to a high drop-out rate. Each participant will be provided with 150 RMB as financial compensation to improve compliance.

This study is the major sub-project focusing on stroke recovery, which is sponsored and funded by the National Administration of Traditional Chinese Medicine of China. This protocol describes the first pilot randomized controlled trial evaluating the feasibility to conduct a research to assess the efficacy and safety of ginger-salt-indirect moxibustion on UUI after stroke. Results of this preliminary study will provide essential information for the design of subsequent large-scale trials. Further trials will focus on assessment of urodynamic parameters and evaluation of efficacy and safety of moxibustion on UUI after stroke.

Trial status

The trial is currently in the recruitment phase.

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Contributors LPW and HLL conceived this study and prepared the initial protocol. LLW drafted the manuscript and participated in design of the study. GXS, YY, LZ, TZ participated in revising the protocol. LZ plans for the statistical analysis. LPW and HLL made amendments of the trial protocol. All authors read and approved the final manuscript.

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Ethics approval Research ethics approval was attained from the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094).

Competing interests None.

Figure 1. Trial flowchart

Figure 2. Moxa cone moxibustion

Figure 3. Moxa box moxibustion

Figure 4. 72-hour frequency-volume chart

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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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ABSTRACT

Introduction: Ginger-salt-indirect moxibustion is widely applied to treat urge urinary incontinence after stroke, which is a common complication in stroke survivors. Moxa cone moxibustion and moxa box moxibustion are main techniques ~~patterns~~ of ginger-salt-indirect moxibustion. Our previous study had shown that ginger-salt-indirect moxibustion using moxa cones was feasible and effective for urination disorders post-stroke. This pilot study aims to assess the feasibility of conducting research to evaluate the efficacy and safety of ginger-salt-indirect moxibustion for patients with post-stroke urge urinary incontinence.

Methods and analysis: This is a multicenter, prospective, single-blinded, pilot randomized controlled trial. 120 eligible patients will be randomly allocated to three groups. Treatment group A (n = 40) will receive moxa cone moxibustion and routine care; treatment group B (n = 40) will receive moxa box moxibustion and routine care; control group (n = 40) will only receive routine care for stroke recovery. The entire moxibustion treatment will consist of a total of 28 sessions during the course of 4 weeks. Primary outcome measure will be increase of mean volume per void assessed at week 4 from the baseline, based on the data of a 72-hour frequency-volume chart. Secondary outcome measures will include mean frequency of urination per day and quality of life assessments measured by completion of Incontinence Quality of Life Questionnaire and Barthel Index. All outcome measures will be assessed before the first moxibustion session (baseline) , at 4 weeks and 16 weeks from baseline~~after the first moxibustion session~~. Adverse events in three groups will be recorded to assess safety of moxibustion.

Ethics and dissemination: Research ethics was approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). Written informed consent will be obtained ~~achieved~~ from all participants. Study results will be published in peer-reviewed journals.

Trial Registration number: ISRCTN 44706974.

Strengths and limitations of this study

- First pilot study to evaluate the feasibility of conducting research to assess the efficacy and safety of ginger-salt-indirect moxibustion as treatment for urge urinary incontinence after stroke
- Multicentre, randomised controlled trial with pragmatic design
- Interventions conducted by certified acupuncturists according to the STRICTOM and GCP.
- Lack of blinding of acupuncturists and participants

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary leakage of urine that causes hygienic or social problems by International Continence Society (ICS) [1]. Prevalence of UI after stroke varies from 32–79% at admission[2-4], 25% at hospital discharge and 15% after one year[4]. Urge urinary incontinence (UUI) is a common type of UI[5] after stroke. It ~~urge urinary incontinence (UUI) after stroke~~ is characterized by involuntary leakage of urine ~~loss~~ accompanied or preceded by urgency[1], ~~which arises from acute cerebral accident onset~~.

Results of previous review[6] suggested that there were three major causes of urinary incontinence after stroke: detrusor hyperreflexia caused by infarction; stroke-related cognitive or language deficits; bladder hyporeflexia with resultant overflow incontinence. UUI can be caused by detrusor overactivity due to the loss of inhibitory neurons after stroke[7]. Detrusor overactivity is characterized by involuntary detrusor contractions during the filling and storage phase[1, 7, 8]. When intra-detrusor pressure generated by abnormal detrusor contractions exceeds sphincter pressure, urinary incontinence occurs[7]. UI is a strong prognostic indicator for stroke recovery, which is associated with high rates of mortality [9, 10], disability[11] and increasing admission to institutional care[12]. Micturition disorders may result in urinary infection, nephritis, fungal dermatitis[13], and even bedsore. Typical symptoms, including frequent micturition, nocturia and urgency ~~(compelling desire to void which is difficult to defer)~~, could lead to impaired quality of life[14] and heavy economic burdens[15, 16].

Initial treatments for UUI after stroke recommended by ICS are behavioral therapy and pharmacotherapy[1]. Behavioral therapies, including healthy bladder habits and training techniques, aim at changing patients' lifestyle and at teaching patients to control urgency and enhance continence ability[17]. For habit modification, patients are guided to re-establish a healthy voiding schedule, eliminate bladder irritants from the diet, manage fluid intake and bowel regularity, control weight and give up smoking[18-24]. Training techniques consist of bladder training, urgency control techniques, pelvic muscle exercises, delayed voiding and multicomponent behavioral training[17]. Behavioral interventions are applied in the primary care setting, with or without pharmacotherapy[25-27]. Among these strategies, behavioral training and bladder training have the strongest efficacy evidence for the treatment of UUI[28-31]. Antimuscarinic drugs can reduce

urgency and improve bladder function by ~~with the mechanism of~~ controlling detrusor muscle overactivity through inhibition of M2 and M3 muscarinic bladder receptors on bladder[32-34]. Several meta-analyses have shown that the most widely used antimuscarinic drugs have significant clinical benefits on UUI[35-38]. However, use ~~Nevertheless, application~~ of antimuscarinic agents is complicated ~~influenced~~ by dose ~~dosing~~ convenience, drug contraindication and financial concern~~sconsideration~~[39]. A Cochrane systematic review[40] concluded that no ~~rigorously~~ studies designed to manage urinary incontinence after stroke in secondary care had been rigorously conducted by far[42]. Although there is clinical guideline for the management of urinary incontinence after stroke[1], to date there is insufficient good quality evidence to support the current clinical practices[41]. ~~Evidences of relevant trials were insufficient to guide clinical practices[43]~~. More available therapies and well-designed studies are required to provide further evidences for management of UUI after stroke.

Moxibustion is a therapy using ignited materials (usually moxa) to heat selected points of the skin surface. This therapy is widely used for ~~as a treatment for cold syndrome and~~ chronic deficiency diseases[42] and is commonly indicated for UUI ~~UUI was regarded as one of common indications[43]~~. The mechanism of ~~Despite uncertain modern mechanisms, it is generally identified that~~ action of moxibustion combines ~~is produced by the meridian system combining with~~ thermal, radiation and pharmacological effects of the materials used, acting on the meridian system [44]. Following the theory of Traditional Chinese Medicine (TCM), kidney *qi* regulates voiding function and ensures voluntary urination. Deficiency of kidney *qi* is known to be the primary pathogenesis of UI according to "ZhuBingYuanHouLun" (a famous ancient TCM literature). Ginger and salt are typically used on *Shenque* (CV8) acupoint to warm, tonify and nourish the kidney *qi* thereby controlling bladder and regulating voiding function.

~~In China, ginger-salt-indirect moxibustion on CV8 (Shenque) is frequently applied to treat UUI after stroke.~~ Moxa cone moxibustion and moxa box moxibustion are primary techniques of ginger-salt-indirect moxibustion commonly used in clinical practices in China. Moxa cone moxibustion involves a moxa cone burning directly on the ginger slice and providing thermal stimulus to the skin surface (see Figure 2). Moxa box moxibustion facilitates manipulations and reduces adverse reactions by using the device of moxa box with moxa sticks inside over the ginger slice (see Figure 3). Results of our previous study[45] showed that ginger-salt-partitioned moxibustion with moxa cone could reduce mean daytime and nighttime voiding frequency in the treatment of urination disorders poststroke. In addition~~Besides~~, we also observed that ginger-salt-indirect moxibustion with moxa cones could increase mean volume per void of UI after stroke in an unpublished study. Our previous studies, together with results from an earlier Cochrane review[40, 45] suggest~~A recent cochrane review concluded that~~ ginger-salt-indirect moxibustion may be worth investigating with a more rigorous study design~~effective for UI after stroke and worth further research[48]~~.

METHODS

Objectives

This pilot study is to evaluate the feasibility of a research to assess the efficacy and safety of ginger-salt-indirect moxibustion for the treatment of UUI after stroke.

Recruitment

This is a multicenter, single-blinded, pilot randomized controlled trial. The research consists of

three sequential parts (see Figure 1): a recruitment period before randomization, a treatment period of 4 weeks, and a follow-up period of 12 weeks. 120 eligible participants will be recruited from acupuncture wards of three hospitals according to the inclusion and exclusion criteria. During the first visit, potentially qualified patients will be provided with detailed information about this study, including the research objective, study procedure, potential benefits and risks. If a patient shows willingness to participate, they will be required to sign a written informed consent. This will be followed by baseline assessment and randomization ~~will be conduct afterwards~~.

Design

Randomization and allocation concealment

The randomization scheme is provided by the Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical experts will use the block randomization method (block size of 6) of the SAS package (Version 9.1.3; SAS institute Inc., Cary, NC, USA) to form the random allocation sequence. Then computer-generated opaque sealed envelopes with serial number outside and group number inside will be produced. The envelopes will be kept in a secure locked drawer making it inaccessible to all study personnel. After baseline assessments, the envelopes will be opened sequentially by an independent researcher in front of the participants to ensure adequate concealment. Participants will be allocated to the three groups according to the group number printed inside the envelopes.

Blinding

Due to the feature of the moxibustion, it is difficult to make the therapists or participants blinded to the allocation. Data managers and statisticians will be blinded throughout the trial. During the intervention, therapists and data managers are requested not to communicate with each other about the allocation. Blinded telephone interviewers will collect the follow-up materials to evaluate long term effect of moxibustion at 16 weeks after the baseline ~~first moxibustion session~~.

Participants

Sample size

Because this is a pilot study, a power calculation to determine sample size was not conducted. Sample size calculation ~~will be~~was performed based on estimates of the number of participants we would expect to recruit within 24 months. We therefore plan to recruit five participants per month, according to our previous trial [47]. A sample size of 40 per group and a total number of 120 will be included, which is larger than the minimum of 12 per group suggested for pilot studies[46]. Outcomes of this pilot study will help calculate appropriate sample size for further randomized clinical trials.

Inclusion criteria

1. Male or female, aged 40- 75 years;
2. In-patients with UUI after stroke, according to the diagnosis criteria of the American Stroke Association (ASA) and the International Continence Society (ICS);
3. 4th to 48th week after stroke onset;
4. Normal consciousness, communication ability and recognition;
5. Written informed consent.

Exclusion criteria

1. UUI caused by spinal injury, multiple sclerosis or hyperplasia of prostate gland;
2. Chronic urinary retention or UI before stroke onset;
3. Stress urinary incontinence, mixed urinary incontinence and chronic urinary tract infection;

4. Insufficiency of heart, liver, kidney organs;
5. Participants in another clinical trial.

Discontinuation criteria

Reasons for discontinuation of treatment may include, but are not limited to, the following:

1. Participants' decision of discontinuation of treatment at any time for any reason;
2. Investigators' determination to discontinue the treatment for patient's safety and best interests at any time;
3. Non-compliance of participants with the study procedure (eg, study visits);
4. Concomitant therapy that could affect the study results during the trial;
5. Detection of protocol violations at any time.

Intervention

Ginger-Salt-Indirect Moxibustion is formulated on the basis of description in ancient literature and our clinical experience~~previous research~~[47]. Moxibustion will be manipulated by certified acupuncturists with at least 20 years of clinical experience. All treatment details will be standardized between practitioners by guiding videos and relative trainings before the first acupuncture session. Interventions will be performed in accordance with the STRICTOM[47] and good clinical practice guidelines (GCP).

Treatment group A

Participants in treatment group A will receive moxa cone moxibustion and routine care once a day for 4 weeks. The procedure of each session as it is used in normal practices is described as follows (see figure 2). Participants are asked to lie on a bed in a supine position and remove clothing to fully expose the navel in a temperature controlled room (25 to 30°C)~~room with 25 to 30□ temperature~~. A certain amount of salt is put on the navel to cover *Shenque* (CV8) acupoint and covered by a piece of fresh ginger slice (30mm in diameter and 4-5 mm in thickness). Then a moxa cone (pure wormwood fiber in material; 15 mm in diameter and 30 mm in length; Tongrentang Inc., China.) is placed on the fresh ginger slice and lit by the therapist. Once the moxa cone is burnt out, the therapist removes the whole moxa cone and replaces it with another one. The technique requires a sensation of heat but no painful burning sensation for participants. If participants feel pain or a burning sensation, the ginger slice with burning moxa cone will be removed immediately and reset after several minutes. Each session requires three units of moxa cone. The therapist is required to carefully observe the patient and whisk away the burning ash to avoid burning injury. This study is designed to evaluate moxibustion treatment as it is used in normal practice. The moxibustion group will also receive the usual care provided to the control group.

Treatment group B

Participants in treatment group B will receive moxa box moxibustion and routine care once a day for 4 weeks. The manipulations are generally similar to those in treatment group A. The only difference is that the double-holes moxa box (13 x 8 x 8.5 cm in volume) with two moxa sticks (pure wormwood fiber; 15 mm in diameter and 70 mm in length; Tongrentang Inc., China.) in the holes will be placed on the fresh ginger slice (see figure 3). The moxa sticks will be ignited from the bottom. If patients feel pain, the therapist will remove the lid with the moxa sticks for several minutes. Each session requires three units of moxa sticks.

Control group

According to pragmatic design, the control group will receive routine therapies for stroke recovery.

These include control of blood pressure, inhibition of platelet aggregation, routine physiotherapy, occupational therapy and glucose control treatment. Participants in this group will be suggested to maintain their normal lifestyle, including diet, exercise and workload. Moreover, participants will be encouraged ~~suggested~~ to inform the researchers of any new treatments performed after entry into the trial.

Outcome measures

Primary outcome measures

Increase of mean volume per void at week 4 from baseline, based on 72-hour frequency-volume chart data.

Mean volume per void is one of the main quantitative indicators recorded in bladder dairies or frequency volume charts[17, 31, 48-50]. It is calculated ~~defined~~ by dividing total volume of voluntary urination by total frequency of voluntary urination in 72 hours. Increase of mean volume per void objectively reflects improvement of bladder capacity and detrusor stability in the urine filling and storage period. In a previous study, we observed that mean volume per void increased in the ginger-salt-indirect moxibustion group, compared to the control group with a statistical difference. Consequently, we selected increase of mean volume per void at week 4 from the baseline as primary outcome. We will assess increase of mean volume per void at week 16 from the baseline to evaluate long-term efficacy as well.

Secondary outcome measures

1. The mean frequency of urination per day, including voluntary and incontinence urination.
2. Quality of life assessments measured by completion of the Incontinence Quality of Life Questionnaire (I-QOL)[51] and the Barthel Index (BI)[52].

The average frequency of urination per day is composed of mean frequency of voluntary and incontinent urination, which represents the severity of ~~reduction in~~ frequent micturition and urinary incontinence respectively. This is strongly linked to stability of bladder and detrusor. Questionnaires for quality of life assessment will be completed based on objective condition and subjective sensation of participants.

All outcome measures will be assessed before the baseline, at 4 weeks and 16 weeks from the baseline.

Adverse events

Adverse events (AEs) are defined as negative or unintended clinical manifestation following the treatments. Participants will be instructed to report any abnormal reactions to the clinical research team at any time. In addition, study investigators will collect information about abnormal reactions weekly by visiting the participants. All details of related and unexpected AEs, such as time of occurrence, degree and suspected causes, will be recorded on Case Report Forms (CRFs). The common AEs related to moxibustion ~~Common adverse events~~ include allergy, burn and infection ~~are reported by a systematic review~~[53]. AEs will be classified into 5 grades: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); Moderate (minimal, local or noninvasive intervention indicated); Severe (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated); Very severe (life-threatening consequences; urgent intervention indicated); Death related to adverse events. Participants with mild and moderate AEs will receive symptomatic treatment and will be closely followed up by the research team. Severe AEs will be reported to the Research Ethics Committee within 48 hours. The Research Ethics Committee will

offer medical advice to the research team and determine whether the patient is eligible for further treatment. ~~Adverse reactions should be reported by patients or caregivers and solved by the therapists.~~

Data management

Before recruitment, the whole research group, including therapists, data administrators and outcome assessors, will participate in a training seminar about research contents and data management. Baseline characteristics of participants will be recorded on CRFs by a research assistant. Data collection of urination and questionnaires will be conducted by a researcher who remains blinded to the group allocation at the baseline, 4 and 16 weeks after the baseline. Occupational caregivers will be trained to identify urinary incontinence and voluntary urination. Caregivers will collect urine of voluntary urination and measure it with a pot-shaped urine collector with scales. They will be trained to record accurate voiding time, voluntary urinary volume and urinary incontinence episodes on a 72-hour frequency-volume chart (see Figure 4). The record will be started at 8AM and last for 72 hours. If caregivers failed to collect urine in time, they will note voiding time and specific reasons on the chart. The blinded researcher will complete the urination section on CRFs according to the 72-hour frequency-volume charts handed in by caregivers.

Two independent researchers blinded to the group allocation will enter the data on Excel spreadsheet after the completion of the CRFs separately. Another independent researcher will compare the two data sets for check-up. If different data entry is discovered, data will be compared with the original CRFs to verify inconsistency. All modification will be marked on the CRFs. Research data will be gathered and saved abiding by the Data Protection Act 1998. Paper files will be kept in a locked filing cabinet and electronic documents will be stored in a password protected computer, with access restricted to the principal investigator. All research documents will be preserved for at least 5 years after publication.

Statistical analysis

Data analysis will be performed in a blinded pattern by statisticians of Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical analyses will be conducted on an intention-to-treat basis using the SPSS statistical package program (ver.18.0). Missing data will be replaced in accordance with the principle of the last observation carried forward. A P value < 0.05 will be ~~is~~ considered statistically significant with two-sided test. Baseline characteristics including gender, age and previous duration are described as n (%) for categorical data and mean ± SD (standard deviation) for continuous data. To compare the differences among groups, we will perform analysis of variance (ANOVA) for normally distributed data, Kruskal-Wallis test for abnormally distributed data and chi-squared test for categorical data. Comparisons between two groups will be conducted using Bonferroni method of post hoc multiple comparisons.

Ethical considerations

This study adheres to the principles of the Declaration of Helsinki and has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). We will conduct the research in the following hospitals: Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, Beijing Huguosi Hospital of Traditional Chinese Medicine and China Rehabilitation Research Center. Each participant will sign written informed consents voluntarily.

DISCUSSION

~~Exploration of UI dates back to the era of Yellow Emperor's Inner Canon in China. The term of UI after stroke was first recorded in "JingYueQuanShu", a Chinese ancient book by Zhang Jiebin. Ancient physicians began to realize that apoplexy was one of the causes of UI since then. In the theory of traditional Chinese medicine (TCM), kidney qi could regulate voiding function and ensure voluntary urination. Deficiency of kidney qi was known to be the primary pathogenesis referring to "ZhuBingYuanHouLun", a famous ancient TCM literature. Ginger and salt are able to warm and tonify the kidney Qi in TCM theory. Shenque (CV8) is applied as a principal acupoint for nourishing kidney Qi, which is only allowed to be used with moxibustion. Owing to the features of materials and usage, ginger-salt-indirect moxibustion is likely to warm and nourish kidney Qi, thereby controlling bladder and regulating voiding function.~~

Placebo or sham control is encouraged in clinical trials to avoid bias[54]. To our knowledge, no consensus has been established to recommend valid placebo or sham methods of moxibustion by far. Sham moxibustion is impractical to achieve blinding because of the common knowledge ~~cognition~~ of moxibustion in Chinese patients. Because of preference for moxibustion, incompliance of Chinese patients will make it difficult to use standard therapies as control treatment. Following pragmatic purpose, we set a usual care group as a blank control group, rather than a certain effective therapy or a sham device.

Concerning evaluation instruments, we selected 72-hour frequency-volume chart to record urination details and I-QOL together with Barthel Index to assess quality of life. The frequency volume chart and bladder diary is highly recommended in clinical trials by ICS[1]. Frequency-volume charts record the time and volume of each voiding, as well as incontinence episodes. ICS suggested that frequency-volume charts should be recorded for at least 24 hours[1]. ~~Recent literatures[48, 55-58]~~ A ~~considered that a~~ minimum of 72 hours was~~is~~ required to ensure reliability for diary parameters[48, 55-58]. Thus, we will use a 72-hour frequency-volume chart to alleviate burdens for patients and improve compliance[59, 60].

As for the assessment of quality of life, I-QOL is strongly recommended to assess the effect of urinary incontinence on patients' quality of life[61]. Previous ~~A recent~~ research[51] has affirmed the reliability and validity of I-QOL as an incontinence-related QOL instrument in neurogenic UI patients. The items of I-QOL focus on three dimensions, namely social embarrassment, avoidance behaviors and psychosocial impacts, without physical mobility and self-care ability. Barthel Index is added to evaluate patients' activities of daily living, which is recognized as a valid and reliable outcome measurement for stroke survivors[52].

One limitation of this pilot study is that we will be unable ~~fail~~ to prevent therapists and participants from knowing the group allocation because of the characteristics of moxibustion. To minimize the bias, acupuncturists will receive professional training and strict quality control. In order to homogenize the psychological effects, participants are informed that effects of the two moxibustion techniques are uncertain. The words 'placebo' or 'control' will be avoided. Similar strategies have been applied in previous trials[62, 63]. Noncompliance of the control group is another limitation ~~deficiency~~ of this pilot trial and may lead to a high drop-out rate. Each participant will be provided with 150 RMB as financial compensation to improve compliance. ~~We will solve this problem by providing participants with financial compensations and free moxibustion therapies after the completion of the entire trial.~~

This study is the major sub-project focusing on stroke recovery, which is sponsored and funded by the National Administration of Traditional Chinese Medicine of China. This protocol describes the first pilot randomized controlled trial evaluating the feasibility to conduct a research to assess the efficacy ~~curative effects~~ and safety of ginger-salt-indirect moxibustion on UUI after stroke. Results of this preliminary study will provide essential information for the design of subsequent large-scale trials. Further trials will focus on assessment of urodynamic parameters and evaluation of efficacy and safety of moxibustion on UUI after stroke.

Trial status

The trial is currently in the recruitment phase.

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Contributors LPW and HLL conceived this study and prepared the initial protocol. LLW drafted the manuscript and participated in design of the study. GXS, YY, LZ, TZ participated in revising the protocol. LZ plans for the statistical analysis. LPW and HLL made amendments of the trial protocol. All authors read and approved the final manuscript.

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Ethics approval Research ethics approval was attained from the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094).

Competing interests None.

Figure 1. Trial profile

Figure 2. Moxa cone moxibustion

Figure 3. Moxa box moxibustion

Figure 4. 72-hour frequency-volume chart

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Figure 1 Trial profile

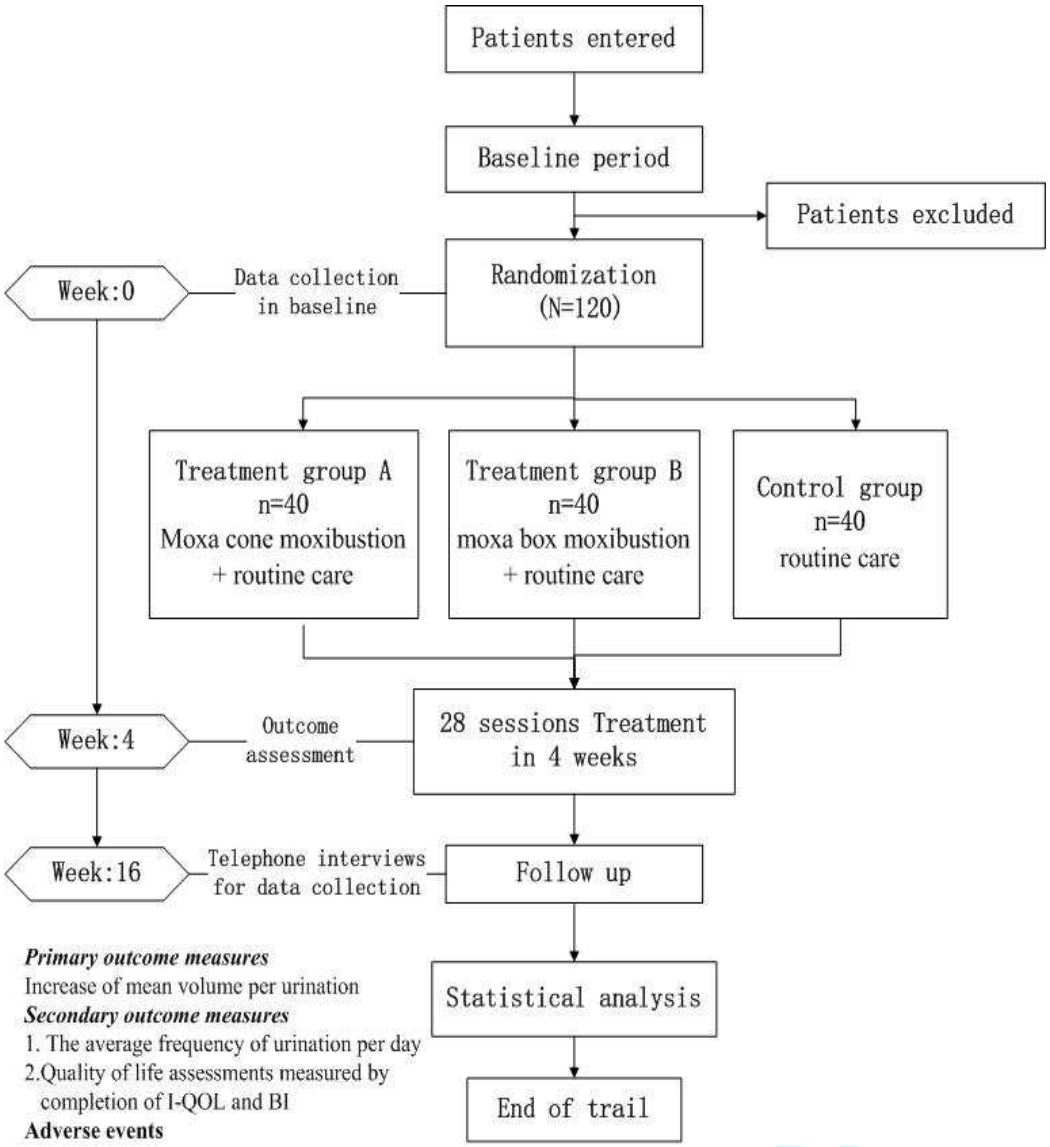


Figure 2. Moxa cone moxibustion

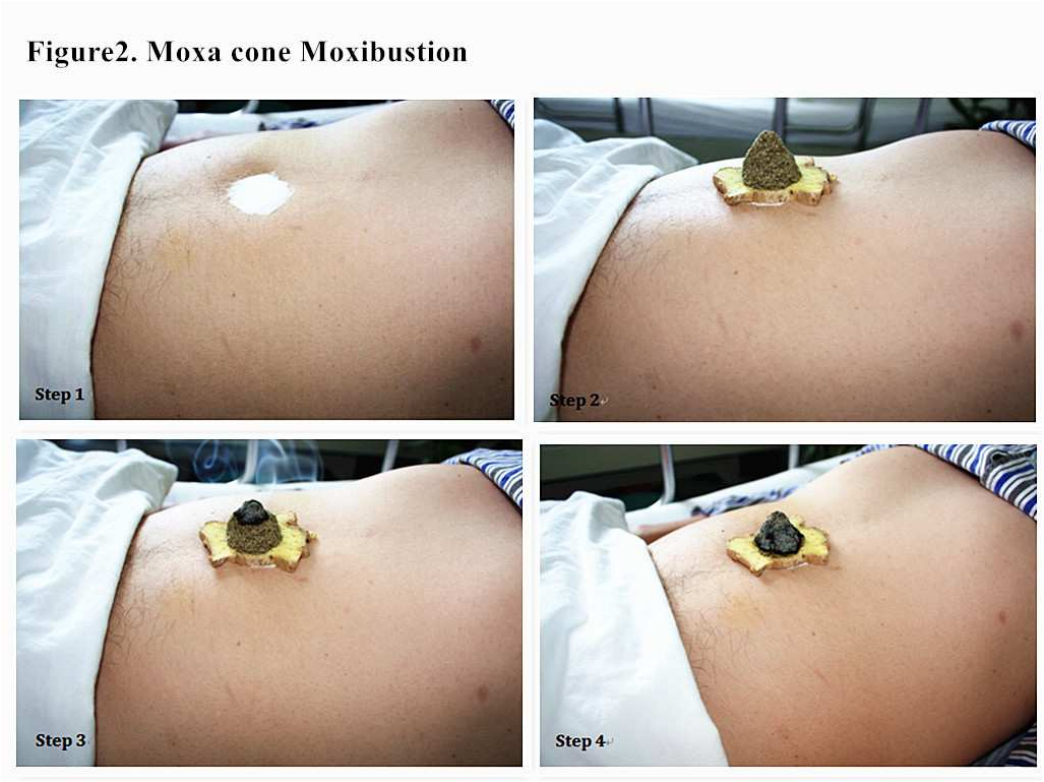
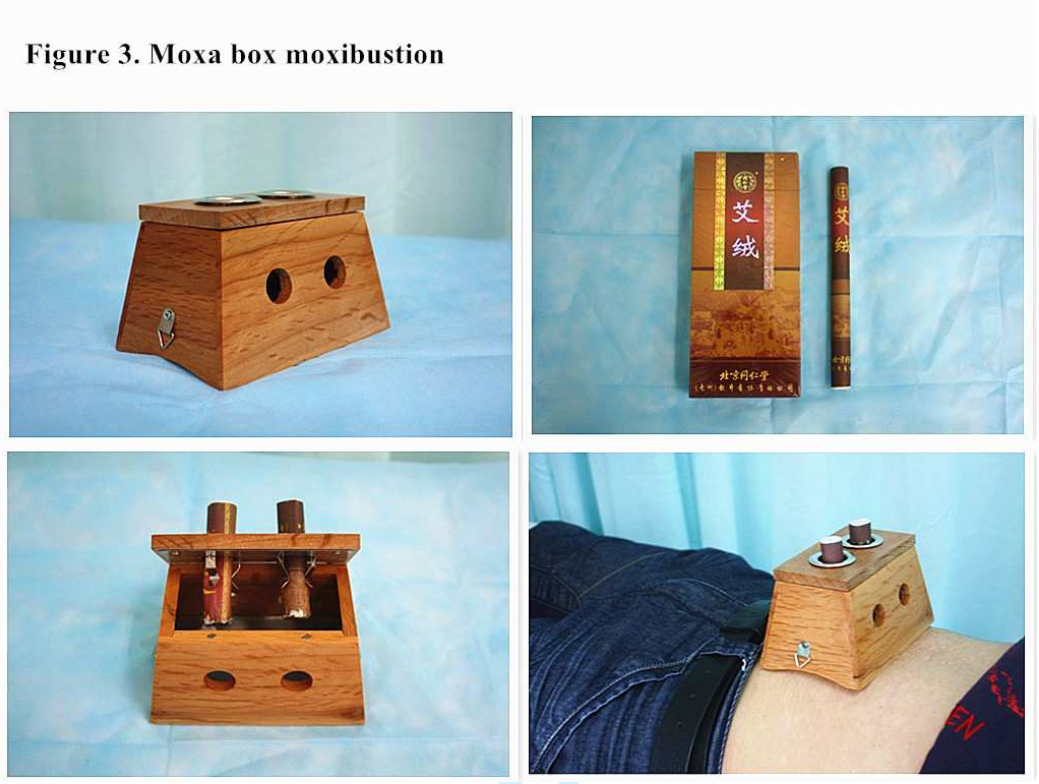


Figure 3. Moxa box moxibustion



72-hour frequency-volume chart

Date	Time (a.m/p.m)	Volume voided (ml)	urinary incontinence (tick in the blank)	notes

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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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ABSTRACT

Introduction: Ginger-salt-indirect moxibustion is widely applied to treat urge urinary incontinence after stroke, which is a common complication in stroke survivors. Moxa cone moxibustion and moxa box moxibustion are main techniques of ginger-salt-indirect moxibustion. Our previous study had shown that ginger-salt-indirect moxibustion using moxa cones was feasible and effective for urination disorders post-stroke. This pilot study aims to assess the feasibility of conducting research to evaluate the efficacy and safety of ginger-salt-indirect moxibustion for patients with post-stroke urge urinary incontinence.

Methods and analysis: This is a multicenter, prospective, single-blinded, pilot randomized controlled trial. 120 eligible patients will be randomly allocated to three groups. Treatment group A (n = 40) will receive moxa cone moxibustion and routine care; treatment group B (n = 40) will receive moxa box moxibustion and routine care; control group (n = 40) will only receive routine care for stroke recovery. The entire moxibustion treatment will consist of a total of 28 sessions during the course of 4 weeks. Primary outcome measure will be the increase of mean volume per void assessed at week 4 from the first moxibustion session (baseline). Secondary outcome measures will include mean frequency of urination per day and quality of life assessments measured by completion of Incontinence Quality of Life Questionnaire and Barthel Index. All outcome measures will be assessed at the baseline, 4 weeks and 16 weeks from baseline. Adverse events in three groups will be recorded to assess safety of moxibustion.

Ethics and dissemination: Research ethics was approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). Written informed consent will be obtained from all participants. Study results will be published in peer-reviewed journals.

Trial Registration number: ISRCTN 44706974.

Strengths and limitations of this study

- First pilot study to evaluate the feasibility of conducting research to assess the efficacy and safety of ginger-salt-indirect moxibustion as treatment for urge urinary incontinence after stroke
- Multicentre, randomised controlled trial with pragmatic design
- Interventions conducted by certified acupuncturists according to the STRICTOM and GCP
- Lack of blinding of acupuncturists and participants

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary leakage of urine that causes hygienic or social problems by International Continence Society (ICS) [1]. Prevalence of UI after stroke varies from 32–79% at admission[2-4], 25% at hospital discharge and 15% after one year[4]. Urge urinary incontinence (UUI) is a common type of UI[5] after stroke. It is characterized by involuntary leakage of urine accompanied or preceded by urgency[1].

Results of previous review[6] suggested that there were three major causes of urinary incontinence after stroke: detrusor hyperreflexia caused by infarction; stroke-related cognitive or language deficits; bladder hyporeflexia with resultant overflow incontinence. UUI can be caused by detrusor overactivity due to the loss of inhibitory neurons after stroke[7]. Detrusor overactivity is characterized by involuntary detrusor contractions during the filling and storage phase[1, 7, 8]. When intra-detrusor pressure generated by abnormal detrusor contractions exceeds sphincter pressure, urinary incontinence occurs[7]. UI is a strong prognostic indicator for stroke recovery, which is associated with high rates of mortality [9, 10], disability[11] and increasing admission to institutional care[12]. Micturition disorders may result in urinary infection, nephritis, fungal dermatitis[13], and even bedsore. Typical symptoms, including frequent micturition, nocturia and urgency, could lead to impaired quality of life[14] and heavy economic burdens[15, 16].

Initial treatments for UUI after stroke recommended by ICS are behavioral therapy and pharmacotherapy[1]. Behavioral therapies, including healthy bladder habits and training techniques, aim at changing patients' lifestyle and at teaching patients to control urgency and enhance continence ability[17]. For habit modification, patients are guided to re-establish a healthy voiding schedule, eliminate bladder irritants from the diet, manage fluid intake and bowel regularity, control weight and give up smoking[18-24]. Training techniques consist of bladder training, urgency control techniques, pelvic muscle exercises, delayed voiding and multicomponent behavioral training[17]. Behavioral interventions are applied in the primary care setting, with or without pharmacotherapy[25-27]. Among these strategies, behavioral training and bladder training have the strongest efficacy evidence for the treatment of UUI[28-31]. Antimuscarinic drugs can reduce urgency and improve bladder function by controlling detrusor muscle overactivity through inhibition of M2 and M3 muscarinic bladder receptors [32-34]. Several meta-analyses have shown that the most widely used antimuscarinic drugs have significant clinical benefits on UUI[35-38].

However, use of antimuscarinic agents is complicated by dose convenience, drug contraindication and financial concerns[39]. A Cochrane systematic review[40] concluded that no studies designed to manage urinary incontinence after stroke in secondary care had been rigorously conducted so far. Although there is clinical guideline for the management of urinary incontinence after stroke[1], to date there is insufficient good quality evidence to support current clinical practices[41]. More available therapies and well-designed studies are required to provide further evidences for management of UUI after stroke.

Moxibustion is a therapy using ignited materials (usually moxa) to heat selected points of the skin surface. This therapy is widely used for chronic deficiency diseases[42] and is commonly indicated for UUI [43]. The mechanism of action of moxibustion combines thermal, radiation and pharmacological effects of the materials used, acting on the meridian system [44]. Following the theory of Traditional Chinese Medicine (TCM), kidney *qi* regulates voiding function and ensures voluntary urination. Deficiency of kidney *qi* is known to be the primary pathogenesis of UI according to "ZhuBingYuanHouLun" (a famous ancient TCM literature). Ginger and salt are typically used on *Shenque* (CV8) acupoint to warm, tonify and nourish the kidney *qi* thereby controlling bladder and regulating voiding function.

Moxa cone moxibustion and moxa box moxibustion are primary techniques of ginger-salt-indirect moxibustion, which are commonly used in clinical practices in China. Moxa cone moxibustion involves a moxa cone burning directly on the ginger slice and providing thermal stimulus to the skin surface (see Figure 2). Moxa box moxibustion facilitates manipulations and reduces adverse reactions by using the device of moxa box with moxa sticks inside over the ginger slice (see Figure 3). Results of our previous study[45] showed that ginger-salt-partitioned moxibustion with moxa cone could reduce mean daytime and nighttime voiding frequency in the treatment of urination disorders poststroke. In addition, we also observed that ginger-salt-indirect moxibustion with moxa cones could increase mean volume per void of UI after stroke in an unpublished study. Our previous studies, together with results from an earlier Cochrane review[40, 45] suggest ginger-salt-indirect moxibustion may be worth investigating with more rigorous study design.

METHODS

Objectives

This pilot study is to evaluate the feasibility of a research to assess the efficacy and safety of ginger-salt-indirect moxibustion for the treatment of UUI after stroke.

Recruitment

This is a multicenter, single-blinded, pilot randomized controlled trial. The research consists of three sequential parts (see Figure 1): a recruitment period before randomization, a treatment period of 4 weeks, and a follow-up period of 12 weeks. 120 eligible participants will be recruited from acupuncture wards of three hospitals according to the inclusion and exclusion criteria. During the first visit, potentially qualified patients will be provided with detailed information about this study, including the research objective, study procedure, potential benefits and risks. If a patient shows willingness to participate, they will be required to voluntarily sign a written informed consent. This will be followed by baseline assessment and randomization.

Design

Randomization and allocation concealment

The randomization scheme is provided by the Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical experts will use the block randomization method (block size of 6) of the SAS package (Version 9.1.3; SAS institute Inc., Cary, NC, USA) to form the random allocation sequence. Then computer-generated opaque sealed envelopes with serial number outside and group number inside will be produced. The envelopes will be kept in a secure locked drawer making it inaccessible to all study personnel. After baseline assessments, the envelopes will be opened sequentially by an independent researcher in front of the participants to ensure adequate concealment. Participants will be allocated to three groups according to the group number printed inside the envelopes.

Blinding

Due to the feature of the moxibustion, it is difficult to make the therapists or participants blinded to the allocation. Data managers and statisticians will be blinded throughout the trial. During the intervention, therapists and data managers will be requested not to communicate with each other about the allocation. Blinded telephone interviewers will collect the follow-up materials to evaluate long term effect of moxibustion at 16 weeks after the baseline.

Participants

Sample size

Because this is a pilot study, a power calculation to determine sample size was not conducted. Sample size calculation was performed based on estimates of the number of participants we would expect to recruit within 24 months. We therefore plan to recruit five participants per month, according to our previous trial. A sample size of 40 per group and a total number of 120 will be included, which is larger than the minimum of 12 per group suggested for pilot studies[46]. Outcomes of this pilot study will help calculate appropriate sample size for further randomized clinical trials.

Inclusion criteria

1. Male or female, aged 40- 75 years;
2. In-patients with UUI after stroke, according to the diagnosis criteria of the American Stroke Association (ASA) and the International Continence Society (ICS);
3. 4th to 48th week after stroke onset;
4. Normal consciousness, communication ability and recognition;
5. Written informed consent.

Exclusion criteria

1. UUI caused by spinal injury, multiple sclerosis or hyperplasia of prostate gland;
2. Chronic urinary retention or UI before stroke onset;
3. Stress urinary incontinence, mixed urinary incontinence and chronic urinary tract infection;
4. Insufficiency of heart, liver, kidney organs;
5. Participants in another clinical trial.

Discontinuation criteria

Reasons for discontinuation of treatment may include, but are not limited to, the following:

1. Participants' decision of discontinuation of treatment at any time for any reason;
2. Investigators' determination to discontinue the treatment for patient's safety and best interests at any time;
3. Non-compliance of participants with the study procedure (eg, study visits);
4. Concomitant therapy that could affect the study results during the trial;

5. Detection of protocol violations at any time.

Intervention

Ginger-Salt-Indirect Moxibustion is formulated on the basis of description in ancient literature and our clinical experience. Moxibustion will be manipulated by certified acupuncturists with at least 20 years of clinical experience. All treatment details will be standardized between practitioners by guiding videos and relative trainings before the first acupuncture session. Interventions will be performed in accordance with the STRICTOM[47] and good clinical practice guidelines (GCP).

Treatment group A

Participants in treatment group A will receive moxa cone moxibustion and routine care once a day for 4 weeks. The procedure of each session as it is used in normal practices is described as follows (see figure 2). Participants are asked to lie on a bed in a supine position and remove clothing to fully expose the navel in a temperature controlled room (25 to 30°C). A certain amount of salt is put on the navel to cover *Shenque* (CV8) acupoint and covered by a piece of fresh ginger slice (30mm in diameter and 4-5 mm in thickness). Then a moxa cone (pure wormwood fiber in material; 15 mm in diameter and 30 mm in length; Tongrentang Inc., China.) is placed on the fresh ginger slice and lit by the therapist. Once the moxa cone is burnt out, the therapist removes the whole moxa cone and replaces it with another one. The technique requires a sensation of heat but no painful burning sensation for participants. If participants feel pain or a burning sensation, the ginger slice with burning moxa cone will be removed immediately and reset after several minutes. Each session requires three units of moxa cone. The therapist is required to carefully observe the patient and whisk away the burning ash to avoid burning injury. Because this study is designed to evaluate moxibustion treatment as it is used in normal practice, the moxibustion group will also receive the usual care provided to the control group.

Treatment group B

Participants in treatment group B will receive moxa box moxibustion and routine care once a day for 4 weeks. The manipulations are generally similar to those in treatment group A. The only difference is that the double-holes moxa box (13 x 8 x 8.5 cm in volume) with two moxa sticks (pure wormwood fiber; 15 mm in diameter and 70 mm in length; Tongrentang Inc., China.) in the holes will be placed on the fresh ginger slice (see figure 3). The moxa sticks will be ignited from the bottom. If patients feel pain, the therapist will remove the lid with the moxa sticks for several minutes. Each session requires three units of moxa sticks.

Control group

According to pragmatic design, the control group will receive routine therapies for stroke recovery. These include control of blood pressure, inhibition of platelet aggregation, routine physiotherapy, occupational therapy and glucose control treatment. Participants in this group will be suggested to maintain their normal lifestyle, including diet, exercise and workload. Moreover, participants will be encouraged to inform the researchers of any new treatments performed after entry into the trial.

Outcome measures

Primary outcome measures

Increase of mean volume per void at week 4 from the baseline.

Mean volume per void is one of the main quantitative indicators recorded in bladder dairies or frequency volume charts[17, 31, 48-50]. It is calculated by dividing total volume of voluntary urination by total frequency of voluntary urination, based on 72-hour frequency-volume chart data. Increase of mean volume per void objectively reflects improvement of bladder capacity and detrusor

stability in the urine filling and storage period. In a previous study, we observed that mean volume per void increased in the ginger-salt-indirect moxibustion group, compared to the control group with a statistical difference. Consequently, we selected increase of mean volume per void at week 4 from the baseline as primary outcome. We will assess increase of mean volume per void at week 16 from the baseline to evaluate long-term efficacy as well.

Secondary outcome measures

1. The mean frequency of urination per day, including voluntary and incontinence urination.
2. Quality of life assessments measured by completion of the Incontinence Quality of Life Questionnaire (I-QOL)[51] and the Barthel Index (BI)[52].

The average frequency of urination per day is composed of mean frequency of voluntary and incontinent urination, which represents the severity of frequent micturition and urinary incontinence respectively. This is strongly linked to stability of bladder and detrusor. Questionnaires for quality of life assessment will be completed based on objective condition and subjective sensation of participants.

All outcome measures will be assessed before the baseline, at 4 weeks and 16 weeks from the baseline.

Adverse events

Adverse events (AEs) are defined as negative or unintended clinical manifestations following the treatment. Participants will be instructed to report any abnormal reactions to the clinical research team at any time. In addition, study investigators will collect information about abnormal reactions weekly by visiting the participants. All details of related and unexpected AEs, such as time of occurrence, degree and suspected causes, will be recorded on Case Report Forms (CRFs). The common AEs related to moxibustion include allergy, burn and infection[53]. AEs will be classified into 5 grades: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); Moderate (minimal, local or noninvasive intervention indicated); Severe (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated); Very severe (life-threatening consequences; urgent intervention indicated); Death related to adverse events. Participants with mild and moderate AEs will receive symptomatic treatment and will be closely followed up by the research team. Severe AEs will be reported to the Research Ethics Committee within 48 hours. The Research Ethics Committee will offer medical advice to the research team and determine whether the patient is eligible for further treatment.

Data management

Before recruitment, the whole research group, including therapists, data administrators and outcome assessors, will participate in a training seminar about research contents and data management. Baseline characteristics of participants will be recorded on CRFs by a research assistant. Data collection of urination and questionnaires will be conducted by a researcher who remains blinded to the group allocation at the baseline, 4 and 16 weeks from the baseline. Occupational caregivers will be trained to identify urinary incontinence and voluntary urination. Caregivers will collect urine of voluntary urination and measure it with a pot-shaped urine collector with scales. They will be trained to record accurate voiding time, voluntary urinary volume and urinary incontinence episodes on a 72-hour frequency-volume chart (see Figure 4). The record will be started at 8AM and last for 72 hours. If caregivers failed to collect urine in time, they will note voiding time and specific reasons on the chart. The blinded researcher will complete

the urination section on CRFs according to the 72-hour frequency-volume charts handed in by caregivers.

Two independent researchers blinded to the group allocation will enter the data on Excel spreadsheet after the completion of the CRFs separately. Another independent researcher will compare the two data sets for check-up. If different data entry is discovered, data will be compared with the original CRFs to verify inconsistency. All modification will be marked on the CRFs. Research data will be gathered and saved abiding by the Data Protection Act 1998. Paper files will be kept in a locked filing cabinet. Electronic documents will be stored in a password protected computer, with access restricted to the principal investigator. All research documents will be preserved for at least 5 years after publication.

Statistical analysis

Data analysis will be performed in a blinded pattern by statisticians of Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical analyses will be conducted on an intention-to-treat basis using the SPSS statistical package program (ver.18.0). Missing data will be replaced in accordance with the principle of the last observation carried forward. A P value < 0.05 will be considered statistically significant with two-sided test. Baseline characteristics including gender, age and previous duration are described as n (%) for categorical data and mean ± SD (standard deviation) for continuous data. To compare the differences among groups, we will perform analysis of variance (ANOVA) for normally distributed data, Kruskal-Wallis test for abnormally distributed data and chi-squared test for categorical data. Comparisons between two groups will be conducted using Bonferroni method of post hoc multiple comparisons.

Ethical considerations

This study adheres to the principles of the Declaration of Helsinki and has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). We will conduct the research in the following hospitals: Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, Beijing Huguosi Hospital of Traditional Chinese Medicine and China Rehabilitation Research Center. Each participant will sign written informed consents voluntarily.

DISCUSSION

Placebo or sham control is encouraged in clinical trials to avoid bias[54]. To our knowledge, no consensus has been established to recommend valid placebo or sham methods of moxibustion so far. Sham moxibustion is unpractical to achieve blinding because of the common knowledge of moxibustion in Chinese patients. Owing to the preference for moxibustion, incompliance of Chinese patients will make it difficult to use standard therapies as control treatment. Following the pragmatic purpose, we set a usual care group as a blank control group, rather than a certain effective therapy or a sham device.

Concerning evaluation instruments, we selected 72-hour frequency-volume chart to record urination details and I-QOL together with Barthel Index to assess quality of life. The frequency volume chart and bladder diary is highly recommended in clinical trials by ICS[1]. Frequency-volume charts record the time and volume of each voiding, as well as incontinence episodes. ICS suggested that frequency-volume charts should be recorded for at least 24 hours[1]. A minimum of 72 hours was required to ensure reliability for diary parameters[48, 55-58]. Thus, we

will use a 72-hour frequency-volume chart to alleviate burdens for patients and improve compliance[59, 60].

As for the assessment of quality of life, I-QOL is strongly recommended to assess the effect of urinary incontinence on patients' quality of life[61]. Previous research[51] has affirmed the reliability and validity of I-QOL as an incontinence-related QOL instrument in neurogenic UI patients. The items of I-QOL focus on three dimensions, namely social embarrassment, avoidance behavior and psychosocial impact. Barthel Index is added to evaluate patients' activities of daily living, which is recognized as a valid and reliable outcome measurement for stroke survivors[52].

One limitation of this pilot study is that we will be unable to prevent therapists and participants from knowing the group allocation because of the characteristics of moxibustion. To minimize the bias, therapists will receive professional training and strict quality control. In order to homogenize the psychological effects, participants are informed that effects of the two moxibustion techniques are uncertain. The words 'placebo' or 'control' will be avoided. Similar strategies have been applied in previous trials[62, 63]. Noncompliance of the control group is another limitation of this pilot trial. It may lead to a high drop-out rate. Participants will be provided with 150 RMB as financial compensation to improve compliance.

This study is the major sub-project focusing on stroke recovery, which is sponsored and funded by the National Administration of Traditional Chinese Medicine of China. This protocol describes the first pilot randomized controlled trial evaluating the feasibility to conduct a research to assess the efficacy and safety of ginger-salt-indirect moxibustion on UUI after stroke. Results of this preliminary study will provide essential information for the design of subsequent large-scale trials. Further trials will focus on assessment of urodynamic parameters and evaluation of efficacy and safety of moxibustion on UUI after stroke.

Trial status

The trial is currently in the recruitment phase.

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Contributors LPW and HLL conceived this study and prepared the initial protocol. LLW drafted the manuscript and participated in design of the study. GXS, YY, LZ, TZ participated in revising the protocol. LZ plans for the statistical analysis. LPW and HLL made amendments of the trial protocol. All authors read and approved the final manuscript.

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Ethics approval Research ethics approval was attained from the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094).

Competing interests None.

Figure 1. Trial flowchart

Figure 2. Moxa cone moxibustion

Figure 3. Moxa box moxibustion

Figure 4. 72-hour frequency-volume chart

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Efficacy and safety of Ginger-Salt-Indirect Moxibustion for urge urinary incontinence after stroke: protocol for a pilot multicenter randomized controlled trial

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ABSTRACT

Introduction: Ginger-salt-indirect moxibustion is widely applied to treat urge urinary incontinence after stroke, which is a common complication in stroke survivors. Moxa cone moxibustion and moxa box moxibustion are main techniques ~~patterns~~ of ginger-salt-indirect moxibustion. Our previous study had shown that ginger-salt-indirect moxibustion using moxa cones was feasible and effective for urination disorders post-stroke. This pilot study aims to assess the feasibility of conducting research to evaluate the efficacy and safety of ginger-salt-indirect moxibustion for patients with post-stroke urge urinary incontinence.

Methods and analysis: This is a multicenter, prospective, single-blinded, pilot randomized controlled trial. 120 eligible patients will be randomly allocated to three groups. Treatment group A (n = 40) will receive moxa cone moxibustion and routine care; treatment group B (n = 40) will receive moxa box moxibustion and routine care; control group (n = 40) will only receive routine care for stroke recovery. The entire moxibustion treatment will consist of a total of 28 sessions during the course of 4 weeks. Primary outcome measure will be increase of mean volume per void assessed at week 4 from the baseline, based on the data of a 72-hour frequency-volume chart. Secondary outcome measures will include mean frequency of urination per day and quality of life assessments measured by completion of Incontinence Quality of Life Questionnaire and Barthel Index. All outcome measures will be assessed before the first moxibustion session (baseline) , at 4 weeks and 16 weeks from baseline~~after the first moxibustion session~~. Adverse events in three groups will be recorded to assess safety of moxibustion.

Ethics and dissemination: Research ethics was approved by Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). Written informed consent will be obtained ~~achieved~~ from all participants. Study results will be published in peer-reviewed journals.

Trial Registration number: ISRCTN 44706974.

Strengths and limitations of this study

- First pilot study to evaluate the feasibility of conducting research to assess the efficacy and safety of ginger-salt-indirect moxibustion as treatment for urge urinary incontinence after stroke
- Multicentre, randomised controlled trial with pragmatic design
- Interventions conducted by certified acupuncturists according to the STRICTOM and GCP.
- Lack of blinding of acupuncturists and participants

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary leakage of urine that causes hygienic or social problems by International Continence Society (ICS) [1]. Prevalence of UI after stroke varies from 32–79% at admission[2-4], 25% at hospital discharge and 15% after one year[4]. Urge urinary incontinence (UUI) is a common type of UI[5] after stroke. It ~~urge urinary incontinence (UUI) after stroke~~ is characterized by involuntary leakage of urine ~~loss~~ accompanied or preceded by urgency[1], ~~which arises from acute cerebral accident onset~~.

Results of previous review[6] suggested that there were three major causes of urinary incontinence after stroke: detrusor hyperreflexia caused by infarction; stroke-related cognitive or language deficits; bladder hyporeflexia with resultant overflow incontinence. UUI can be caused by detrusor overactivity due to the loss of inhibitory neurons after stroke[7]. Detrusor overactivity is characterized by involuntary detrusor contractions during the filling and storage phase[1, 7, 8]. When intra-detrusor pressure generated by abnormal detrusor contractions exceeds sphincter pressure, urinary incontinence occurs[7]. UI is a strong prognostic indicator for stroke recovery, which is associated with high rates of mortality [9, 10], disability[11] and increasing admission to institutional care[12]. Micturition disorders may result in urinary infection, nephritis, fungal dermatitis[13], and even bedsore. Typical symptoms, including frequent micturition, nocturia and urgency ~~(compelling desire to void which is difficult to defer)~~, could lead to impaired quality of life[14] and heavy economic burdens[15, 16].

Initial treatments for UUI after stroke recommended by ICS are behavioral therapy and pharmacotherapy[1]. Behavioral therapies, including healthy bladder habits and training techniques, aim at changing patients' lifestyle and at teaching patients to control urgency and enhance continence ability[17]. For habit modification, patients are guided to re-establish a healthy voiding schedule, eliminate bladder irritants from the diet, manage fluid intake and bowel regularity, control weight and give up smoking[18-24]. Training techniques consist of bladder training, urgency control techniques, pelvic muscle exercises, delayed voiding and multicomponent behavioral training[17]. Behavioral interventions are applied in the primary care setting, with or without pharmacotherapy[25-27]. Among these strategies, behavioral training and bladder training have the strongest efficacy evidence for the treatment of UUI[28-31]. Antimuscarinic drugs can reduce

urgency and improve bladder function by ~~with the mechanism of~~ controlling detrusor muscle overactivity through inhibition of M2 and M3 muscarinic bladder receptors on bladder[32-34]. Several meta-analyses have shown that the most widely used antimuscarinic drugs have significant clinical benefits on UUI[35-38]. However, use ~~Nevertheless, application~~ of antimuscarinic agents is complicated ~~influenced~~ by dose ~~dosing~~ convenience, drug contraindication and financial concern~~sconsideration~~[39]. A Cochrane systematic review[40] concluded that no ~~rigorously~~ studies designed to manage urinary incontinence after stroke in secondary care had been rigorously conducted by far[42]. Although there is clinical guideline for the management of urinary incontinence after stroke[1], to date there is insufficient good quality evidence to support the current clinical practices[41]. ~~Evidences of relevant trials were insufficient to guide clinical practices[43]~~. More available therapies and well-designed studies are required to provide further evidences for management of UUI after stroke.

Moxibustion is a therapy using ignited materials (usually moxa) to heat selected points of the skin surface. This therapy is widely used for ~~as a treatment for cold syndrome and~~ chronic deficiency diseases[42] and is commonly indicated for UUI ~~UUI was regarded as one of common indications[43]~~. The mechanism of ~~Despite uncertain modern mechanisms, it is generally identified that~~ action of moxibustion combines ~~is produced by the meridian system combining with~~ thermal, radiation and pharmacological effects of the materials used, acting on the meridian system [44]. Following the theory of Traditional Chinese Medicine (TCM), kidney *qi* regulates voiding function and ensures voluntary urination. Deficiency of kidney *qi* is known to be the primary pathogenesis of UI according to "ZhuBingYuanHouLun" (a famous ancient TCM literature). Ginger and salt are typically used on *Shenque* (CV8) acupoint to warm, tonify and nourish the kidney *qi* thereby controlling bladder and regulating voiding function.

~~In China, ginger-salt-indirect moxibustion on CV8 (Shenque) is frequently applied to treat UUI after stroke.~~ Moxa cone moxibustion and moxa box moxibustion are primary techniques of ginger-salt-indirect moxibustion commonly used in clinical practices in China. Moxa cone moxibustion involves a moxa cone burning directly on the ginger slice and providing thermal stimulus to the skin surface (see Figure 2). Moxa box moxibustion facilitates manipulations and reduces adverse reactions by using the device of moxa box with moxa sticks inside over the ginger slice (see Figure 3). Results of our previous study[45] showed that ginger-salt-partitioned moxibustion with moxa cone could reduce mean daytime and nighttime voiding frequency in the treatment of urination disorders poststroke. In addition~~Besides~~, we also observed that ginger-salt-indirect moxibustion with moxa cones could increase mean volume per void of UI after stroke in an unpublished study. Our previous studies, together with results from an earlier Cochrane review[40, 45] suggest~~A recent cochrane review concluded that~~ ginger-salt-indirect moxibustion may be worth investigating with a more rigorous study design~~effective for UI after stroke and worth further research[48]~~.

METHODS

Objectives

This pilot study is to evaluate the feasibility of a research to assess the efficacy and safety of ginger-salt-indirect moxibustion for the treatment of UUI after stroke.

Recruitment

This is a multicenter, single-blinded, pilot randomized controlled trial. The research consists of

three sequential parts (see Figure 1): a recruitment period before randomization, a treatment period of 4 weeks, and a follow-up period of 12 weeks. 120 eligible participants will be recruited from acupuncture wards of three hospitals according to the inclusion and exclusion criteria. During the first visit, potentially qualified patients will be provided with detailed information about this study, including the research objective, study procedure, potential benefits and risks. If a patient shows willingness to participate, they will be required to sign a written informed consent. This will be followed by baseline assessment and randomization ~~will be conduct afterwards~~.

Design

Randomization and allocation concealment

The randomization scheme is provided by the Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical experts will use the block randomization method (block size of 6) of the SAS package (Version 9.1.3; SAS institute Inc., Cary, NC, USA) to form the random allocation sequence. Then computer-generated opaque sealed envelopes with serial number outside and group number inside will be produced. The envelopes will be kept in a secure locked drawer making it inaccessible to all study personnel. After baseline assessments, the envelopes will be opened sequentially by an independent researcher in front of the participants to ensure adequate concealment. Participants will be allocated to the three groups according to the group number printed inside the envelopes.

Blinding

Due to the feature of the moxibustion, it is difficult to make the therapists or participants blinded to the allocation. Data managers and statisticians will be blinded throughout the trial. During the intervention, therapists and data managers are requested not to communicate with each other about the allocation. Blinded telephone interviewers will collect the follow-up materials to evaluate long term effect of moxibustion at 16 weeks after the baseline ~~first moxibustion session~~.

Participants

Sample size

Because this is a pilot study, a power calculation to determine sample size was not conducted. Sample size calculation ~~will be~~was performed based on estimates of the number of participants we would expect to recruit within 24 months. We therefore plan to recruit five participants per month, according to our previous trial [47]. A sample size of 40 per group and a total number of 120 will be included, which is larger than the minimum of 12 per group suggested for pilot studies[46]. Outcomes of this pilot study will help calculate appropriate sample size for further randomized clinical trials.

Inclusion criteria

1. Male or female, aged 40- 75 years;
2. In-patients with UUI after stroke, according to the diagnosis criteria of the American Stroke Association (ASA) and the International Continence Society (ICS);
3. 4th to 48th week after stroke onset;
4. Normal consciousness, communication ability and recognition;
5. Written informed consent.

Exclusion criteria

1. UUI caused by spinal injury, multiple sclerosis or hyperplasia of prostate gland;
2. Chronic urinary retention or UI before stroke onset;
3. Stress urinary incontinence, mixed urinary incontinence and chronic urinary tract infection;

4. Insufficiency of heart, liver, kidney organs;
5. Participants in another clinical trial.

Discontinuation criteria

Reasons for discontinuation of treatment may include, but are not limited to, the following:

1. Participants' decision of discontinuation of treatment at any time for any reason;
2. Investigators' determination to discontinue the treatment for patient's safety and best interests at any time;
3. Non-compliance of participants with the study procedure (eg, study visits);
4. Concomitant therapy that could affect the study results during the trial;
5. Detection of protocol violations at any time.

Intervention

Ginger-Salt-Indirect Moxibustion is formulated on the basis of description in ancient literature and our clinical experience~~previous research~~[47]. Moxibustion will be manipulated by certified acupuncturists with at least 20 years of clinical experience. All treatment details will be standardized between practitioners by guiding videos and relative trainings before the first acupuncture session. Interventions will be performed in accordance with the STRICTOM[47] and good clinical practice guidelines (GCP).

Treatment group A

Participants in treatment group A will receive moxa cone moxibustion and routine care once a day for 4 weeks. The procedure of each session as it is used in normal practices is described as follows (see figure 2). Participants are asked to lie on a bed in a supine position and remove clothing to fully expose the navel in a temperature controlled room (25 to 30°C)~~room with 25 to 30□ temperature~~. A certain amount of salt is put on the navel to cover *Shenque* (CV8) acupoint and covered by a piece of fresh ginger slice (30mm in diameter and 4-5 mm in thickness). Then a moxa cone (pure wormwood fiber in material; 15 mm in diameter and 30 mm in length; Tongrentang Inc., China.) is placed on the fresh ginger slice and lit by the therapist. Once the moxa cone is burnt out, the therapist removes the whole moxa cone and replaces it with another one. The technique requires a sensation of heat but no painful burning sensation for participants. If participants feel pain or a burning sensation, the ginger slice with burning moxa cone will be removed immediately and reset after several minutes. Each session requires three units of moxa cone. The therapist is required to carefully observe the patient and whisk away the burning ash to avoid burning injury. This study is designed to evaluate moxibustion treatment as it is used in normal practice. The moxibustion group will also receive the usual care provided to the control group.

Treatment group B

Participants in treatment group B will receive moxa box moxibustion and routine care once a day for 4 weeks. The manipulations are generally similar to those in treatment group A. The only difference is that the double-holes moxa box (13 x 8 x 8.5 cm in volume) with two moxa sticks (pure wormwood fiber; 15 mm in diameter and 70 mm in length; Tongrentang Inc., China.) in the holes will be placed on the fresh ginger slice (see figure 3). The moxa sticks will be ignited from the bottom. If patients feel pain, the therapist will remove the lid with the moxa sticks for several minutes. Each session requires three units of moxa sticks.

Control group

According to pragmatic design, the control group will receive routine therapies for stroke recovery.

These include control of blood pressure, inhibition of platelet aggregation, routine physiotherapy, occupational therapy and glucose control treatment. Participants in this group will be suggested to maintain their normal lifestyle, including diet, exercise and workload. Moreover, participants will be encouraged ~~suggested~~ to inform the researchers of any new treatments performed after entry into the trial.

Outcome measures

Primary outcome measures

Increase of mean volume per void at week 4 from baseline, based on 72-hour frequency-volume chart data.

Mean volume per void is one of the main quantitative indicators recorded in bladder dairies or frequency volume charts[17, 31, 48-50]. It is calculated ~~defined~~ by dividing total volume of voluntary urination by total frequency of voluntary urination in 72 hours. Increase of mean volume per void objectively reflects improvement of bladder capacity and detrusor stability in the urine filling and storage period. In a previous study, we observed that mean volume per void increased in the ginger-salt-indirect moxibustion group, compared to the control group with a statistical difference. Consequently, we selected increase of mean volume per void at week 4 from the baseline as primary outcome. We will assess increase of mean volume per void at week 16 from the baseline to evaluate long-term efficacy as well.

Secondary outcome measures

1. The mean frequency of urination per day, including voluntary and incontinence urination.
2. Quality of life assessments measured by completion of the Incontinence Quality of Life Questionnaire (I-QOL)[51] and the Barthel Index (BI)[52].

The average frequency of urination per day is composed of mean frequency of voluntary and incontinent urination, which represents the severity of ~~reduction in~~ frequent micturition and urinary incontinence respectively. This is strongly linked to stability of bladder and detrusor. Questionnaires for quality of life assessment will be completed based on objective condition and subjective sensation of participants.

All outcome measures will be assessed before the baseline, at 4 weeks and 16 weeks from the baseline.

Adverse events

Adverse events (AEs) are defined as negative or unintended clinical manifestation following the treatments. Participants will be instructed to report any abnormal reactions to the clinical research team at any time. In addition, study investigators will collect information about abnormal reactions weekly by visiting the participants. All details of related and unexpected AEs, such as time of occurrence, degree and suspected causes, will be recorded on Case Report Forms (CRFs). The common AEs related to moxibustion ~~Common adverse events~~ include allergy, burn and infection ~~are reported by a systematic review~~[53]. AEs will be classified into 5 grades: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); Moderate (minimal, local or noninvasive intervention indicated); Severe (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated); Very severe (life-threatening consequences; urgent intervention indicated); Death related to adverse events. Participants with mild and moderate AEs will receive symptomatic treatment and will be closely followed up by the research team. Severe AEs will be reported to the Research Ethics Committee within 48 hours. The Research Ethics Committee will

offer medical advice to the research team and determine whether the patient is eligible for further treatment. ~~Adverse reactions should be reported by patients or caregivers and solved by the therapists.~~

Data management

Before recruitment, the whole research group, including therapists, data administrators and outcome assessors, will participate in a training seminar about research contents and data management. Baseline characteristics of participants will be recorded on CRFs by a research assistant. Data collection of urination and questionnaires will be conducted by a researcher who remains blinded to the group allocation at the baseline, 4 and 16 weeks after the baseline. Occupational caregivers will be trained to identify urinary incontinence and voluntary urination. Caregivers will collect urine of voluntary urination and measure it with a pot-shaped urine collector with scales. They will be trained to record accurate voiding time, voluntary urinary volume and urinary incontinence episodes on a 72-hour frequency-volume chart (see Figure 4). The record will be started at 8AM and last for 72 hours. If caregivers failed to collect urine in time, they will note voiding time and specific reasons on the chart. The blinded researcher will complete the urination section on CRFs according to the 72-hour frequency-volume charts handed in by caregivers.

Two independent researchers blinded to the group allocation will enter the data on Excel spreadsheet after the completion of the CRFs separately. Another independent researcher will compare the two data sets for check-up. If different data entry is discovered, data will be compared with the original CRFs to verify inconsistency. All modification will be marked on the CRFs. Research data will be gathered and saved abiding by the Data Protection Act 1998. Paper files will be kept in a locked filing cabinet and electronic documents will be stored in a password protected computer, with access restricted to the principal investigator. All research documents will be preserved for at least 5 years after publication.

Statistical analysis

Data analysis will be performed in a blinded pattern by statisticians of Research Center of Clinical Epidemiology Affiliated to Peking University Third Hospital in China. Statistical analyses will be conducted on an intention-to-treat basis using the SPSS statistical package program (ver.18.0). Missing data will be replaced in accordance with the principle of the last observation carried forward. A P value < 0.05 will be ~~is~~ considered statistically significant with two-sided test. Baseline characteristics including gender, age and previous duration are described as n (%) for categorical data and mean ± SD (standard deviation) for continuous data. To compare the differences among groups, we will perform analysis of variance (ANOVA) for normally distributed data, Kruskal-Wallis test for abnormally distributed data and chi-squared test for categorical data. Comparisons between two groups will be conducted using Bonferroni method of post hoc multiple comparisons.

Ethical considerations

This study adheres to the principles of the Declaration of Helsinki and has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094). We will conduct the research in the following hospitals: Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, Beijing Huguosi Hospital of Traditional Chinese Medicine and China Rehabilitation Research Center. Each participant will sign written informed consents voluntarily.

DISCUSSION

~~Exploration of UI dates back to the era of Yellow Emperor's Inner Canon in China. The term of UI after stroke was first recorded in "JingYueQuanShu", a Chinese ancient book by Zhang Jiebin. Ancient physicians began to realize that apoplexy was one of the causes of UI since then. In the theory of traditional Chinese medicine (TCM), kidney qi could regulate voiding function and ensure voluntary urination. Deficiency of kidney qi was known to be the primary pathogenesis referring to "ZhuBingYuanHouLun", a famous ancient TCM literature. Ginger and salt are able to warm and tonify the kidney Qi in TCM theory. Shenque (CV8) is applied as a principal acupoint for nourishing kidney Qi, which is only allowed to be used with moxibustion. Owing to the features of materials and usage, ginger-salt-indirect moxibustion is likely to warm and nourish kidney Qi, thereby controlling bladder and regulating voiding function.~~

Placebo or sham control is encouraged in clinical trials to avoid bias[54]. To our knowledge, no consensus has been established to recommend valid placebo or sham methods of moxibustion by far. Sham moxibustion is impractical to achieve blinding because of the common knowledge ~~cognition~~ of moxibustion in Chinese patients. Because of preference for moxibustion, incompliance of Chinese patients will make it difficult to use standard therapies as control treatment. Following pragmatic purpose, we set a usual care group as a blank control group, rather than a certain effective therapy or a sham device.

Concerning evaluation instruments, we selected 72-hour frequency-volume chart to record urination details and I-QOL together with Barthel Index to assess quality of life. The frequency volume chart and bladder diary is highly recommended in clinical trials by ICS[1]. Frequency-volume charts record the time and volume of each voiding, as well as incontinence episodes. ICS suggested that frequency-volume charts should be recorded for at least 24 hours[1]. ~~Recent literatures[48, 55-58]~~ A ~~considered that a~~ minimum of 72 hours was~~is~~ required to ensure reliability for diary parameters[48, 55-58]. Thus, we will use a 72-hour frequency-volume chart to alleviate burdens for patients and improve compliance[59, 60].

As for the assessment of quality of life, I-QOL is strongly recommended to assess the effect of urinary incontinence on patients' quality of life[61]. Previous ~~A recent~~ research[51] has affirmed the reliability and validity of I-QOL as an incontinence-related QOL instrument in neurogenic UI patients. The items of I-QOL focus on three dimensions, namely social embarrassment, avoidance behaviors and psychosocial impacts, without physical mobility and self-care ability. Barthel Index is added to evaluate patients' activities of daily living, which is recognized as a valid and reliable outcome measurement for stroke survivors[52].

One limitation of this pilot study is that we will be unable ~~fail~~ to prevent therapists and participants from knowing the group allocation because of the characteristics of moxibustion. To minimize the bias, acupuncturists will receive professional training and strict quality control. In order to homogenize the psychological effects, participants are informed that effects of the two moxibustion techniques are uncertain. The words 'placebo' or 'control' will be avoided. Similar strategies have been applied in previous trials[62, 63]. Noncompliance of the control group is another limitation ~~deficiency~~ of this pilot trial and may lead to a high drop-out rate. Each participant will be provided with 150 RMB as financial compensation to improve compliance. ~~We will solve this problem by providing participants with financial compensations and free moxibustion therapies after the completion of the entire trial.~~

This study is the major sub-project focusing on stroke recovery, which is sponsored and funded by the National Administration of Traditional Chinese Medicine of China. This protocol describes the first pilot randomized controlled trial evaluating the feasibility to conduct a research to assess the efficacy ~~curative effects~~ and safety of ginger-salt-indirect moxibustion on UUI after stroke. Results of this preliminary study will provide essential information for the design of subsequent large-scale trials. Further trials will focus on assessment of urodynamic parameters and evaluation of efficacy and safety of moxibustion on UUI after stroke.

Trial status

The trial is currently in the recruitment phase.

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Contributors LPW and HLL conceived this study and prepared the initial protocol. LLW drafted the manuscript and participated in design of the study. GXS, YY, LZ, TZ participated in revising the protocol. LZ plans for the statistical analysis. LPW and HLL made amendments of the trial protocol. All authors read and approved the final manuscript.

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Ethics approval Research ethics approval was attained from the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (ref: 2013BL-094).

Competing interests None.

Figure 1. Trial profile

Figure 2. Moxa cone moxibustion

Figure 3. Moxa box moxibustion

Figure 4. 72-hour frequency-volume chart

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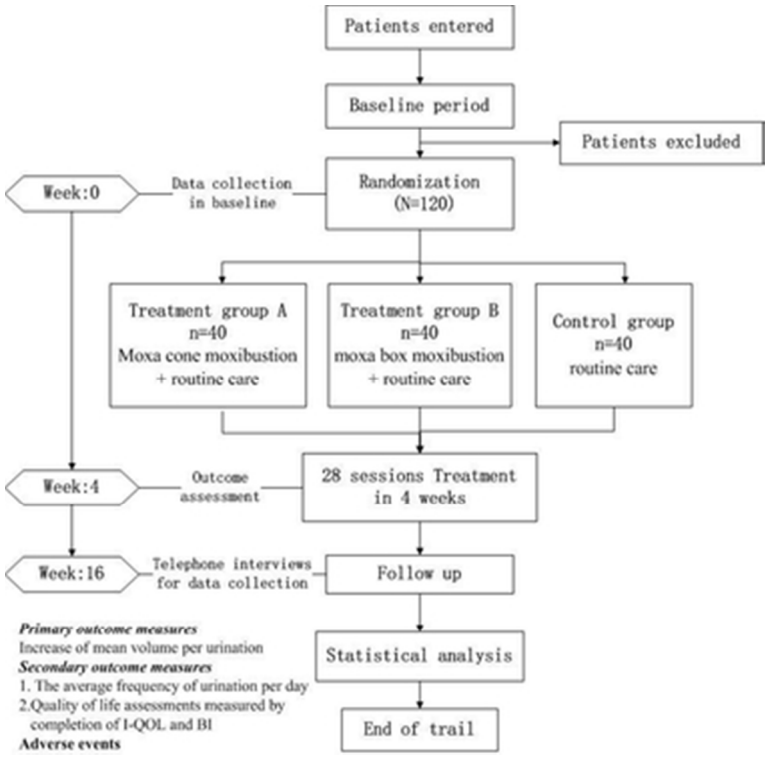

Figure1. Trail flowchart
32x31mm (300 x 300 DPI)

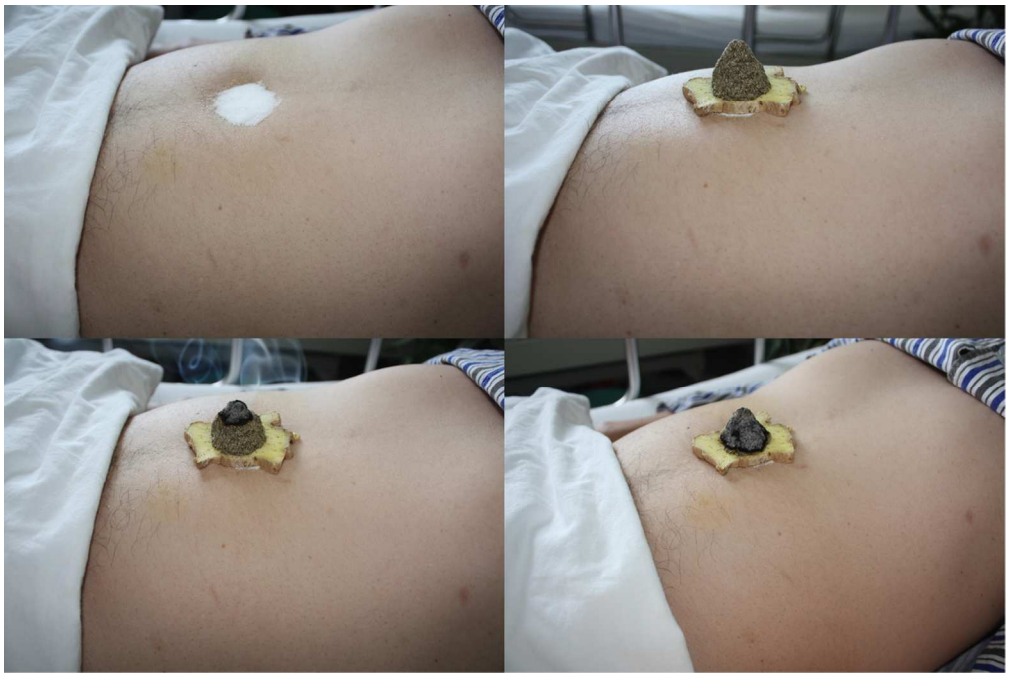

Figure 2. Moxa cone moxibustion
115x77mm (300 x 300 DPI)

Figure 3. Moxa box moxibustion
92x61mm (600 x 600 DPI)

72-hour frequency-volume chart

Date	Time (a.m/p.m)	Volume voided (ml)	urinary incontinence (tick in the blank)	notes

Figure 4. 72-hour frequency-volume chart
100x53mm (300 x 300 DPI)