This is the accepted version of the publication Chen H, Wang C, Zhou M, et al, Electroacupuncture for post-stroke overactive bladder: a multi-centre pilot randomized controlled trial Acupuncture in Medicine (2021;39(3)) pp. 175-183. © 2020 The Author(s) . DOI:10.1177/0964528420925488.

Electroacupuncture for post-stroke overactive bladder: A multi-center pilot randomized controlled trial

ABSTRACT

Background: Although acupuncture has been shown to be effective in treating stroke overactive bladder (OAB), no RCT examining the effects of acupuncture on patients with post-stroke OAB has been conducted. This study is to explore the effects of electroacupuncture in the treatment of post-stroke OAB.

Methods: This study was a multi-site randomized, assessor-blind, controlled trial of patients with post-stroke OAB. Thirty-four post-stroke subjects (mean age 71.0 years; 32.4% female) with OAB symptoms were randomly assigned to the electroacupuncture treatment group or the control group at a 1:1 ratio. The subjects in the treatment group were treated with 6 sessions of acupuncture for 4 weeks, while the subjects in the control group receive the usual care. The primary outcome measure was the Overactive Bladder Symptom Scale. Secondary outcome measures included a 3-day bladder diary and the Stroke Specific Quality of Life Scale (SSQoL).

Results: The electroacupuncture treatment group showed a moderate effect size on improving the perceived severity OAB symptoms as measured by the OABSS at week 5 (1 week posttreatment, effect size = 0.57, P = 0.034) and week 8 (4 weeks posttreatment, effect size = 0.60, P = 0.021), although the result became insignificant after Bonferroni correction. No significant differences in the bladder diary or SSQoL score were found. The electroacupuncture treatment was well tolerated by the post-stroke subjects.

Conclusion: The 6-session electroacupuncture treatment appears to reduce OAB symptoms in post-stroke patients. Further fully powered trials are warranted to confirm the efficacy of electroacupuncture for those with post-stroke OAB.

Trial registration number: NCT02568774

INTRODUCTION

Stroke is a devastating vascular neurological disease that can have both short and long-term complications.[1] Bladder dysfunction is common in stroke patients, with cases of overactive bladder (OAB) being more frequent than those of underactive bladder during the acute stage.[2 3] Voiding symptoms most often experienced after stroke include urgency, frequency and incontinence. The incidence of urinary incontinence can be as high as 28–40% for patients three months after suffering from stroke.[4] The causes of post-stroke OAB can be attributed to direct damage to the neuromicturition pathways caused by the stroke lesion, detrusor hyporeflexia with overflow incontinence, and impaired awareness after stroke.[5]

Current practices for managing OAB are quite limited. Interventions include behavioural training, such as pelvic floor exercises and pharmacological treatments with anti-muscarinic agents and neuro-modulation.[6] However, in many cases, pharmacological treatments are discontinued due to bothersome adverse effects such as dry mouth and constipation.[7] A surgical intervention with augmentation cystoplasty is the last resort, but the procedure is expensive and a long convalescence period is required.[6] Acupuncture, which is a major treatment modality of traditional Chinese medicine, has also been suggested to have a favourable therapeutic effect on OAB.

A number of randomized controlled trials (RCTs) examining acupuncture for OAB suggest a potential role of acupuncture as an alternative treatment to help improve OAB symptoms.[8] A recent meta-analysis of 10 RCTs involving a total of 794 patients with OAB found a significantly greater reduction in the number of 24-hour voiding episodes with the use of electroacupuncture (EA) compared to sham EA (mean difference (MD) 1.76). EA in combination with tolterodine was better than tolterodine alone at reducing the number of incontinence episodes (MD -0.56), increasing the maximum cystometric capacity (MD 44.05), and enhancing the quality of life (MD -1.35) of people with OAB. The results suggested that acupuncture could be a potentially effective treatment for the relief of OAB symptoms. However, none of the included RCTs focused on post-stroke patients.

Although acupuncture has been shown to be effective at treating OAB in general, no RCT examining the effects of acupuncture on patients with post-stroke OAB has been conducted.

Given the high incidence of OAB in post-stroke patients, potentially effective alternative treatments should be investigated. We therefore proposed a pilot RCT with rigorous methodology, adequate allocation concealment and validated outcome measures to explore the preliminary effects of acupuncture on those with post-stroke OAB and examine the feasibility of a future full-scale clinical trial.

Objectives

To explore the effects of acupuncture in the treatment of post-stroke OAB using a randomized, assessor-blind, controlled pilot trial design.

METHODS

Clinical trial design

This study was a multi-site, randomized, assessor-blind, controlled trial in patients with post-stroke OAB. Eligible subjects were randomly assigned to the EA treatment group or care as usual (CAU) group in a 1:1 ratio. Block randomization with a block size of 6 was performed by an independent researcher, using a computer-generated randomization list. The allocation codes were enclosed in sequentially numbered opaque envelopes and were only revealed after the subjects had completed all baseline assessments. Research ethics approval was obtained from the local institutional review boards (IRBs) of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW15-192), Hong Kong East Cluster Research Ethics Committee (HKEC-2015-63) and the Shanghai TCM-integrated Hospital, Shanghai University of TCM (2017-024-1). This study was prospectively registered at ClinicalTrials.gov on 6 October 2015 (ref. NCT02568774), and conducted and reported in accordance with the CONSORT[9] and STRICTA[10] guidelines.

Subjects

The subjects were recruited between October 2015 and June 2018 at the outpatient clinic of the Rehabilitation Unit of Tung Wah Hospital, the Department of Geriatrics and Rehabilitative Medicine of Tung Wah Eastern Hospital, Hong Kong and the Department of Encephalopathy, Shanghai TCM-integrated Hospital. Eligible subjects were: (1) Chinese aged 18 years or above; (2) suffering from their first ever stroke or from a recurrent stroke with no urinary symptoms

during previous episode(s); (3) presenting OAB symptoms, i.e. urgency, urinary frequency or urge incontinence, and an overactive bladder symptom scale (OABSS) score of ≥3, with the item for urgency rated as ≥2 points; (4) not taking any medication for OAB; (5) able to comprehend Chinese; and (6) not currently undergoing acupuncture or transcutaneous electrical nerve stimulation (TENS) treatment. Exclusion criteria were: (1) urinary retention with a post-void urinary volume of >100ml; (2) current urinary tract infection; (3) a pre-existing history of OAB or bladder outlet obstruction or underactive bladder; (4) significant cognitive impairment as indicated by a mini mental state test score of <20 or Saint Louis University mental status (SLUMS) score <20; (5) Alzheimer's disease, Parkinson's disease, spinal cord disorder or a progressive neurological disease such as multiple sclerosis; (6) active skin lesions or open wounds over the planned needle placement areas; (7) valvular heart defects, severe cardiac diseases, or bleeding disorders; (8) having been fitted with any kind of implanted electrical device such as a pacemaker, defibrillator or brain stimulator; (9) pregnancy; (10) malignancy at the sites of the selected traditional acupuncture points; and (11) having received acupuncture treatment 1 month before the baseline period.

Electroacupuncture treatment group

The subjects in this group lay supine and were needled at the "scalp reproduction area" and "motor area" of the unaffected side; afterwards, the subjects were told to lie on their unaffected side and then be treated bilaterally at traditional acupuncture points in the following sequence: BL32 (*Ciliao*), BL33 (*Zhongliao*), BL28 (*Pangguangshu*) and BL39 (*Weiyang*). A total of 12 needles were used. During the intervention, the practitioner inserted sterilized, disposable needles into the aforementioned traditional acupuncture points and elicited *de qi* if possible. The needles were inserted to a depth of 1 to 1.5 *cun* at all of the traditional acupuncture points except for BL32 and BL33, which were needled to a depth of 3 *cun*. Next, an electrical stimulator (AWQ 104L, Electronic Acupunctoscope, Hong Kong) was connected to the needles and used to deliver a constant-current, 0.4-ms, square-wave, brief-pulse stimulus of 4-Hz frequency to the subjects. The needles were left for 20 min and then removed. After the removal of the needles, the auricular traditional acupuncture points *Urinary Bladder* and *Uterus* on each side were needled alternately using disposable, sterile, 0.2-mm-long thumbtack needles, which were inserted, adhered to the point locations and retained until they were replaced during the following visit.

These traditional acupuncture points, stimulation at which has historically been used to treat OAB, were selected according to a review by Xu et al.[11] and expert opinion. The subjects were treated with acupuncture for 4 weeks (twice a week for the first 2 weeks and once a week for the third and fourth weeks, i.e. 6 treatments in total). The frequency and treatment schedule were determined by our team's senior acupuncturists. A registered Chinese medicine practitioner with at least 5 years of experience delivered the acupuncture treatment.

Care as usual group

The subjects in the CAU group did not receive acupuncture treatment; rather, they received the usual conventional rehabilitation provided by the hospital, which included standard physiotherapy, bladder training and general advice on the intake of fluids. For compensation, they were offered the same acupuncture treatment after the end of the study period.

Assessment

The subjects in both groups were assessed a total of seven times: at baseline, week 1, week 2, week 3, week 4, week 5 (1-week post-treatment) and week 8 (4-week post-treatment). The period covered the short-term and medium-term effects of the intervention. The investigators who performed the assessment and analysis were blinded to the treatment allocation. The acupuncturists who delivered the treatment did not participate in data collection or entry.

The primary outcome was the severity of the OAB symptoms measured by the OABSS scale. The OABSS is a four-item questionnaire that quantifies overactive bladder symptoms in a single score.[12] The OABSS was originally developed by bilingual Japanese urologists, concurrently in both Japanese and English. A validated Hong Kong Chinese version of the OABSS was adopted.[13] The test-retest reliability (Pearson's r) of the Hong Kong Chinese version of the OABSS was 0.82, and moderate to high construct validity was shown with other measures, including the number of episodes of micturition (r=0.422), incontinence (r=0.406) and urgency (r=0.298) in a 3-day micturition diary, with r=0.283 for total international prostate symptom score (IPSS) and r=0.516 for patient perception of bladder control (PPBC) score.

Secondary outcome measures

The number of urgency episodes, voiding episodes and incontinence episodes over three days were recorded using a bladder diary.[14] The subjects were asked to keep a 3-day bladder diary at baseline, week 5 and week 8. The subjects recorded the frequency of day- and night-time voiding and incontinence episodes over a 3-day period. Bladder diaries are commonly used to assess treatment outcomes in both clinical practice and research studies of OAB.[15 16] However, on the Shanghai site, the research personnel found that it was not feasible to collect the bladder diaries because many subjects encountered difficulties recording their voiding patterns, even after having been provided with instructions and a briefing from our research personnel. Thus, there were many missing values in the bladder diaries collected at the Shanghai site and the data were therefore not considered to be valid. For the Hong Kong sites, the subjects could fill in their incontinent episodes, urgency episodes and number of voids, but the majority of the subjects failed to make a reliable estimation on their voided volumes. Therefore, data on incontinence episodes, urgency episodes and number of voids from the bladder diaries were only available from the Hong Kong site.

The subjects' quality of life was assessed using the Chinese version of the stroke specific quality of life scale (SS-QoLS)[17] at baseline, week 5 and week 8. The SS-QoLS is a 49-item self-reported scale. Performance was scored on a 5-point Likert scale to indicate the amount of help required to complete a task (from total help to no help needed), the amount of trouble experienced when performing a task (from could not do it at all to no trouble at all) or the level of agreement with a statement about functioning (from strongly agree to strongly disagree). Higher scores indicate better function.

Sample size estimation and statistical analysis

For the pilot study, it was suggested that a sample of 12 would provide sufficient methodological experience and a reasonable estimation of effect size to conduct a fully powered study.[18] Assuming a dropout rate of 20%, 15 subjects per group were needed (total 30 subjects). All data were entered and analysed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). A linear mixed-effects model was used to compare the between-group differences in OABSS scores and the secondary outcomes of the two groups by time point (from baseline to week 8) interaction effect. An intention-to-treat analysis was conducted and the mixed-effects model, assuming a random effect, was used to deal with

missing data. Bonferroni correction was used to adjust multiple comparisons (six time points) in the primary outcome measure with a conservative threshold of $P < 0.0083$. The between-group effect size (ES) was computed according to Cohen's *d*, with the difference in means divided by the pooled standard deviations.[19]

RESULTS

All of the enrolled participants received face-to-face screening for eligibility, and 34 subjects were randomized (Figure 1). Three subjects in the acupuncture group withdrew (18.8%) due to needle site pain (n = 1, 6.3%) and two were lost to follow-up (n = 2, 12.5%). Two subjects in the care as usual group (11.1%) withdrew their consent. Table 1 shows that the recruited subjects were mainly male (67.6%) with a mean age of 71.0 years (SD = 12.9). The mean baseline OABSS score was 6.1 (SD = 2.6).

Table 1. Socio-demographic and clinical characteristics of the subjects

Variables [a]	Whole sample (n=34)	Electroacupuncture group (n=16)	CAU group (n=18)
Age, years	71.0 ± 12.9	73.3 ± 12.9	68.9 ± 12.8
Female, %	11 (32.4)	6 (37.5)	5 (27.8)
Recruitment site			
Hong Kong	20 (58.8)	9 (56.3)	11 (61.1)
Shanghai	14 (41.2)	7 (43.8)	7 (38.9)
Marital status, % [b]			
Single/widowed	5 (15.2)	2 (13.3)	3 (16.7)
Married	28 (84.8)	13 (86.7)	15 (83.3)
Education level, % [b]			
Primary education or below	15 (45.5)	7 (46.7)	8 (44.4)
Secondary education or above	18 (54.5)	8 (53.3)	10 (55.6)
Employment status, % [b]			
Employed	5 (16.1)	3 (20.0)	2 (11.1)
Retired/unemployed/housewife	26 (83.9)	12 (80.0)	16 (88.9)
Duration of post-stroke interval, months	25.7 (23.7)	24.6 (29.1)	26.7 (18.3)
Bladder diary [b]			
Urgency episodes	20.3 ± 10.8	24.0 ± 8.2	17.2 ± 12.0
Incontinence episodes	0.4 ± 0.7	0.3 ± 0.7	0.4 ± 0.8
Frequency of voids	28.0 ± 7.3	28.1 ± 5.7	27.9 ± 8.7
OABSS, 0-15	6.1 ± 2.6	6.1 ± 2.7	6.1 ± 2.6
SSQoL, 0-60	39.6 ± 8.9	39.7 ± 8.1	39.6 ± 9.9

Abbreviations: CAU, care as usual; OABSS, overactive bladder symptom scale; SSQoL, stroke specific quality of life scale.
[a] Data are presented as mean ± standard deviation or number (%).
[b] Different from total "n" due to missing data / refusal to answer.

Primary outcome - severity of overactive bladder symptoms

Table 2 shows the OABSS scores across the study time points. Compared with the control group, the acupuncture group experienced a significantly greater reduction in OAB symptoms at week 5 (ES = 0.57, P = 0.034) and week 8 (ES = 0.60, P = 0.021). However, the differences were not significant after the application of the Bonferroni correction for multiple comparisons.

Table 2. Primary outcomes across study time points

Outcomes	Electroacupuncture group (n=16)	CAU group (n=18)	*P* value[a]	Between-group effect size (95% CI)
	Estimated mean ± SE	Estimated mean ± SE		
OABSS				
Baseline	6.1 ± 0.61	6.1 ± 0.57		
Week 1	5.5 ± 0.61	5.7 ± 0.57	0.71	0.08 (-0.59, 0.75)
Week 2	4.7 ± 0.61	5.6 ± 0.57	0.16	0.37 (-0.32, 1.04)
Week 3	5.3 ± 0.62	5.2 ± 0.58	0.87	-0.04 (-0.71, 0.63)
Week 4	4.9 ± 0.62	5.2 ± 0.58	0.63	0.12 (-0.56, 0.79)
Week 5	4.2 ± 0.62	5.6 ± 0.58	0.034	0.57 (-0.13, 1.24)
Week 8	4.1 ± 0.62	5.6 ± 0.59	0.021	0.60 (-0.10, 1.28)
SSQoL				
Baseline	39.7 ± 2.39	39.6 ± 2.25		
Week 5	41.2 ± 2.40	39.9 ± 2.27	0.25	0.14 (-0.54, 0.81)
Week 8	40.1 ± 2.42	40.4 ± 2.27	0.73	-0.03 (-0.70, 0.64)

Abbreviations: CAU, care as usual; OABSS, overactive bladder symptom scale; SE, standard error; SSQoL, stroke specific quality of life scale.
[a] *P* value for the group by time interaction of the mean score using linear mixed-effects models.

Secondary outcomes

No differences were seen between the acupuncture group and the CAU group in SSQoL scores across the study time points (Table 2). Nor were significant differences observed in their

frequency of voiding, urgency episodes and incontinence episodes at week 5 and week 8 (all $p > 0.05$, Table 3).

Table 3. Secondary outcomes across study time points

Outcomes	Electroacupuncture group (n=9) [a]	CAU group (n=11) [a]	*P* value [b]	Between-group effect size (95% CI)
	Estimated mean ± SE	Estimated mean ± SE		
No. of incontinence episodes / 3 days				
Baseline	0.33 ± 0.21	0.36 ± 0.19		
Week 5	0.48 ± 0.22	0.17 ± 0.20	0.29	-0.47 (-1.34, 0.44)
Week 8	0.11 ± 0.22	0.26 ± 0.21	0.74	0.22 (-0.67, 1.09)
No. of urgency episodes / 3days				
Baseline	24.00 ± 3.91	17.18 ± 3.53		
Week 5	17.03 ± 4.06	13.19 ± 3.78	0.57	-0.31 (-1.18, 0.59)
Week 8	21.82 ± 4.11	11.65 ± 3.85	0.59	-0.81 (-1.69, 0.14)
No. of voids / 3 days				
Baseline	28.11 ± 3.31	27.91 ± 2.99		
Week 5	24.69 ± 3.35	26.72 ± 3.07	0.41	0.20 (-0.69, 1.07)
Week 8	24.11 ± 3.31	25.49 ± 3.07	0.66	0.14 (-0.75, 1.01)

Abbreviations: CAU, care as usual; SE, standard error

[a] Data were only available on the subjects recruited from the Hong Kong site (n = 20)

[b] *P* value for the group by time interaction of the mean score using linear mixed-effects models.

Adverse events

Five adverse events were reported which included: numbness (n = 1, 2.9%), pain at needle sites (n = 1, 2.9%), cramping (n = 1, 2.9%), vomiting (n = 1, 2.9%) and low back pain (n = 1, 2.9%). One subject complained of needle pain and withdrew from the study at week 2. However, all of the reported adverse events were mild in severity and resolved spontaneously. The frequency of adverse events did not significantly differ between the two groups ($p > 0.05$). Two serious adverse events were reported in the EA treatment group; one subject was hospitalized due to drooping of eyelids and hyperglycemia during the intervention period (week 3); another was hospitalized after fainting during the follow-up period (week 5). These two serious adverse events were not considered to have been caused by the EA treatment.

Sample size estimation for further trials

The effect size of the difference in OABSS at week 5 (1-week post-treatment) was 0.57 and at week 8 (4-week post-treatment) was 0.60. The effect size estimated in this study suggested that a sample size of at least 50 in each group would be needed to detect between-group differences in OABSS scores at week 5 with a power level of 80%.

DISCUSSION

This is the first multi-site RCT to examine the effects of EA on OAB symptoms in post-stroke patients. We have demonstrated that a six-session electroacupuncture intervention was feasible in post-stroke patients with OAB. The preliminary evidence suggested that the EA treatment produced a moderate positive effect on perceived severity of OAB symptoms as measured by the OABSS at 1 week and 4 weeks post-treatment, although it became insignificant after Bonferroni corrections and therefore could represent a chance observation related to multiple testing. Given the small sample size of this pilot trial, no significant differences in bladder diary or SSQoL score were found. The EA treatment was well tolerated by the post-stroke subjects.

The preliminary evidence suggested that acupuncture might have moderate beneficial effects on overall OAB symptoms as measured by the OABSS. Previous studies on OAB symptoms in post-stroke patients are scarce. However, our findings are in line with those of previous studies of OAB in female subjects, which showed that acupuncture was able to relieve OAB symptoms.[14 20] The absence of a statistically significant difference in the quality of life outcome is inconsistent with past findings by Aydogmus et al.[20] One explanation for the discrepancy in the findings is that, apart from a lack of power due to the small size of our pilot study, our sample consisted of older, post-stroke subjects. The factors affecting their quality of life are likely to be multi-factorial and more complex than those for younger subjects, i.e. their quality of life might not have improved dramatically after relief of their OAB symptoms. Nevertheless, our results demonstrated that acupuncture was feasible when applied to a sample of post-stroke patients consisting of a high proportion of male subjects.

The mechanism underlying the effects of acupuncture on OAB is not fully understood.[8] The traditional acupuncture points selected for this study were located around the sacral region. They included: BL28, located paravertebrally from the second sacral foramina; and BL32 and BL33, located near the second and third sacral foramina, respectively. In both clinical and animal studies, it was discovered that acupuncture at these locations can increase bladder capacity and

suppress bladder overactivity.[21-23] A clinical study found that sacral (S3) segmental nerve stimulation decreased voiding frequency in incontinent patients with detrusor instability.[24] Our intervention involved deep needling, together with electrical stimulation, at BL32 and BL33, during which the needles were inserted close to the second and third sacral nerve roots. Therefore, our intervention may act similarly to sacral segmental nerve stimulation and stimulate the somatic afferent in the pudendal nerve to elicit inhibitory mechanisms.

We found that it was not always feasible to use a bladder diary with post-stroke patients. Data from this source were only available from the subjects recruited from the Hong Kong site, but still the voided volume was not adequately reported by the subjects. The subjects at the Shanghai site failed to properly fill in their diary, especially regarding information on voided volumes. Although we tried to instruct the subjects or their caregivers to fill in the diary, they either did not return the diary or returned it with blank pages. Eventually, the coordinator in the Shanghai site deemed it unfeasible to use the bladder diary. The failure to collect bladder diaries can probably be attributed to the older age and relatively lower levels of education of the subjects on the Shanghai site. Emmons et al. encountered a similar situation; in their acupuncture trial of OAB in women, 15% of the subjects failed to complete the diary.[14] The keeping of an electronic diary using a smartphone app might provide a solution to the poor completion rates for traditional pen-and-paper diaries.[25] These apps are usually implemented with a friendly interface and involve an interactive component, which may help the subjects to complete the diary and hence boost compliance rates.[26]

Limitations

This study had several limitations besides a small sample size. First, the trial was limited by its open-label design, meaning that the subjects were aware of their allocation. The subjects in the CAU control group may have experienced the nocebo effect due to their disappointment in not being treated.[27] This may have resulted in an overestimation of the effect of the intervention. Therefore, in an attempt to minimize the nocebo effect as much as possible, we offered the CAU patients the same treatment as those in the treatment group after they had completed the study. Second, the subjects were recruited through posters in the hospitals. They might have had higher expectations of the acupuncture treatment and, hence, a better treatment response than patients recruited through other means,[28] although it has been put forward that the response to

acupuncture is difficult to predict.[29 30] Further studies could include a measure of the subjects' expectations of the treatment. Third, we did not exclude those with prostate diseases, which may have increased the heterogeneity of the sample. Since most of the post-stroke patients were of older age and are vulnerable to prostate diseases, excluding those with prostate diseases may have decreased the generalizability of the findings. However, we included only those who developed OAB symptoms after the stroke episode, therefore their urinary problems are more likely to have been due to the post-stroke OAB. Finally, the study relied on subjective measures, but was limited by the lack of an objective urodynamic measure such as uroflowmetry, post-void residual measurements or cystometric testing. The use of an objective measure would enhance the validity of the findings, especially given the difficulties of administering a subjective bladder diary in an elderly group. As mentioned before, the compliance of filling the bladder diaries was rather poor, resulting in there being no reliable bladder diary data from the Shanghai site.

In conclusion, our pilot study suggested that a six-session EA treatment was feasible and well tolerated in post-stroke patients. Our preliminary finding suggested that EA treatment might have a beneficial effect on OAB symptoms in post-stroke patients. Further fully powered trials are warranted to confirm the efficacy of EA for post-stroke OAB.

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