Clinical Trial/Experimental Study

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Effectiveness and safety of moxibustion for alleviating symptoms of overactive bladder

A prospective, randomized controlled, crossover-design, pilot study

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Abstract

Background: This study aimed to evaluate trial feasibility and explore the potential efficacy and safety of moxibustion in the treatment of overactive bladder (OAB).

Method: A randomized, controlled, cross-over, assessor blinded design was used. This study was conducted in an outpatient department of a university hospital in Republic of Korea. The overall study period was 8 weeks. Participants were randomly allotted to either Group A or Group B. Group A participants underwent 8 to 12 sessions of moxibustion with behavioral training during the first 4 weeks, while the Group B participants received behavioral training only. Over the next 4 weeks, the treatment offered to the 2 groups was reversed (Group A participants received behavioral training only, while Group B participants underwent the moxibustion session with behavioral training). The OAB-validated 8-question awareness tool (OAB-V8), OAB symptom scores (OABSS), visual analog scale (VAS) for lower urinary tract symptoms, and frequency voiding chart were used to assess outcomes. For analysis, we used effect size, measured as Hedge's *g*, to present descriptive results indicating the actual difference between the groups.

Results: Compared to that in Group B, the Hedge's *g* of OAB-V8 for the former 4 weeks in Group A was −0.248, that of OABSS was −1.531, and that of VAS was −0.713. During the latter 4 weeks, Group B showed similar effect with $g = 0.465$, 1.207, and 0.427 for OAB-V8, OABSS, and VAS, respectively, compared to Group A. The portion of nocturnal voiding volume decreased ($g = -0965$), the mean voiding volume increased ($g = 0.690$), and the voiding frequency decreased ($g = -0.498$) with moxibustion.

Conclusions: Moxibustion might be considered as an alternative for OAB. A full-sized randomized controlled trial may be feasible with minimal modification in outcome measures and comparator population.

Other information: This clinical trial has been registered on clinicaltrials.gov (NCT02271607).

Abbreviations: ADLs = activities of daily living, AEs = adverse events; ANS = autonomic nervous system, BT = body temperature, CONSORT = consolidated standards of reporting trials, DBP = diastolic blood pressure, DITI = digital infrared thermal imaging, FVC = frequency-volume chart, ICI = inter-contraction interval, IPSS = international prostate symptoms score, IRB = Institutional Review Board, ITT = intention-to-treat, KHQ = King's health questionnaire score, KMD = doctor of Korean medicine, LUTS = lower urinary tract symptoms, MI = multiple imputation, NGF = neural growth factor, OAB = overactive bladder, OABSS = OAB symptom scores, OAB-V8 = OAB-validated 8-question awareness tool, PPS = per-protocol-set, PR = pulse rate, QoL = quality of life, SBP = systolic blood pressure, sd = standard deviation, STRICTA = standards for reporting interventions in clinical trials of acupuncture, UA = urine analysis, UTI = urinary tract infection, VAS = visual analog scale.

Keywords: CV4, lower urinary tract symptoms, LR3, moxibustion, overactive bladder, SP6

Editor: Giovanni Tarantino.

Declarations: Ethics approval and consent to participate: This study was approved by the institutional review board (IRB) of Pusan National University Korean Medicine Hospital (IRB No. 2014005).

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors have no funding and no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:34(e12016)

Received: 22 April 2018 / Accepted: 31 July 2018

http://dx.doi.org/10.1097/MD.0000000000012016

1. Introduction

Overactive bladder (OAB) is defined as "having urgency with or without urgency incontinence in the absence of urinary tract infection (UTI) or other obvious causes" by the International Continence Society.[1] The prevalence of OAB in South Korea has been reported to be 12.2% in a 2006 study involving 2,000 individuals; with regard to gender, 10.0% of men and 14.3% of women had OAB. The major symptoms of OAB are urinary frequency during night and urinary urgency, with or without urgency incontinence.[2,3]

Behavioral training is generally recommended as a first step in the management of OAB along with pharmacological therapy. This behavioral training includes bladder training, bladder control strategies, pelvic floor muscle training, and fluid management. Pharmacological treatments, mainly anti-muscarinics, are advised when behavioral training fails to improve symptoms.[4,5] Anti-muscarinics inhibit acetylcholine receptors, which play a role in bladder hypersensitivity and detrusor muscle over-activity.[4,6,7] However, side effects of anti-muscarinic use including dry mouth, constipation, dry eyes, blurred vision, dyspepsia, UTI, urinary retention, or cognitive function decline have been reported. Further, studies have revealed that "side effect" or "no effect" were the main reasons for not opting for conventional treatment, indicating that side effects and other limitations impede the continuation of conventional treatments, even though the side effects are not life-threatening.[5,8]

The symptoms of OAB can lead to a depressive mood and decreases in productivity, confidence, and sexual satisfaction, thereby reducing quality of life (QoL).[9,10] Although there are several management options available for OAB, only 27% of patients are reported to have received treatment for OAB.[11] This may reflect the need for more effective and safe alternative treatments that could alleviate OAB symptoms.

Moxibustion has been traditionally used for alleviating various lower urinary tract symptoms (LUTS) in Asian countries.[12,13] A prospective, single group study revealed that a combination of acupuncture, moxibustion, and herbal medication was effective in alleviating symptoms and reducing urinary frequency associated with OAB.[14] Several other studies have reported similar outcomes in different conditions. Yun et al[15] reported that moxibustion on cervical vertebrae 3, 4 and 6 (CV3, CV4, and CV6) was associated with significant improvement in poststroke urinary disability. Moxibustion and acupuncture were also useful in alleviating LUTS in chronic prostatitis[16] and female urethral syndrome,[17] and in improving poststroke urinary incontinence.[18]

Studies evaluating the efficacy of moxibustion alone for the management of OAB are not widely available. However, studies on the use of acupuncture for the management of OAB can be used as a reference because moxibustion and acupuncture are based on the common principle of stimulating acupuncture points to gain therapeutic benefit. Kitakoji et al[19] reported that acupuncture on BL33 increased maximum bladder capacity and bladder compliance, while Zhang et al[20] reported that compared to sham-electroacupuncture, electroacupuncture on BL32, BL33, and BL34 improved OAB symptoms including the first sensation of bladder filling, first urge to void, and maximum cystometric capacity. Some preclinical studies reported that stimulation of SP6 can prolong the intercontraction interval (ICI) in rats with OAB[21] and decrease c-Fos expression in certain specific areas of brain[22] wherein c-Fos expression increases in response to bladder stimulation.[23,24]

Traditional medical approaches that stimulate acupuncture points have been widely used for treating urinary disturbance, and thus, based on previous studies, moxibustion can be regarded as an alternative for OAB management. Therefore, we planned a pilot randomized controlled trial to assess trial feasibility, possible effectiveness, and safety of moxibustion for OAB management.

2. Methods

2.1. Study design

This was a pilot clinical trial investigating the feasibility, effectiveness, and safety of moxibustion for OAB management. We adopted a prospective, randomized, controlled, 1:1 allocated, assessor-blinded, and crossover design. This study was conducted in an outpatient department of a university hospital in South Korea from September 2014 to October 2015. Twenty-eight participants with OAB were registered and assigned to either Group A or Group B; each group included 14 participants.

Behavioral training was provided to both groups during the 8-week study period. For the initial 4 weeks, Group A participants underwent 8 to 12 sessions of moxibustion with behavioral training, and Group B participants received behavioral training only. Over the next 4 weeks, the treatment was reversed between the groups.

2.2. Ethical review

The study was approved by the Institutional Review Board (IRB) of Pusan National Korean Medicine Hospital (PNUKH, IRB No. 2014005) and has been registered on clinicaltrials.gov (NCT02271607). This clinical trial was conducted and reported in compliance with the consolidated standards of reporting trials (CONSORT) 2010 guidelines.

2.3. Recruitment

Information for recruiting participants to the clinical trial was posted on a notice board at the research institute and on the institute webpage. Flyers containing information about the trial were also distributed with newspapers. We explained the details of the clinical trial and provided written information to participants who willingly volunteered to participate, and asked these participants to provide written consent if they agreed to enrol in the trial. The enrolled participants were evaluated for eligibility based on medical history, physical examination, questionnaires, and urine analysis (UA). Participants who finally registered in the trial were randomly allocated to either Group A or B. The CONSORT flowchart can be found in the flow diagram.

2.4. Participants

This study was conducted in a university hospital located in Yangsan, South Korea. Participants who were aged between 20 and 75 years, were diagnosed with OAB and had OAB symptoms for $\geq$3 months, were able to identify the hot sensation of moxibustion promptly and exactly, and provided written consent were included in the pilot study. Participants who had any malignancy; were diagnosed with obstructive disease of urinary tract, cystocele, vaginocele, rectocele, or diabetes mellitus; had sensory disturbance, communication problems due to cognitive

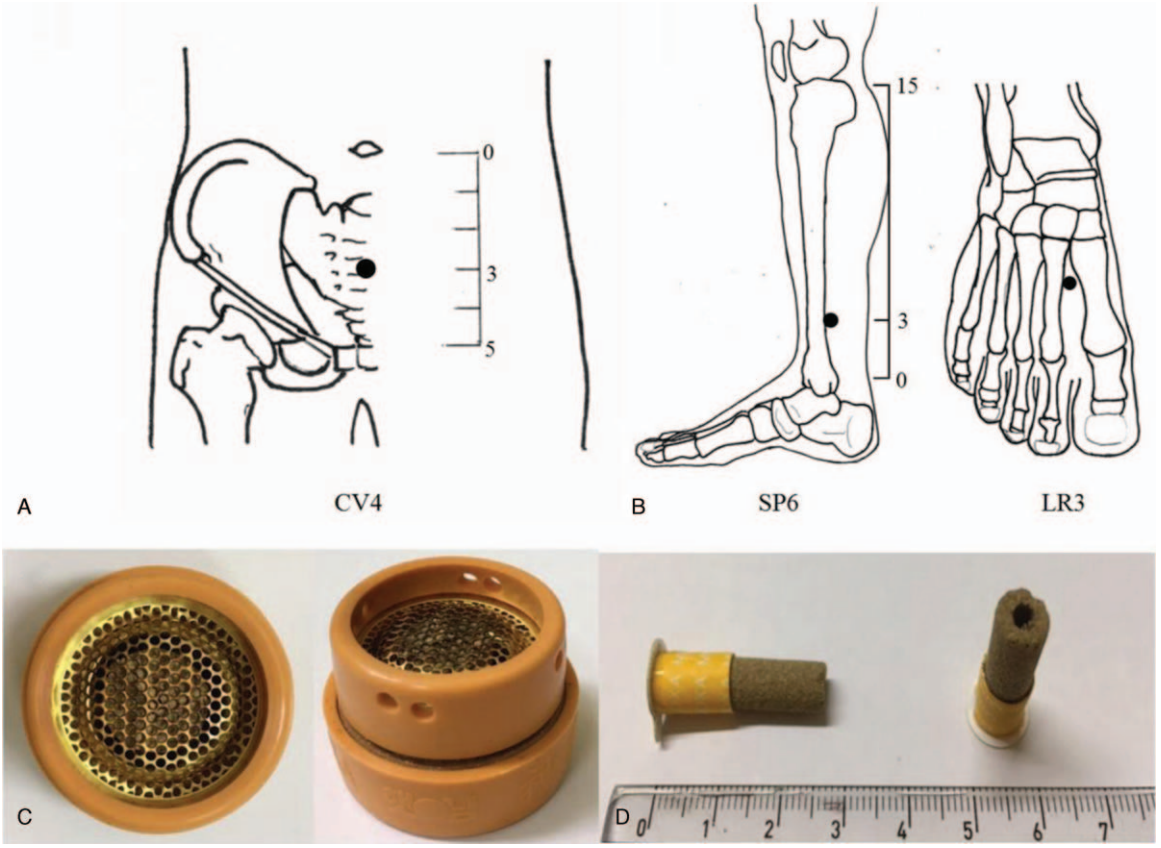

Figure 1. Location of the acupuncture points. (A) The location of CV4; (B) the location of SP6 and LR3; (C) an apparatus type moxibustion (Haitnim device with moxa pillar); (D) an indirect moxibustion stick (Kanghwa mini-moxa).

dysfunction or severe psychiatric illnesses; had systemic disease demanding active treatments; or were currently receiving any other treatment for OAB were excluded from the study. Participants in whom UTI was noted following UA or those who were pregnant or planning a pregnancy were also excluded.

2.5. Interventions

Apparatus-type moxibustion on CV4 (located 7.5 cm inferior to the center of the umbilicus on the anterior median line) and indirect moxibustion on SP6 (located 7.5 cm superior to the prominence of the medial malleolus posterior to the medial border of the tibia on the tibial aspect of the leg) and LR3 (located on the dorsum of the foot, between the 1st and 2nd metatarsal bones, in the depression distal to the junction of the bases of the 2 bones, over the dorsalis pedis artery) were conducted during the treatment sessions (Fig. 1A and B). These points were selected according to clinical use,[12,13] preclinical studies,[21,22,24,25] and previous clinical studies.[14,26,27] The treatment was carried out in 2 to 3 sessions per week, leading to a total of 8 to 12 sessions over a period of 4 weeks. The details of moxibustion can be found in the revised standards for reporting interventions in clinical trials of acupuncture (STRICTA), but the terms "acupuncture" and "needle" have been changed adequately for moxibustion[28] (Additional file 1, http://links.lww.com/MD/C417).

2.5.1. Intervention for Group A. Patients in Group A received moxibustion therapy and behavioral training for the first 4 weeks and only behavioral training for the next 4 weeks.

We employed indirect moxibustion and apparatus-type moxibustion in our study. Moxibustion treatment was conducted by a licensed doctor of Korean medicine (KMD) with >2 years of clinical experience.

The moxibustion apparatus comprises a moxa pillar, which is located within a device (Haitnim-moxa; Bosungsa, Incheon, South Korea) (Fig. 1C). Apparatus-type moxibustion was performed on CV4 for about 30 minutes with the patient in a supine position during each session. Indirect moxibustion on bilateral LR3 and SP6 was performed with the Kanghwa mini-moxa of the "lowest" intensity (Ehwadang, Seoul, South Korea) (Fig. 1D), for 1 to 7 times, per session. The number of times moxibustion was repeated on each acupuncture point varied depending on the patients' ability to tolerate the temperature of the moxibustion device. Indirect moxibustion was ceased either when the moxa cone was completely burned and the fire went out or when the participants asked for it to be removed (when the temperature became intolerable). Indirect moxibustion was not repeated on the points where the temperature was reported to be intolerable by the participants. Repeated application of indirect moxibustion was carried out only on the acupuncture points where participants did not express any intolerance to the temperature during the previous application. This course was repeated up to 7 times on each acupuncture point.

During subsequent sessions, the previously treated acupuncture points were assessed, and moxibustion was performed only on acupuncture points that had no signs of a burn.[12]

Behavioral training included instructions related to scheduled voiding and bladder training (gradually increasing the time

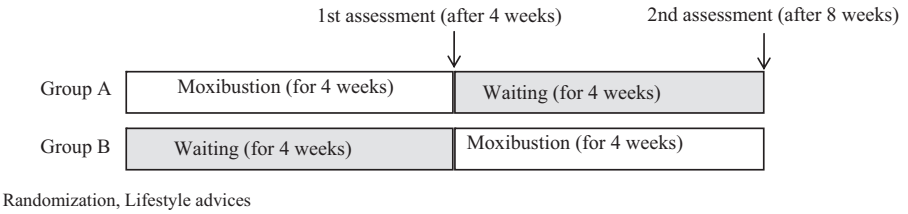

Figure 2. Treatment courses of each group.

between bathroom visits). The participants were also asked to avoid coffee, tea, alcohol, soda, artificial sweeteners, chocolate, and spicy foods.

All treatments for OAB including pharmacological treatment (such as propiverine, oxybutynin, flavoxate or imipramine) and nonpharmacological treatment (such as electric-stimuli, extracorporeal magnetic stimulation) were monitored during the study period.

2.5.2. Intervention for Group B. Group B received only behavioral training for the first 4 weeks and underwent moxibustion and behavioral training for the next 4 weeks. Moxibustion therapy was provided in the same manner as in Group A.

The course of treatment for both groups is shown in Figure 2.

2.6. Outcomes

The overactive bladder-validated 8-question awareness tool (OAB-V8)[29–31] and OABSS[32–34] were administered at baseline (T1) and at 4 weeks (T2) and 8 weeks (T3) after randomization. The visual analog scale (VAS), a scale for patient-reported outcomes regarding subjective symptoms,[35] was used to assess LUTS once every 2 weeks. The patients were instructed to record the frequency-volume chart (FVC)[36,37] for a period of 3 days before the T1 and T2 visits. Adverse events (AEs) were evaluated at every visit. The surface temperature at CV4 was evaluated at T1, T2, and T3, with a medical thermograph (IRIS-XP; Medicore, Seoul, South Korea), which can measure temperature in 0.1°C increments through digital infrared thermal imaging (DITI).[38,39] Participants were prohibited from taking a shower or applying a hot bag, an ice bag or lotion, on the day of evaluation or from consuming alcohol or caffeine or from smoking within 24 hours of the treatment session. The room where the medical thermograph test was performed was maintained at a temperature of 20–25°C, with 50% to 70% humidity. The schedule for intervention and outcome measurement can be found in Table 1.

2.7. Sample size

This was a pilot study aimed at determining feasibility and effect size but not for testing any hypotheses. Thus, the sample size was calculated based on the number of participants available for enrolment but not based on the statistical power. We are certain that this sample size exceeded the minimum sample size required

Table 1

Schedule for intervention and outcome measurement.

		moxibustion+behavioural training (Group A); behavioural training (Group B)				behavioural training (Group A); moxibustion+behavioural training (Group B)												
Week	**-1**	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**
Visit	**Group A**	**1**	**2–3**	**4**	**5–6**	**7**	**8–9**	**10**	**11–12**	**13**‡	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**14**§
	Group B	**1**	**–**	**–**	**–**	**–**	**–**	**–**	**–**	**2**	**3–4**	**5**	**6–7**	**8**	**9–10**	**11**	**12–13**	**14**§
Consent/Eligibility	◐																	
Vital sign	◐	◐	○	○	○	○	○	○	○	◐	●	●	●	●	●	●	●	◐
Randomization		◐																
Lifestyle advice		◐																
Moxibustion		○	○	○	○	○	○	○	○	●	●	●	●	●	●	●	●	
DITI		◐								◐								◐
Adverse events		○	○	○	○	○	○	○	○	◐	●	●	●	●	●	●	●	◐
Urine analysis	◐																	
FVC distribution	◐*	◐†																
FVC collection		◐*								◐†								
VAS		◐		○		○		○		◐		●		●		●		◐
OAB-V8		◐								◐								◐
OABSS		◐								◐								◐
Completion																		◐

DITI = digital infrared thermal imaging, FVC = frequency-volume chart, OABSS = overactive bladder symptom scores, OAB-Validated 8-question Awareness Tool, VAS = visual analog scale. ○, Group A; ●, Group B; ◐, both of Group A and Group B.

* Distributed on the screening day and collected on visit 1.

† Distributed on visit 1 and collected after 4 weeks.

‡ 3–5 days after visit 12 in Group A.

§ 3–5 days after visit 13 in Group B or 8 weeks after visit 1 in Group A.

for a pilot study; thus, the effect size, average, and standard deviation would be reliable.[40] Accordingly, we planned to enroll 15 participants for each group, adding up to a total of 30 participants.

2.8. Random sequence generation and allocation concealment

An independent researcher who did not participate in the intervention, assessment, and data analysis, generated the random sequence by using the website sealedenvelope.com. The allocated group was noted on a sheet of paper, which was placed within a double-opaque envelope that was then sealed. A KMD, who was in charge of intervention, opened the allotted sealed envelope in front of each participant to identify the allocated group and proceed with the intervention accordingly.

2.9. Blinding

Although participants and the practitioner were not blinded, the assessors including those who were involved in checking vital signs, in the DITI, and in the UA, as well as the statistician, were blinded. The participants were instructed to complete the patient-reported outcome charts independently.

2.9.1. Data presentation and statistical analysis. Continuous data were presented as mean ± standard deviation (sd), while categorical data were presented as number and percentage. Statistical analyses were performed according to the intention-to-treat (ITT) principal. Per-protocol-set (PPS) analysis was also performed and is presented as an additional file, http://links.lww.com/MD/C417. Multiple imputation (MI) approach was used to replace the missing data. The PPS included participants who received at least 80% of the intervention, were evaluated for all outcome measures, and did not have any significance violations during the trial. The FVC of only those participants who reported as directed (at the baseline and 4 weeks later, during 3 days for each time) were analyzed.

Clinical outcomes were evaluated at recruitment (T1, baseline), after 4 weeks (T2), and after 8 weeks (T3). The changes noted at T2 relative to T1, indicated the therapeutic effect of moxibustion in Group A compared to the waiting-list participants in Group B. The changes between T3 and T2 indicated the therapeutic effect of moxibustion in Group B and the prolonged effect of moxibustion in Group A. The changes between T3 and T1 indicated the therapeutic effect along with the prolonged effect in Group A and the effect of delayed treatment in Group B.

We used Hedge's g to compare differences between the 2 groups in terms of effect size because descriptive analysis has been recommended for pilot studies.[41] Hedge's g supplies an estimated effect size, which enables the determination of numerical information regarding differences between the 2 values[42,43] and allows for comparison of the results to those from other studies.[41,44] The effect size was interpreted as follows: 0.2, small; 0.5, medium; 0.8, large; 1.2, very large; 2.0, huge.[45,46]

Additionally, we present P-values derived from statistical tests to support our findings. Intergroup comparison using the Mann–Whitney U test for continuous data, the Chi-square test for categorical data whose proportion of expended frequency > 5 was $< 25\%$, and the Fisher's exact test for other categorical data. The Wilcoxon signed rank test was used for intra-group comparison. All statistical analyses were performed with 2-sided tests using the strategic applications software (SAS, version 9.4; SAS Institute Inc., Cary, NC).

3. Results

3.1. Participant recruitment and baseline characteristics

We recruited 28 participants from September 2014 to October 2015. Details of the participant flow are shown in the flow diagram.

The mean age, height, and body weight of the participants were similar in Groups A and B. Body temperature (BT), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) also did not differ significantly between the 2 groups (Table 2).

Regarding the characteristics, OAB symptoms evaluated using OAB-V8, OABSS, and VAS for LUTS and using DITI for CV4 were similar in both groups. The mean voiding volume, maximum voiding volume, 24-hour (24-h) voiding volume, nocturnal voiding volume, nocturnal polyuria index (NPi) calculated as nocturnal volume divided by 24-h volume, 24-h frequency, and nocturnal frequency were obtained from the FVC. None of these values showed statistically significant differences between groups (Table 2).

3.2. Feasibility outcomes

The first participant was registered on October 6, 2014 and the last participant was registered on August 11, 2015, resulting in a recruitment rate of 0.63 person per week. Thirty-four participants were screened and 28 participants were finally registered (84.85%). The target was to recruit 30 subjects and 28 (93.33%) were registered.

Table 2

Baseline characteristics and treatment sessions.

Variables (mean ± sd)	Group A (n = 14)	Group B (n = 14)	*P*-value
Age	51.79 ± 18.29	53.71 ± 14.64	1.0000†
Female (n, [%])	14 (100%)	14 (100%)	1.0000‡
Height, cm	158.71 ± 4.38	155.29 ± 6.13	.1137†
Weight, kg	55.64 ± 9.59	52.00 ± 5.68	.3303†
BT, °C	36.56 ± 0.29	36.54 ± 0.15	.8713†
SBP, mm Hg	109.29 ± 16.49	111.29 ± 12.53	.6657†
DBP, mm Hg	69.43 ± 10.13	72.00 ± 6.29	.2332†
PR, per minute	77.00 ± 8.01	74.79 ± 10.30	.3657†
OAB-V8	14.57 ± 6.79	18.07 ± 9.97	.3451†
OABSS	7.14 ± 3.03	6.79 ± 2.78	.7982†
VAS	57.93 ± 19.55	63.07 ± 22.77	.3460†
DITI, °C	29.89 ± 3.30	29.02 ± 1.24	.7303†
FVC*	Group A (n = 12)	Group B (n = 11)	*P*-value
Mean volume, mL	183.20 ± 58.36	186.73 ± 56.28	.9757†
Max volume, mL	344.17 ± 60.82	328.18 ± 73.19	.7138†
24-h volume, mL	1534.64 ± 469.83	1637.42 ± 477.64	.6061†
Nocturnal volume, mL	318.89 ± 241.49	251.97 ± 191.83	.6273†
Nocturnal volume/24-h volume (%)	20.44 ± 12.95	13.95 ± 9.30	.2312†
24-h frequency	8.68 ± 1.82	9.03 ± 2.26	.7607†
Nocturnal frequency	1.19 ± 0.87	1.09 ± 0.79	.9020†

BT = body temperature, DBP = diastolic blood pressure, DITI = digital infrared thermal imaging, FVC = frequency-volume chart, OABSS = overactive bladder symptom scores, OAB-V8 = OAB-validated 8-question awareness tool, PR = pulse rate, SBP = systolic blood pressure, VAS = visual analog scale.

* Obtained from 12 in group A and 11 in group B.

† Mann–Whitney U test.

‡ Chi-square test.

Table 3

Treatment sessions.

	Group A	Group B	*P*-value
ITT set	9.64 ± 1.74	6.64 ± 3.97	.0526
PP set	9.64 ± 1.74	8.90 ± 1.29	.3767

P-value, by Mann–Whitney *U* test.
PP = per protocol, ITT = intend-to-treat.

Of the 28 participants, 4 participants (14.3%) dropped-out. The drop-out occurred only in Group B, resulting in a drop out percentage of 28.6% in Group B; 3 of these 4 participants (21.4% of Group B) withdrew just after being allotted into Group B.

We assessed the FVC recovery rate and treatment sessions to evaluate compliance. The FVC recovery rate was 82.14% (n = 23); 10.71% (n = 3) participants did not submit the chart at both instances, while 7.14% (n = 2) submitted it only once.

We allowed participants to receive 8 to 12 sessions of intervention and compared the number of visits between 2 groups. The number of actual sessions was 9.64 ± 1.74 in Group A and 8.90 ± 1.29 in Group B, which were not significantly different ($P = .3767$), as shown in Table 3 as results of the PPS analysis.

3.3. Clinical outcomes

As this was a pilot study, clinical outcomes were assessed mainly to explore possible effects and safety and to evaluate effect size.[41,47]

3.3.1. OAB-V8. Scores decreased between T1 and T2 in both groups, but the decrease was greater in Group A, where participants were treated with moxibustion during the T1–T2 period ($g = -0.248$). Scores decreased between T2 and T3 in both groups, but a greater decrease was observed in Group B, where participants were treated with moxibustion during the T2–T3 period ($g = 0.465$).

3.3.2. OABSS. In the T1–T2 period, OABSS scores decreased in Group A but remained consistent in Group B ($g = -1.531$, $P = .0003$). In the T2–T3 period, OABSS scores increased in Group A but decreased in Group B ($g = 1.207$, $P = .0032$). The changes in OABSS scores between T1 and T3 were not significantly different between the 2 groups ($g = -0.044$).

3.3.3. VAS. VAS scores for LUTS decreased in both groups during the T1–T2 period, but a greater decrease was observed in Group A ($g = -0.713$). VAS scores decreased in both groups during the T2–T3 period, but a greater decrease was observed in Group B ($g = 0.427$). The overall decrease in VAS scores from T1 to T3 was relatively greater in Group A than in Group B ($g = -0.403$).

3.3.4. Temperature at CV4 measured using DITI. Skin temperature at CV4 decreased in Group A during the T1–T2 period ($g = -0.480$) and decreased in Group B during the T2–T3 period ($g = 0.635$). Through the entire study period, skin temperature decreased in both groups ($g = -0.256$) (Table 4).

3.3.5. FVC. Participants were asked to record observations on the FVC for a period of 3 days before T1 and before T2. Twelve participants in Group A and 11 participants in Group B completed the FVC; thus, FVCs of these 23 participants were analyzed. Values at T1 and T2 were compared.

Table 4

Effects of treatment with moxibustion.

		Changes between the baseline (T1) and T2			Changes between the T2 and T3			Changes between the baseline (T1) and T3		
		After 4 weeks (T2)	Mean change* (*P*-value)	MD [95% CI], (*P*-value)** Hedge's *g*	After 8 weeks (T3)	Mean change* (*P*-value)	MD [95% CI], (*P*-value)** Hedge's *g*	Mean change* (*P*-value)	MD [95% CI], (*P*-value)** Hedge's *g*
OAB-V8	Gr. A (n = 14)	11.07 ± 5.68	−3.50 ± 7.07 (*P* = .1670)	1.51 [−3.08, 6.10] (*P* = .6289)	8.57 ± 4.55	−2.50 ± 4.50 (*P* = .3213)	−3.39 [−8.98, 2.21] (*P* = .4339)	−6.00 ± 6.25* (*P* = .0140)	−1.87 [−8.77, 5.03] (*P* = .9266)
	Gr. B (n = 14)	16.09 ± 8.01	−1.99 ± 4.46 (*P* = .8001)	−0.248	10.20 ± 7.50	−5.89 ± 8.94 (*P* = .1068)	0.465	−7.87 ± 10.89 (*P* = .0762)	0.204
OABSS	Gr. A (n = 14)	4.14 ± 2.44	−3.00 ± 2.00 (*P* = .0275*)	3.00 [1.52, 4.48] (*P* = .0003*)	4.57 ± 3.11	0.43 ± 2.24 (*P* = .7267)	−2.85 [−4.64, −1.07] (*P* = .0032*)	−2.57 ± 3.23 (*P* = .0461*)	0.15 [−2.25, 2.54] (*p* = 1.0000)
	Gr. B (n = 14)	6.79 ± 2.86	0.00 ± 1.80 (*P* = .8346)	−1.531	4.36 ± 2.45	−2.43 ± 2.36 (*P* = .0484*)	1.207	−2.43 ± 2.94 (*P* = .0941)	−0.044
VAS	Gr. A (n = 14)	33.43 ± 23.93	−24.50 ± 24.73 (*P* = .0035*)	16.99 [−1.00, 34.97] (*P* = .0508)	27.71 ± 22.79	−5.71 ± 15.10 (*P* = .6126)	−8.35 [−23.14, 6.43] (*P* = .2319)	−30.21 ± 19.45 (*P* = .0011*)	8.63 [−7.52, 24.79] (*P* = .2411)
	Gr. B (n = 14)	55.56 ± 19.70	−7.51 ± 21.44 (*P* = .4902)	−0.713	41.49 ± 22.68	−14.07 ± 22.27 (*P* = .1350)	0.427	−21.58 ± 22.06 (*P* = .0454*)	−0.403
DITI	Gr. A (n = 14)	28.50 ± 1.60	−1.39 ± 3.68 (*P* = .6132)	1.43 [−0.86, 3.72] (*P* = .3827)	28.73 ± 0.99	0.24 ± 1.08 (*P* = .9085)	−0.80 [−1.77, 0.16] (*P* = .0536)	−1.15 ± 3.05 (*P* = .8542)	0.62 [−1.24, 2.49] (*P* = .8904)
	Gr. B (n = 14)	29.06 ± 1.45	0.04 ± 1.78 (*P* = .9450)	−0.480	28.49 ± 0.83	−0.57 ± 1.38 (*P* = .3229)	0.635	−0.53 ± 1.31 (*P* = .3460)	−0.256

DITI = Digital Infrared Thermal Imaging, MD = mean difference, OABSS = overactive bladder symptom scores, OAB-V8 = OAB-validated 8-question awareness tool, VAS = visual analog scale; data are presented as mean ± standard deviation, mean difference (95% CI), or Hedge's g (0.2, small; 0.5, medium; 0.8, large; 1.2, very large; 2.0, huge); T1, baseline; T2, 4-weeks after baseline; T3, 8-weeks after baseline.
* Wilcoxon signed rank test within each group.
** Mann–Whitney U test between the 2 groups for the changes.

Table 5

Changes in frequency-volume chart.

	After 4 weeks Mean ± sd	Mean change	MD [95% CI], Hedge's *g*	*P*-value*	*P*-value**
Mean volume, mL					
Group A (n = 12)	204.07 ± 64.21	20.87 ± 44.87	−30.46 [−67.39, 6.48]	.1763	.1622
Group B (n = 11)	177.14 ± 54.41	−9.59 ± 39.83	0.690	.6377	
Max volume, mL					
Group A (n = 12)	349.17 ± 48.52	5.00 ± 33.17	−37.73 [−86.27, 10.82]	.6250	.2380
Group B (n = 11)	295.45 ± 62.19	−32.73 ± 68.13	0.689	.2031	
24-h volume, mL					
Group A (n = 12)	1618.83 ± 485.85	84.19 ± 395.5	−151.0 [−478.1, 176.0]	.4648	.4499
Group B (n = 11)	1570.61 ± 377.36	−66.82 ± 355.0	0.386	.7002	
Nocturnal volume, mL					
Group A (n = 12)	124.58 ± 158.59	−194.3 ± 175.1	179.3 [23.34, 335.3]	.0010*	.0237*
Group B (n = 11)	236.97 ± 179.58	−15.00 ± 183.4	−0.965	.8984	
Nocturnal volume/24-h volume (%)					
Group A (n = 12)	6.91 ± 7.13	−13.53 ± 10.68	13.85 [4.72, 22.98]	.0010*	.0120*
Group B (n = 11)	14.27 ± 9.64	0.32 ± 10.34	−1.269	.9658	
24-h frequency					
Group A (n = 12)	8.24 ± 2.17	−0.44 ± 1.46	0.70 [−0.47, 1.88]	.2725	.2196
Group B (n = 11)	9.29 ± 2.47	0.26 ± 1.23	−0.498	.7871	
Nocturnal frequency					
Group A (n = 12)	0.65 ± 0.67	−0.54 ± 0.87	0.78 [0.10, 1.47]	.3281	.0149*
Group B (n = 11)	1.33 ± 0.83	0.24 ± 0.68	−0.883	.0625	

Hedge's g indicates 0.2, small; 0.5, medium; 0.8, large; 1.2, very large; 2.0, huge.

* Wilcoxon signed rank test within each group.

** Mann–Whitney *U* test between 2 groups for the changes.

The mean voiding volume, maximum voiding volume, and 24-h urination volume increased in Group A but decreased in Group B ($g = 0.690$, 0.689, and 0.386 respectively). The total nocturnal volume decreased in both groups, but this decrease was relatively greater in Group A ($g = -0.965$; $p = 0.0237$).

The NPi, nocturia frequency, and 24-h urinary frequency decreased in Group A but increased in Group B ($g = -1.269$, −0.883, and −0.498, respectively; $P = .0120$, .0149, and .2196, respectively) (Table 5).

3.4. Safety

We checked the occurrence of adverse events (AEs) at every visit. AEs were noted in 2 participants in Group A during the first 4 weeks (14.29% of Group A, and 7.1% of the total participants). The AEs noted in both cases were superficial second-degree burns.

In summary, moxibustion leads to a decrease in OABSS and OAB-V8 scores, and VAS scores for LUTS also showed a tendency to decrease owing to moxibustion. FVC findings suggested that moxibustion lead to a decrease in nocturnal voiding in terms of NPi, volume, and frequency, and lead to an increase in bladder capacity in terms of mean and maximum voiding volume. AEs, especially burns, related to the moxibustion were observed in 2 participants.

4. Discussion

It has been emphasized that the analysis of pilot studies should mainly be descriptive[41]; thus the changes observed in this trial were interpreted largely in terms of effect size and clinical importance.

On comparison of changes between Group A (moxibustion + behavioral training) and Group B (behavioral training) at T2, a clinically meaningful change was noted in OABSS scores in Group A ($g = -1.531$), which changed from moderate to mild (according to the criteria of ≤5, mild; 6–11, moderate; and ≥12, severe).[48] However, the effect size in terms of the change in OAB-V8 scores was 'small' ($g = -0.248$). Although both OABSS and OAB-V8 are standardized questionnaires for the diagnosis and evaluation of severity of OAB symptoms, OABSS mainly focuses on the frequency of symptoms while OAB-V8 focuses on the degree of discomfort caused by the symptoms. Our results were similar to those reported in previous studies where OABSS scores decreased with acupuncture on BL31–34[20] or moxibustion on CV4 and acupuncture on SP6.[14] The effect size in terms of the change in VAS scores was 'medium' ($g = -0.713$).

The effect of moxibustion was evaluated in Group B during the latter 4-week period (from T2 to T3). OABSS scores decreased from moderate to mild and showed 'very large effect' in Group B compared to the changes in Group A, during the T2–T3 period ($g = 1.207$). Based on these outcomes, moxibustion could be a possible alternative for OAB management, and future full-sized randomized control trials are warranted.

Furthermore, prolonged effects of moxibustion were observed in Group A based on the changes from T2 to T3. The improvement in OABSS, OAB-V8 and VAS scores noted in the first 4-week period was maintained over the next 4-week period. Therefore, the effects of moxibustion appear to not be limited to the treatment period and lasted for at least 4 weeks after treatment. Similarly, a previous study on detrusor over-activity revealed that effects of electroacupuncture on BL35 was maintained for 5 weeks.[49] Thus, further studies and full-sized randomized control trials should be conducted to evaluate the long-term effect of moxibustion.

In terms of FVC findings at T1 and T2, the NPi decreased from 20.44% to 6.91% in Group A, but remained consistent in Group B (13.95% in T1 and 14.27% in T2). The difference between the

2 groups was considered to correspond to a 'very large' effect size ($g=-1.269$). These results could be meaningful as the NPi is a clinically important indicator for the diagnosis of nocturnal polyuria.[50,51] In addition, the volume and frequency of nocturnal voiding decreased with a 'large' effect size ($g=-0.965$ and -0.883, respectively). Similar to the present study, Yuan et al[26] reported that acupuncture on CV4 and SP6 was effective for reducing nocturia frequency. Patients with nocturia may potentially benefit from moxibustion; thus, future studies including patients with nocturia or employing a sub-group analysis for evaluating nocturia would be helpful.

The mean voiding volume and the maximum voiding volume increased with a 'medium' effect size ($g=0.690$ and 0.689, respectively). The optimal voiding volume is known to be 200 to 300 mL, but the mean voiding volume of the participants was under 200 ml. Accordingly, the use of moxibustion as a treatment to increase bladder capacity seems feasible, and the influence of moxibustion on patients with urinary retention or on normal participants needs to be evaluated in future studies. In addition, urinary frequency (voiding over 8 times per day) improved with a "small" effect size ($g=0.498$). Previous studies have revealed a decrease in urinary frequency, an increase in mean voiding volume,[26,27] and an increase in the maximum bladder volume[19,20] with the use of acupuncture, as well as an improvement in voiding frequency, incontinence, and mean voiding volume with the use of electroacupuncture in Parkinson's disease patients with OAB,[52] and an improvement in bladder capacity and bladder compliance with the use of electroacupuncture in stroke patients with OAB.[49] Storage LUTS account for the majority of LUTS with an incidence of 44.6%[3] and may potentially respond to treatment employing the stimulation of acupuncture points. Since our study observed an improvement in storage LUTS by moxibustion, further studies to confirm these findings are warranted; furthermore, it would be helpful to evaluate the differences between acupuncture and moxibustion and the possible responders for each method.

We did not evaluate the mechanism of moxibustion directly, but instead tried to accumulate related data by measuring the temperature at CV4 with medical thermography. We expected the basic temperature at CV4 to increase during the period when moxibustion was performed, but opposite results were obtained. The temperature in Group A decreased while that in Group B increased during the first 4-week period, showing a 'medium' effect size ($g=-0.480$), and the temperature in Group A increased while that in Group B decreased in the next 4-week period ($g=0.635$). Over the entire study period, the temperature at CV4 decreased by 1.15°C and 0.53°C in Group A and B, respectively. The reasons for this change could not be determined in our study, and further studies with more detailed measurements[39] and limited recruitment periods (example, within the same season) are needed.

Previous studies have assessed the mechanism of acupuncture point stimulation and moxibustion. The autonomic nervous system (ANS) and the serotonin system are considered to play vital roles in OAB.[7,53] Decreased ANS activity as measured by a heart rate variability test, especially in terms of the reduced ability for para-sympathetic nerve regulation, has been reported in OAB patients.[54,55] Depression is usually noted in patients with OAB, and anti-depressant drugs are often used to treat OAB. Thus, the serotonin system, which plays a role in depression and micturition, is being evaluated.[7,56] Moxibustion treatments have been reported to regulate the ANS,[57] and far-infrared irradiation on acupuncture points including SP6 has been reported to increase serotonin levels significantly.[58] In addition, Aydogmus et al[27] reported that acupuncture, including that at SP6 and LR3, decreased levels of neural growth factor (NGF), especially among those who experience alleviated symptoms in OAB. Therefore, future studies should also investigate the physiological mechanism underlying the effects of moxibustion.

Two instances of AEs were reported, which included superficial second-degree burns at CV4 and occurred during the treatment period in Group A. No serious adverse events were reported. Accordingly, it can be suggested that moxibustion is safe. However, further studies with long-term observation are needed.

For the purposes of the pilot study, we assessed the feasibility of recruitment, intervention procedures, and outcome measures. Drop-outs were noted only in Group B, thus, an active comparator would be more appropriate in future studies than a waiting-list. As a qualitative study has reported that OAB patients have a strong desire to enroll for any type of treatment,[8] the wait-list comparator does not appear to be adequate and may lead to drop-out. There were no reports of other pharmacological or non-pharmacological treatments in both groups during the study period. The participants who dropped out were considered to have withdrawn from the study to receive other treatments. FVC compliance was good (82.14%), but procedures to maintain or promote compliance (such as offering detailed instructions and FVC versions that are easier to complete) in a long-term study would be helpful.

During the intervention procedures, although adequate precautions were taken and specific instructions were provided, some patients preferred to continue with moxibustion even though the temperature began to exceed their tolerance. A Korean study has reported that some people believe that more effective results are obtained with higher temperatures for moxibustion, and hence, they do not comply with instructions.[59] Three types of moxibustion procedures are included in the Korean national health insurance system: direct, indirect, and apparatus-type moxibustion. We used indirect and apparatus-type moxibustion with the burning of mugwort. In future studies, especially for participants in Eastern countries who have experience with moxibustion, it would be important to consider the type of moxibustion or timing of the removal to minimize the risk of burns.

With respect to outcome measures, OABSS, OAB-V8 and VAS scores showed somewhat inconsistent results. The emotional state of participants should be taken into consideration as they were not blinded. Emmons and Otto[60] have reported that acupuncture was effective for urinary frequency and urgency, but sham-acupuncture was also effective in relieving the discomfort of urination. Similarly, placebo treatments were effective for some instances of subjective discomfort.[61] Therefore, these aspects should be considered in future clinical trials. Furthermore, regular visits may be an influencing factor. Hence, we suggest that the visiting schedule of the participants in each group should be identical in future trials.

This study has some limitations. First, this is a pilot study, and thus, the results cannot be used as evidence for the efficacy and safety of moxibustion for management of OAB. Second, all participants were female; therefore, the results cannot be generalized to all OAB patients. Third, we did not set a wash-out period apart from the general cross-over design study. We planned to observe the prolonged effects of moxibustion during the second 4-week period for Group A and decided to administer moxibustion treatment to Group B participants to improve

compliance. This was also done because data were insufficient to set a proper wash-out period. We hope that our data will be used as baseline data in this aspect. Furthermore, objective tests such as urodynamic studies would be helpful to obtain more reliable and clinically important data[62] and to understand the influence of moxibustion on changes in biological activity.[39] Lastly, we could not exclude the placebo effect because we did not employ a sham-control. However, we confirmed the feasibility of moxibustion for OAB management and observed a significant improvement in OAB symptoms, especially in voiding frequency and nocturia. Therefore, the results herein can be used as baseline data for future randomized controlled trials.

5. Conclusion

We suggest that moxibustion might be considered as an alternative for OAB management. Further studies employing placebo control, larger sample size, and longer observation period are warranted to confirm the efficacy and safety of moxibustion.

Acknowledgments

This manuscript is a revision of the first author's (HYL) doctoral dissertation from Pusan National University. We are grateful to Hyungi Lee of A-CRO in Pusan National University Hospital for assistance in data analysis.

Author contributions

HYL and JNK proposed and designed the study. HYL served as a KMD, drafted the manuscript, and interpreted the results. SHP, JYC, IL, YJY, and JWH contributed to critical revisions of the manuscript. YJY also contributed as double-license holder of medical doctor (MD) and traditional medical doctor (KMD), and provided critical revisions of the manuscript. JNK directed the clinical trial and was responsible for this study. All the authors read and approved the final manuscript.

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