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Moxibustion as an adjunct for lower urinary tract symptoms associated with benign prostate enlargement

A randomized controlled pilot trial

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Abstract

Background: Benign prostatic enlargement (BPE) causes discomfort in daily life, including lower urinary tract symptoms (LUTSs) caused by the enlarged prostate, and requires long-term management as a chronic, irreversible disease. To improve LUTS, certain complementary therapies have been used with or without doctors' directions. Conventional treatments and complementary therapies tend to be combined unsystematically, depending on patient preference; thus, research for safe and efficient combination therapy is warranted.

Methods: Twenty-nine participants were randomly assigned to an integrative group (IG, n = 15) or a conventional group (CG, n = 14). The IG received moxibustion (twice weekly for 4 weeks, at the acupuncture points SP6, LR3, and CV4) and conventional medication for 4 weeks, followed by conventional medication alone for 8 weeks. The CG received conventional medication alone for 12 weeks. The outcome measures were International Prostate Symptom Score (IPSS), patient's global impression of changes (PGIC), maximum urinary flow rate (Q_{max}), postvoid residual urine volume (PVR), and frequency-volume chart.

Results: Total IPSS (IG, −2.4 ± 4.2; CG, 0.9 ± 4.0; $P = .039$), PGIC-A (IG, 3.5 ± 1.0; CG, 2.2 ± 1.0; $P = .001$), and PGIC-B (IG, 3.5 ± 0.1; CG, 4.7 ± 0.6; $P = .004$) were significantly improved in the IG compared with the CG, 4 weeks after baseline. Among the IPSS items, incomplete emptying (IG, −0.6 ± 0.7; CG, 0.4 ± 1.2; $P = .019$), straining (IG, −0.6 ± 0.8; CG, 0.2 ± 1.2; $P = .046$), and nocturia (IG, −0.8 ± 1.4; CG, 0.1 ± 1.0; $P = .045$) showed significant differences. The Q_{max} and PVR volume did not differ significantly at 12 weeks after the baseline.

Conclusion: Moxibustion can be considered an adjunct therapy to improve LUTS in BPE patients. A full-sized randomized controlled trial would be feasible with comparator modifications and an extended study period. The study design should include a placebo group and narrow the eligibility to subjects who do not respond well to conventional treatments.

Abbreviations: AE = adverse event, 5-ARIs = 5α-reductase inhibitors, AUA = American Urological Association, BOO = bladder outlet obstruction, BPE = benign prostatic enlargement, BPH = benign prostatic hyperplasia, CAM = complementary and alternative medicine, CG = conventional group, FVC = frequency-volume chart, IG = integrative group, IPSS = International Prostate Symptom score, ITT = intention to treat, KMD = doctor of Korean medicine, LUTS = lower urinary tract symptom, MCID = minimum clinically important difference, MD = medical doctor, NPi = nocturnal polyuria index, PGIC = patient's global impression of changes, PSA =

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HYL and GEB contributed equally to the work.

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Written informed consent was obtained from all participants, who were treated respectfully according to the Declaration of Helsinki throughout the study.

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prostate-specific antigen, PVR = postvoid residual urine volume, Q_{max} = maximum urinary flow rate, QoL = quality of life, RCT = randomized controlled trial, SD = standard deviation, UD = clinical urologist.

Keywords: benign prostatic enlargement, benign prostatic hyperplasia, moxibustion, lower urinary tract symptoms, SP6, LR3, CV4

1. Introduction

Benign prostatic hyperplasia (BPH) is a "histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone."[1] Clinically, the diagnosis is often based on an enlarged prostate and/or lower urinary tract symptoms (LUTSs), without other causes of LUTS.[2] LUTS is classified as "storage, voiding, and postmicturition symptoms,"[3] and the enlarged prostate in BPH causes bladder outlet obstruction (BOO) and increase in smooth muscle, which are associated with LUTS.[4–6] The prevalence of BPH with LUTS has been reported to be 50% to 75% in men older than 50 years.[7] A Korean study showed that 70.6% of men older than 40 years experience LUTS, with the prevalence increasing with age.[8] Although LUTS and BPH are not considered as risk factors for prostate cancer, LUTS in BPH causes considerable discomfort in daily activities and it is usually the primary indication for diagnosing diseases of the prostate or urinary system.[5,9]

Conservative treatment, including watchful waiting and behavioral and dietary modification, is recommended as a 1st step for men with mild or moderate symptoms, and pharmacologic treatment is recommended as a following step. Pharmacologic treatments are determined by prostate size, level of prostate-specific antigen (PSA), accompanying symptoms, or risk factors. Usually, α1-adrenoceptor antagonists (α-blockers), 5α-reductase inhibitors (5-ARIs), muscarinic receptor antagonists, phosphodiesterase-5 inhibitors, and beta-3 agonists are used alone or in combination. In patients recalcitrant to medication or having BPH-related complications, surgical therapy is recommended. α-Blockers are usually considered as the first treatment option owing to good efficacy and low risk of severe adverse events (AEs), but they cannot prevent progression (i.e., urinary retention or conditions requiring operation) and can induce ejaculatory dysfunction. A 5-ARI can complement some aspects of α-blockers and prevent disease progression, but it induces reduced libido or ejaculation disorders.[10]

Some complementary and alternative medicine (CAM) therapies have been introduced, but they are mainly health supplements perceived to be useful for patients who have mild symptoms and are reluctant to receive standard treatments.[11] In Asian countries, acupuncture and moxibustion are widely used for the treatment of LUTS. Acupuncture or electroacupuncture has shown positive effects on urinary retention,[12] International Prostate Symptom Score (IPSS), maximum urinary flow rate (Q_{max}), and postvoid residual urine volume (PVR) in LUTS.[13,14]

Moxibustion, a treatment method similar to acupuncture, involves the stimulation of acupuncture points using heat, and it has been used to manage LUTS traditionally.[15] Recent studies have reported that moxibustion is effective in treating poststroke urinary incontinence,[16] stress urinary incontinence,[17] and overactive bladder,[18] and in preventing dysuria after surgery for prolapse and hemorrhoids.[19] In addition, it is effective against urinary retention after surgery,[20] poststroke urinary incontinence,[21] and LUTS in chronic prostatitis[22] when combined with acupuncture. A meta-analysis focusing on BPH reported the positive effect of moxibustion on IPSS, quality of life (QoL), and Q_{max} compared to oral medication; however, the study indicated that the number of included studies was small and the reliability of the findings of these studies was low.[23] In addition, some studies have compared moxibustion with conventional therapies or other CAM therapies, but they do not reflect clinical interventions used in addition to conventional treatment.[24,25] Therefore, clinical urologists (UDs), doctors of Korean medicine (KMDs), and a dual-licensed medical doctor (MD and KMD) designed a randomized controlled trial (RCT) through collaborative discussions. In this trial, we evaluated the effectiveness and safety of additional moxibustion in combination with conventional treatment compared to conventional treatment only.

2. Methods

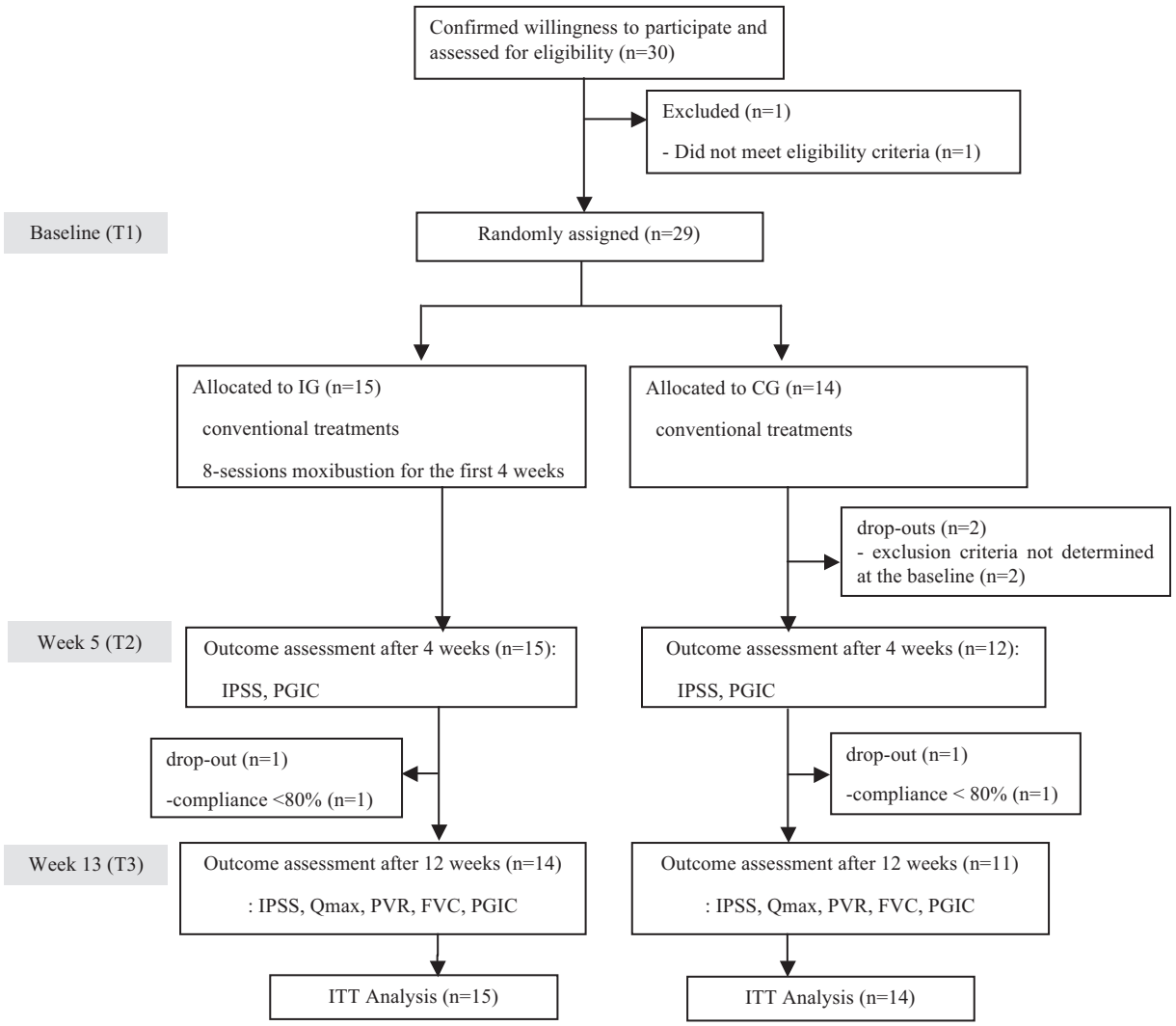
2.1. Study design and setting

A randomized, controlled, parallel-group, 1:1 allocation, assessor- and analyzer-blinded pilot trial was conducted. Patients were randomly allocated to either a conventional group (CG) or an integrative group (IG). The IG received moxibustion plus conventional therapy during the first 4 weeks, followed by only conventional therapy during the following 8 weeks. The CG received conventional therapy alone during the 12 weeks of the study. Before we obtained consent from the participants, we clearly explained that the chance of them being assigned to the IG and therefore receiving moxibustion was 50%. We also informed them that those who got selected to the CG and would not receive moxibustion therapy during the 12-week study period could receive it after the study period if they so wished. Participants were recruited from the outpatient department of university-affiliated conventional and Korean medicine hospitals (Fig. 1).

This study was approved by the institutional review boards of Pusan National University Korean Medicine Hospital (PNUKH: approval no 2013021) and Pusan National University Yangsan Hospital (PNUYH: 03-2013-013). The study has been registered at ClinicalTrials.gov (trial registration number: NCT02051036, registered on January 31, 2014) and was conducted between March 2014 and June 2015. The protocol of this study was published in 2015,[26] and it adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.CONSORT-statement.org).

2.2. Participants and recruitment

Participants were men aged between 51 and 79 years, with prostate size determined to be >20 g and symptoms of IPSS >8, who were able to check their symptom severity using the IPSS and had submitted informed written consent. Exclusion criteria were a diagnosis of bladder or prostate malignancy, diabetes mellitus, or neurogenic bladder; history of brain disease that could cause voiding difficulty; symptoms of acute urinary tract infection; difficulty in answering the IPSS due to cognitive impairment, or



IG, integrative group; CG, conventional group; IPSS, international prostate symptom score; Qmax, maximum urinary flow rate; PVR, post-void residual urine volume; FVC, frequency-volume chart; PGIC, patient's global impression of changes

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow chart of the study. CG = conventional group, FVC = frequency-volume chart, IG = integrative group, IPSS = International Prostate Symptom Score, PGIC = patient's global impression of changes, PVR = postvoid residual urine volume, Q_{max} = maximum urinary flow rate.

traditional Korean medical intervention for LUTS within the previous 4 weeks. In addition, participants whose compliance rate was under 80% during the study period or who were determined to fulfill any exclusion criteria after the enrollment were dropped.

Recruitment information related to the study was posted on noticeboards and the website of the study hospital and distributed through the local newspaper. Subjects who were interested in the study were provided with detailed written and verbal information, and those who decided to voluntarily participate in the study and submitted written consent were finally enrolled. During this process, all the subjects were treated respectfully according to the Declaration of Helsinki and had opportunities to ask enough questions.

2.3. Interventions

The IG and CG received conventional treatments during the overall study period. The IG additionally received moxibustion for the first 4 weeks.

2.3.1. Conventional treatment. Clinical urology specialists administered the conventional treatments according to the guidelines of the American Urological Association (AUA)[1] and Korean Prostate Society.[27] Specifically, lifestyle advice with watchful waiting was recommended to patients who were beginning treatments for BPH; medications, including α-blockers, 5-ARIs, or anticholinergic agents, were prescribed for those who showed insufficient improvement with the lifestyle advice. Accordingly, the conventional treatments were not controlled in this trial, and each

patient received the optimal treatment that they would have been administered under normal clinical conditions. The lifestyle modification consisted of restriction of water, caffeine, and alcohol intake to avoid urinary incontinence.[27]

2.3.2. Moxibustion. Two types of indirect moxibustion were used: apparatus and mini-pillar types. Apparatus-type moxibustion (Haitnim-moxa; Bosungsa, Incheon, Republic of Korea) was applied to CV4 using the Haitnim-moxa for approximately 30 minutes (Fig. 2A and C). If a patient complained that the heat sensation was intolerable before the 30 minutes elapsed, the moxibustion apparatus was removed. Mini-pillar type moxibustion (Kanghwa mini moxa at the "lowest" intensity; Ehwadang, Seoul, Republic of Korea) was administered at 4 points, bilateral SP6 and LR3 (Fig. 2B and D). The Kanghwa mini moxa runs for approximately 5 minutes before totally burning out. The Kanghwa mini moxa was applied to a maximum of 7 layers for each acupuncture point. If the patient complained that the heat sensation was unbearable, the moxa-pillar was removed and not repeated at that point.

Moxibustion treatments were administered by a KMD with >2 years of clinical experience. From the 2nd visit, the KMD examined the treated points and did not conduct further moxibustion if they showed symptoms of 2nd- or higher degree burns.

2.4. Outcomes

The primary clinical outcome was the change in IPSS between the baseline (T1) and week 5 (T2). The total IPSS score was classified as follows: 1 to 7, mild; 8 to 19, moderate; and 20 to 35, severe. The scores of the QoL item were as follows: 0, delighted and 5, unhappy.[28] The secondary clinical outcomes were as follows: changes in IPSS between the baseline and week 13 (T3); patient's global impression of changes (PGICs)[29] assessed at T2 and T3; changes in the Q_{max} score of the uroflowmetry and PVR between T1 and T3[30]; and frequency-volume charts (FVCs), including mean voiding volume, daily voiding frequency, volume of nocturia, and nocturnal polyuria index (NPi), which means the ratio of nocturnal volume to 24-hour volume recorded at T1 and T3.[27] The PGIC comprised 2 questions: PGIC-A, "since the beginning of the treatment at this clinic, how would you describe the change in activity limitations, symptoms, emotions, and overall QoL related to your condition?" (1, no change or condition worsened; 2, almost the same, with hardly any change at all; 3, slightly better but no noticeable change; 4, somewhat better, but the change has not made any real difference; 5, moderately improved, with a slight but noticeable change; 6, better, with a definite improvement that has made a real and worthwhile difference; and 7, a great deal better, with a considerable improvement that has made all the difference), and PGIC-B, "please circle the number below that matches your degree of change since beginning treatment at this clinic" (0, much better; 5, no change; 10 much worse).[29] For the pilot trial, recruitment, compliance, and completion rates were evaluated. We had intended to evaluate 36-Item Short Form health survey (SF-36)[26]; however, it was excluded due to a limited budget.

2.5. Sample size

The sample size was calculated based on the possibility of recruitment and minimal number required to achieve the purpose of this pilot trial. We planned to recruit 30 participants in each group at the beginning of the study.[26] However, the sample size was redetermined to include 15 participants in each group for a total of 30, and the recruitment was concluded with 29

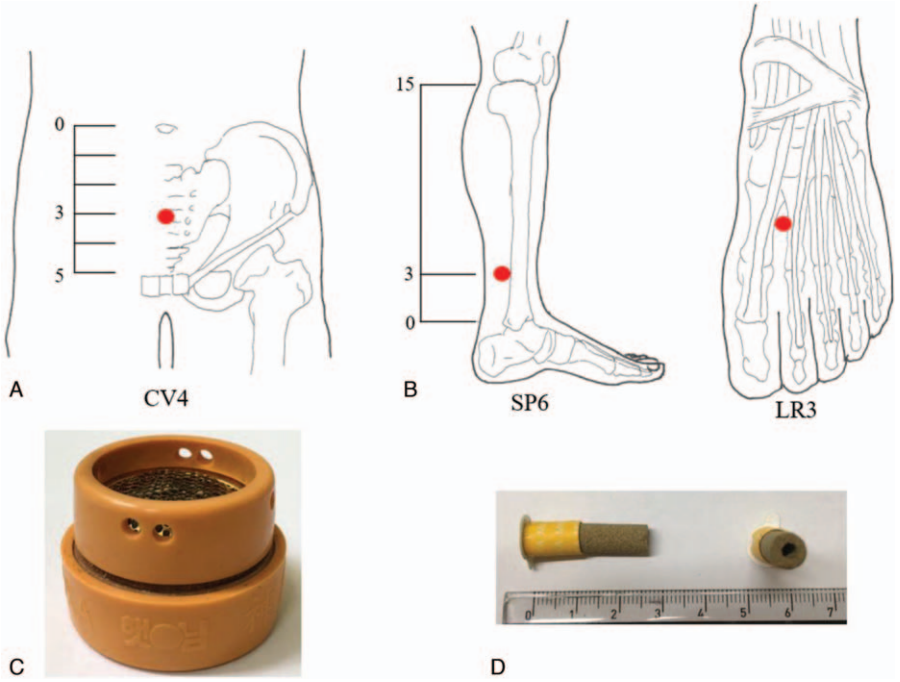


Figure 2. Location of acupuncture points and type of moxibustion used. (A) Location of CV4, (B) location of SP6 and LR3, (C) apparatus-type moxibustion (Haitnim-moxa; Bosungsa, Incheon, Republic of Korea), (D) mini-pillar-type moxibustion (Kanghwa mini moxa: "lowest" intensity; Ehwadang, Seoul, Republic of Korea).

participants (15:14) because the recruitment rate was lower than expected, the interim analysis showed group-wise differences, the drop-out rate (13.8%) was lower than the expected 20%, and it still exceeded the minimum of 12 participants per group that was suggested for precise evaluation in pilot studies.[31]

2.6. Randomization

Sequence generation and allocation concealment: an independent statistician generated the random sequence using sealedenvelope.com and placed the allotted group in individual double-layered opaque envelopes, which were then sealed and numbered in order. Based on the order of visits, the KMD in charge of the intervention opened the corresponding envelope and checked the allotted group.

2.7. Blinding

The assessors and data analyzer, but not the practitioner and participants, were blinded. Outcomes were self-reported by patients without the intervention of researchers.

2.8. Statistical methods

In this study, outcomes and additional analyses were conducted using an intention to treat (ITT) set. Per-protocol (PP) set analysis was also performed, and the results are provided in Supplemental File 1, http://links.lww.com/MD/D660. In the ITT analysis, missing data were replaced with multiple imputation. The data were presented as mean ± standard deviation (SD). To demonstrate the differences between groups, mean difference, 95% confidence interval, and effect size (Hedges' g) were calculated. Hedges' g provides an estimated effect size to show the actual difference between 2 outcomes, whereas *P*-values are affected by sample size and provide a dichotomous result of statistical significance.[32]

P-values were reported referentially. For continuous variables, the Mann–Whitney *U* test was used to compare time-point differences between groups, and the Wilcoxon signed-rank test was used for intragroup comparisons. For categorical variables, Fisher exact test or Chi-squared test was performed; if the proportion of "expected frequency < 5" was larger than 25%, Fisher exact test was used. All the statistical analyses were performed using 2-tailed tests, and the significance level for the *P*-value was set as .05. Statistical Analysis System (SAS), software version 9.4 (SAS Institute Inc, Cary, NC), was used to analyze all the data.

3. Results

3.1. Participant flow

Twenty-nine patients with benign prostatic enlargement (BPE) accompanied by LUTS participated in this study. In the CG, 3 patients dropped out, including 2 who fulfilled the exclusion criteria that were not recognized at baseline: 1 with diabetes mellitus and the other with neurogenic bladder. The other patient dropped out because of a trial compliance of <80%. In total, 25 patients completed the study (Fig. 1). ITT analysis included 29 participants (15 and 14 in IG and CG, respectively).

3.2. Baseline characteristics

In the IG and CG groups, the mean patient age, PSA level, and prostate size were 63.3 ± 7.9 and 64.5 ± 8.1 years, 1.9 ± 0.9 and 6.3 ± 16.5 ng/mL, and 32.7 ± 6.7 and 42.7 ± 19.1 g, respectively. The differences were not statistically significant. Furthermore, the IPSS, QoL, Q_{max}, and PVR were 17.7 ± 5.7 and 17.1 ± 5.7, 4.4 ± 0.7 and 4.2 ± 0.8, 15.2 ± 10.2 and 14.1 ± 8.9 mL/s, and 58.8 ± 60.4 and 52.9 ± 33.9 mL in the IG and CG, respectively. None of the differences were statistically significant (Table 1).

3.3. Clinical outcomes

3.3.1. IPSS. The total IPSS decreased by 2.4 ± 4.2 in the IG and increased by 0.9 ± 4.0 in the CG, with a significant difference between the 2 groups ($g = -0.776$, $P = .039$) from T1 to T2. Between T1 and T3, the total score decreased by 3.0 ± 4.0 in the IG and increased by 0.6 ± 5.3 in the CG, without any statistically significant difference between the 2 groups ($g = -0.749$, $P = .060$).

Specifically, the IG showed significant improvement in incomplete emptying, straining, and nocturia compared to the CG. The changes between T1 and T2 for incomplete emptying, straining, and nocturia were −0.6 ± 0.7 and +0.4 ± 1.2 ($g = -0.933$, $P = .019$), −0.6 ± 0.8 and +0.2 ± 1.1 ($g = -0.803$, $P = .046$), and −0.8 ± 1.4 and +0.07 ± 1.00 ($g = -0.684$, $P = .045$) in the IG and CG, respectively. For changes between T1 and T3, incomplete emptying showed significant improvement in the IG, with changes of +0.3 ± 1.1 and −0.7 ± 1.1 in the IG and CG, respectively ($g = -0.886$, $P = .028$).

The QoL significantly improved in the IG compared to that in the CG, with changes of −0.7 ± 0.9 and +0.1 ± 0.7, respectively ($g = -1.027$, $P = .021$), between T1 and T2. From T1 to T3, the QoL improved more in the IG (−0.8 ± 0.9 in the IG and −0.1 ± 0.6 in the CG) than it did in the CG, but the difference was not statistically significant ($g = -0.894$, $P = .053$, Fig. 3, Supplemental File 2, http://links.lww.com/MD/D661).

3.3.2. Q_{max} and PVR. The Q_{max} and PVR were measured at T1 and T3. The changes in Q_{max} were 1.3 ± 4.5 and −0.03 ± 7.5 mL/s in the IG and CG, respectively, for those who showed decreased

Table 1

Baseline characteristics of the integrative group (IG) and conventional group (CG).

Variables	IG (n = 15)	CG (n = 14)	*P*-value*
Age, yrs	63.3 ± 7.9	64.5 ± 8.1	.726
Height, cm	165.3 ± 5.7	171.2 ± 5.3	.331
Weight, kg	70.3 ± 7.4	68.0 ± 6.3	.325
PSA, ng/mL	1.9 ± 0.9	6.3 ± 16.5	.561
Prostate size, g	32.7 ± 6.7	42.7 ± 19.1	.294
IPSS			
Total score	17.7 ± 5.7	17.1 ± 5.7	.826
Incomplete emptying	2.7 ± 1.3	2.2 ± 1.6	.438
Frequency	2.5 ± 1.3	2.0 ± 1.3	.326
Intermittency	2.3 ± 1.5	2.6 ± 1.6	.452
Urgency	2.7 ± 1.4	1.9 ± 1.2	.105
Weak stream	3.1 ± 1.3	3.6 ± 1.5	.255
Straining	1.6 ± 1.1	2.5 ± 1.6	.157
Nocturia	2.7 ± 1.1	2.0 ± 1.1	.103
QoL	4.4 ± 0.7	4.2 ± 0.8	.488
Q_{max}, mL/s	15.2 ± 10.2	14.1 ± 8.9	.965
PVR, mL	58.8 ± 60.4	52.9 ± 33.9	.647

CG = conventional group, IG = integrative group, IPSS = International Prostate Symptom Score, PSA = prostate-specific antigen, PVR = postvoid residual urine volume, Q_{max} = maximum urinary flow rate, QoL = quality of life.

* Mann–Whitney *U* test.

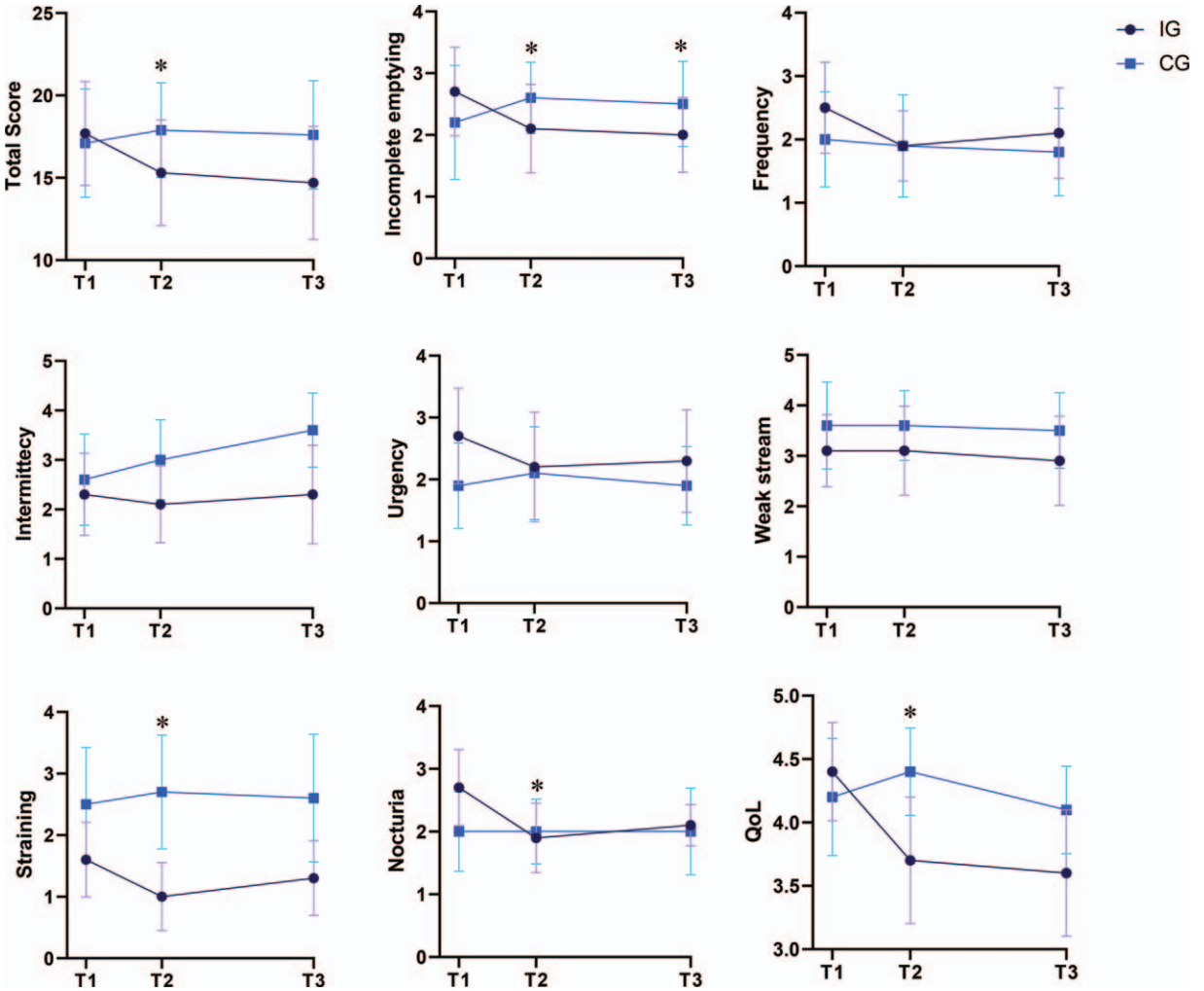


Figure 3. Changes in International Prostate Symptom Score (IPSS). Mean and 95% confidence interval; CG = conventional group, IG = integrative group, QoL = quality of life, T1 = baseline, T2 = week 5, T3 = week 13; *$P < .05$ by the Mann–Whitney *U* test for the changes from the baseline (T1) between IG and CG.

baseline Q_{max} (n = 12:12), but the differences were not statistically significant ($g = 0.211$, $P = .380$). Among those who had within or over the normal range of Q_{max}, the changes were -3.6 ± 7.2 and 11.7 ± 46.1 mL/s in the IG and CG, respectively ($g = -0.408$, $P = 1.00$).

The PVR decreased by 13.4 ± 51.0 and 17.5 ± 47.8 mL ($P = .140$) in the IG and CG, respectively, and there was no statistically significant difference between the 2 groups for either parameter (Table 2).

3.3.3. Frequency-volume charts. The FVC was recorded at T1 and T3. Ten and 9 of the IG and CG patients, respectively, submitted FVC at both T1 and T3. Therefore, the FVC data of these 19 patients were analyzed. In the IG and CG, the mean voiding volume decreased from 215.5 ± 21.6 to 199.4 ± 51.1 mL and increased from 215.1 ± 46.8 to 215.1 ± 33.4 mL, respectively ($g = -4.348$, $P = .333$).

The 24 hour and nocturnal frequencies decreased in the IG (-0.6 ± 1.6 and -0.1 ± 0.9), whereas they increased in the CG (0.7 ± 1.5 and 0.4 ± 0.5), without any statistically significant differences ($g = -0.983$ and -0.583; $P = .086$ and .122, respectively). The NPi decreased in the IG from $14.4\% \pm 9.5\%$ to $12.7\% \pm 11.4\%$, while it increased in the CG from $12.4\% \pm 12.6\%$ to $15.0\% \pm 12.7\%$, but the difference between the groups was not statistically significant ($g = -0.421$, $P = .351$, Table 3).

3.3.4. Patient's global impression of changes

3.3.4.1. PGIC-A. A low PGIC-A score indicated severe symptoms. The scores at T2, which were the changes between T1 and T2, were 3.5 ± 1.0 and 2.2 ± 1.0 in the IG and CG, respectively ($g = 1.309$, $P = .001$). The scores at T3, which indicated the changes between T1 and T3, were 3.1 ± 1.2 and 2.8 ± 0.8 in the IG and CG, respectively ($g = 0.324$, $P = .412$, Table 4).

3.3.4.2. PGIC-B. The higher the PGIC-B score, the more severe were the symptoms. The scores at T2, which indicated the changes between T1 and T2, were 3.5 ± 0.1 and 4.7 ± 0.6 in the IG and CG, respectively ($g = -0.811$, $P = .004$). The values at T3, representing the changes between T1 and T3, were 4.3 ± 1.0 and 4.8 ± 0.6 in the IG and CG, respectively ($g = -0.550$, $P = .188$, Table 4).

3.3.5. Subgroup analysis. The participants were classified into 3 subgroups according to the type of conventional treatment administered: subgroup A was prescribed α-blockers only (n =

Table 2

Changes in Q_{max} and PVR.

Variables		Baseline (T1)	Week 13 (T3)	*P*-value*	MD (95% CI) Hedges' g	*P*-value†
Q_{max}, mL/s						
Overall	IG (n=15)	15.2±10.2	14.1±8.9	.836	−1.3 (−10.4, 7.7)	.715
	CG (n=14)	14.1±8.9	15.8±15.5	.903	*−0.116*	
$Q_{max} < 20$	IG (n=12)	11.0±3.8	12.2±4.3	.412	1.3 (−3.9, 6.5)	.380
	CG (n=12)	11.5±4.6	11.4±6.8	.850	*0.211*	
$20 \leq Q_{max}$	IG (n=3)	10.1±25.2	28.6±9.0	.500	−15.3 (−94.5, 63.9)	1.000
	CG (n=2)	30.1±14.1	41.8±32.0	1.000	*−0.408*	
PVR, mL						
	IG (n=15)	58.8±60.4	45.4±53.1	.352	4.1 (−33.6, 41.8)	.484
	CG (n=14)	52.9±33.9	35.4±31.5	.140	*0.081*	

CG = conventional group, CI = confidence interval, IG = integrative group, MD = mean difference, PVR = postvoid residual urine volume, Q_{max} = maximum urinary flow rate.

* Wilcoxon signed-rank test.

† Mann–Whitney *U* test.

10); subgroup B was prescribed additional medications other than α-blockers, including 5-ARIs, anticholinergic drugs, or both (n=13); and the third group received lifestyle advice only, without any medication (n=6). Subgroup analysis was conducted for subgroups A and B. Demographic characteristics (age, height, weight), baseline PVR, or IPSS score were not different between the subgroups A and B. Subgroup B had significantly lower Q_{max} values (16.2±10.0 and 11.5±0.3 in subgroups A and B, respectively, $P=.026$), larger prostate size (34.7±11.6 and 42.1±18.1 g in subgroups A and B, respectively), and higher PSA levels (2.3±2.3 and 6.5±17.1 ng/mL in subgroups A and B, respectively) but without statistical significance (Supplemental File 3, http://links.lww.com/MD/D662).

For subgroup A, the changes in total IPSS of the IG and CG were −3.2±2.7 and +3.0±3.9, respectively, during the first 4 weeks ($g=-1.662$, $P=.045$), and −4.8±4.6 and +5.0±3.4, respectively, during the 12 weeks ($g=-2.206$, $P=.034$). Among the IPSS questions, the changes in nocturia scores were −1.4±1.1 and +1.0±1.7 in the IG and CG, respectively, during the 12 weeks ($g=-1.480$, $P=.0493$, Supplemental File 4, http://links.lww.com/MD/D663).

For subgroup B, a greater difference was observed between the groups in the PGIC during the first 4 weeks. The changes in PGIC-A were 3.7±1.1 and 1.8±1.0 in the IG and CG, respectively ($g=1.661$, $P=.028$), and those in PGIC-B were 3.4±1.0 and 5.0±0.0 in the IG and CG, respectively ($g=-2.018$, $P=.018$, Supplemental File 5, http://links.lww.com/MD/D664).

Additional analysis was performed according to prostate size because the baseline prostate size differed between the 2 groups, albeit not significantly. We classified the participants according to prostate size into <40 and ≥40 g because BPH with a prostate size of >40 g has a poor prognosis, and different treatments are recommended.[10] Prostate size was similar for IG and CG (30.2±5.2 and 30.9±5.1, respectively) among the participants whose prostate size was <40 g. The IPSS total score of IG significantly decreased during T1 to T3 ($P=.022$), and the change was

Table 3

Changes in frequency-volume chart and comparison between the integrative group (IG, n=10) and conventional group (CG, n=9).

		Baseline (T1)	Week 13 (T3)	*P*-value*	MD (95% CI), Hedges' g	*P*-value†
Mean voiding volume, mL	IG	215.5±51.6	199.4±51.1	.210	−16.2 (−50.5, 18.1)	.333
	CG	215.1±46.8	215.1±33.4	.995	*−0.438*	
Max-voiding volume, mL	IG	353.0±107.1	324.0±69.6	.239	3.2 (−49.7, 56.2)	.895
	CG	393.3±87.8	361.1±84.9	.001*	*0.056*	
24 h voiding volume, mL	IG	1720.5±474.9	1449.5±369.1	.057	−429.4 (−833.6, −25.1)	.039*
	CG	1686.1±814.0	1844.4±714.4	.314	−0.983	
Nocturnal voiding volume, mL	IG	225.3±147.5	199.7±203.9	.739	−129.4 (−334.7, 76.0)	.201
	CG	210.8±187.9	314.4±259.7	.123	*−0.583*	
NPi, %	IG	14.4±9.5	12.7±11.4	.647	−4.3 (−13.6, 5.1)	.351
	CG	12.4±12.6	15.0±12.7	.312	*−0.421*	
24 h frequency, times	IG	8.1±1.6	7.5±2.1	.288	−1.3 (−2.8, 0.2)	.086
	CG	7.7±2.7	8.4±2.7	.183	*−0.801*	
Nocturnal frequency, times	IG	1.0±0.6	0.9±0.8	.637	−0.5 (−1.2, 0.2)	.122
	CG	0.8±0.7	1.2±0.9	.047‡	*−0.716*	

Mean voiding volume = 24 h volume/24 h frequency, max-volume = maximum urination recorded highest 1-time urination volume in frequency-volume chart, 24 h voiding volume = average daily urination volume for 3 days, nocturnal voiding volume = averaging daily nocturia volume for 3 nights, NPi = nocturnal polyuria index (nocturnal volume/24 h volume), 24 h frequency = averaging of the urination times per 1 day, nocturnal frequency = averaging of the nocturia times per 1 night.

CG = conventional group, CI = confidence interval, IG = integrative group, MD = mean difference.

* Wilcoxon signed-rank test.

† Mann–Whitney *U* test.

‡ $P<.05$.

Table 4

Changes in patient's global impression of changes and differences between the integrative (IG, n = 15) and conventional group (CG, n = 14).

		Week 5 (T2)	MD (95% CI) Hedges' g	*P*-value*	Week 13 (T3)	MD (95% CI) Hedges' g	*P*-value*
PGIC-A	IG	3.5 ± 1.0	1.3 (0.6, 2.1)	.001†	3.1 ± 1.2	0.4 (–0.4, 1.1)	.412
	CG	2.2 ± 1.0	*1.309*		2.8 ± 0.8	*0.324*	
PGIC-B	IG	3.5 ± 0.1	–1.2 (–1.8, –0.6)	.004†	4.3 ± 1.0	–0.5 (–1.1, 0.2)	.188
	CG	4.7 ± 0.6	*–0.811*		4.8 ± 0.6	*–0.550*	

CG = conventional group, CI = confidence interval, IG = integrative group, MD = mean difference, NA = nonapplicable, PGIC = patient's global impression of changes.
* Mann–Whitney *U* test.
† $P < .05$.

significantly greater than that of CG ($P = .020$). PGIC-A and PGIC-B in IG at T2 showed significant improvement compared to CG ($P = .002$ and .003, respectively). The participants whose prostate size was ≥40 g showed no significant difference in before-after analysis within the group or intergroup analysis (Supplementary File 6, http://links.lww.com/MD/D665).

3.3.6. Adverse events. During the study period, 1 AE was reported as itching in the CG. No serious AEs were reported in either group.

3.4. Feasibility outcomes

To evaluate feasibility, the recruitment, compliance, and retention rates were determined. The recruitment proportion of screened subjects was 96.7%. The recruitment rate was 0.7/wk, and 100% and 85.7% of the subjects participated up to T2 in the IG and CG, respectively. Furthermore, in the IG and CG, 66.7% and 64.3%, respectively, submitted FVCs, while 93.3% and 78.6%, respectively, adhered till the end of the study.

4. Discussion

This study aimed to explore the effects of add-on moxibustion with conventional therapy. A protocol for the combined treatment of conventional treatment plus moxibustion was developed based on the consensus of UDs, KMDs, and a dual-licensed MD and KMD. The changes during the initial 4 weeks indicated the additional effect of moxibustion, and those over the 12-week treatment period provided information related to the persistent effect of moxibustion (4-week moxibustion plus conventional treatment and 8-week conventional treatment in the IG).

According to the baseline characteristics, the participants were 63.3 and 64.5 years of age, with IPSS of 17.7 and 17.1 in the IG and CG, respectively, which indicated a "moderate" score in both groups. Although the prostate size and PSA levels were relatively higher in the CG than in the IG, there was no significant difference. The interpretation of the results was based on the effect size (Hedges' g) and clinical importance because the sample size in this study was not determined based on power calculation, and pilot study analysis has been recommended to be descriptive.[33] The effect size was interpreted as follows: 0.2, small; 0.5, medium; 0.8, large; 1.2, very large; 2.0, huge.[34,35]

During the initial 4 weeks (from T1 to T2), the effect size of moxibustion on the total IPSS was "medium." Among the scoring parameters, incomplete emptying and straining showed "large" effects, whereas frequency, intermittency, urgency, and nocturia showed "medium" effects. The effect size on the QoL was "large." The observed effect size during the total 12 weeks (from T1 to T3) indicated "medium" for total IPSS score, "large" for intermittency, and "medium" for nocturia. On the basis of these results, moxibustion might have been effective for alleviating the symptoms of prostate enlargement, especially incomplete emptying, straining, intermittency, nocturia, and overall QoL. The reduction in total IPSS in the IG from T1 to T3 was −3.0 ± 4.0, which was similar to the minimum clinically important difference (MCID) of 3 points suggested by the AUA guidelines.[14] This reduction was larger than that of T1 to T2, which was an active-treatment period; thus, we could assume that the effect of moxibustion may have persisted for 8 weeks after the end of the treatment. To reassess these results, studies with larger sample sizes and longer observation periods are warranted.

The nocturia score of the IPSS showed nocturnal frequencies of 2.7 and 2.0 times per day in the IG and CG, respectively. The frequency decreased by 0.8 and 0.7 in the IG at T2 and T3, respectively, whereas little change was observed in the CG ($g = -0.684$ and -0.540 at T2 and T3, respectively). Previous studies reported that nocturia more than twice a day is considered meaningful in patients with BPH,[36,37] and the reduction by terazosin and the placebo was 0.7 and 0.4 times, respectively.[37] Regarding these previous studies, moxibustion might have had an additional effect on reducing nocturia in prostate enlargement.

The FVCs also supplied information about the participants' nocturia. According to the FVC, moxibustion showed "medium" effects on nocturnal frequency ($g = -0.716$) and nocturnal voiding volume ($g = -0.583$) and a "small" effect on NPi ($g = -0.421$). However, the baseline nocturnal frequency in the FVC was reported to be less than that in the IPSS (1.0 and 0.8 in the IG and CG, respectively). This discrepancy might have been because FVC showed symptoms of 3 days, while the IPSS showed the average symptoms of the previous 1 month; hence, there probably was a real difference; participants could have inadvertently exaggerated their symptoms while answering the IPSS; or the FVC might have been recorded incorrectly. A study reported that the reliability of the 1-day FVC of male patients was low, especially for nocturia.[38] The 24-hour voiding volume showed group-wise differences; however, the 24-hour voiding volume was within the normal range in both groups, and the variation was relatively large, possibly due to the small sample size; hence, it is hard to derive any meaningful conclusion based on this result. The response rates to the 3-day FVC in this study were 66.7% and 64.3% in the IG and CG, respectively. This response rate can be regarded reliable, considering that the response rate of 1-day FVC was 69% in a previous study.[38] However, it would be helpful if the FVC could be collected for more patients because it provides an objective measure. Future studies would need to include more participants and identify a strategy to increase the response rate of FVC.

The PGIC, which is a subjective evaluation of the changes after treatment, showed improvement with moxibustion. The effect size of PGIC-A was "very large" at T2 and "small" at T3, and that of PGIC-B was "large" at T2 and "medium" at T3. The results indicated that patients in the IG felt "slightly better" to "somewhat better" (3.5 at T2 and 3.1 at T3), whereas those in the CG felt "almost the same" to "slightly better" (2.2 at T2 and 2.8 at T3) according to the changes in PGIC-A. The changes in PGIC-B, which focused on improvement from the baseline (0, much better; 5, no change), indicated that members of the IG reported to have felt some improvement (3.5 at T2 and 4.3 at T3), while those of the CG felt almost the same (4.7 at T2 and 4.8 at T3).[29] Cautious interpretation is needed because PGIC is a subjective evaluation, and there remains a possibility of exaggeration because the participants were not blinded. However, the changes do not seem to be simply differences in numbers but are clinically meaningful, considering the meaning of the score in terms of improvement.

Uroflowmetry is a simple, noninvasive measurement modality that plays a critical role in the assessment of symptoms of BOO and voiding function.[30,39,40] BOO has been reported to be associated with an enlarged prostate and to have an inverse relationship with the risk of prostate cancer. This is because the increased PSA in patients with BOO is induced by urinary reflux and not due to cancer. BOO causes uncomfortable LUTS that compel the patients to undergo unnecessary intense examination, such as biopsy, and thus, it is an important prostate/urinary-related ailment.[10,41] Although there has been no agreement on the usefulness of uroflowmetry as a clinical prognostic and prediction factor of BPH,[42] Q_{max} and PVR were evaluated referentially. The normal range of Q_{max} is 20 to 25 mL/s, and Q_{max} <10 mL/s indicates a high possibility of BOO.[43] Among those who had Q_{max} <20 mL/s (n = 12:12), those in the IG showed an increase, and those in the CG showed a decrease; however, the result was not statistically significant. Those who had Q_{max} <10 mL/s showed improvements of 4.0 ± 4.3 and 3.3 ± 5.6 in the IG and CG, respectively, without statistical significance (n = 6:5, $P = .929$). Previous studies reported that the improvement induced by an α-blocker and 5-ARI were 1.4 to 3.2 and 1.4 to 2.2 mL/s,[44] and the MCID for Q_{max} was 2 mL/s.[45] The results of our study cannot be directly compared with those of the previous study because the proportion of patients with significantly slower voiding rates was lower than that of the earlier study (which included 45–48% of patients with Q_{max} under 10 mL/s), and the conventional treatment in our study comprised only lifestyle advice before drug use. However, moxibustion might be beneficial in increasing the voiding rate considering the greater improvement of Q_{max} in patients with Q_{max} of <20 and <10 mL/s. Further studies are needed to confirm these findings because the number of participants was not enough to arrive at a meaningful statistical conclusion. The PVR showed no meaningful differences between the groups. Most of the study participants had a PVR value in the normal range; therefore, the treatment progress could not be determined by the change in PVR. Only one patient in the IG had an increased PVR (>200 mL), which decreased to 74 mL after 12 weeks.

Subgroup analysis was conducted to consider the heterogeneity of conventional medication and explore possible responders to the moxibustion. In subgroup A patients who were administered α-blockers only, moxibustion showed a greater effect than it did in subgroup B and the overall participants, especially on the total IPSS and nocturia ("very large" effect), followed by incomplete emptying, frequency, and straining ("large" effect). Subgroup A probably had simpler and more typical symptoms compared to subgroup B despite similar baseline IPSS scores. This result might suggest that patients with typical symptoms of BPH tended to respond adequately to moxibustion, as well as conventional treatments. The subgroup B patients who received α-blockers with other agents (5-ARI, anticholinergics, or both) showed a relatively small improvement in the total IPSS ($g = -0.156$). However, straining showed "large" effects, and incomplete emptying showed "medium" effects at T2. In contrast, PGIC-A and PGIC-B were greatly improved at T2 ($g = 1.661$ and -2.018, respectively). This observation suggested that the subjective satisfaction with that improvement seemed fairly high, although the actual improvement in patients with complicated or nontypical symptoms was not that extensive. Therefore, it would be beneficial to add moxibustion in the treatment regimen of patients who have complicated symptoms and do not respond well to conventional treatments; however, further studies are needed because of the small sample size of the present study.

Results of patients whose prostate size was <40 g revealed that the improvement in the total IPSS score during T1 to T3 was significantly greater in the IG than in the CG ($P = .020$), while the total IPSS score was not different between the 2 groups in the overall participants.

To consider the severity, an additional analysis of patients with moderate (IPSS 8–19, n = 9:10 in IG:CG) or severe (IPSS 20–25, n = 6:4 in IG:CG) symptoms was conducted. Among patients with moderate symptoms, those in the IG showed relatively greater improvement than those in the CG in terms of IPSS total score ($g = -0.808$, $P = .082$) and incomplete emptying ($g = -1.054$, $P = .077$) at T2 and the IPSS total score ($g = -1.155$, $P = .040$) and intermittency ($g = -1.296$, $P = .020$) at T3. The patients with severe symptoms showed no group-wise differences in IPSS parameters. Therefore, moxibustion would be more effective for those with moderate rather than severe symptoms. Collectively, the results of the subgroup analyses indicate that moxibustion could be effective for alleviating the symptoms of BPE in patients with simple, typical, mild-to-moderate symptoms, and smaller prostate size (<40 g), but it would also be useful for patients with complex and nontypical symptoms based on their subjective satisfaction. Further studies on a larger group are needed to confirm these findings.

To explore the trial feasibility, recruitment, compliance, and retention rates were recorded. As the recruitment rate was relatively low at 0.7 per week, strategies to promote recruitment should be considered in future trials. The compliance and retention rates were relatively lower in the CG than in the IG; thus, sham treatment would be more appropriate to ensure that various conditions are equally distributed between the 2 groups. To improve the quality of future studies, some factors need to be supplemented. Considering the results of the present study, investigations focusing on specific participants (i.e., those who had complicated symptoms or lower Q_{max}, or who do not respond well to conventional therapy) would be necessary. The study period needs to be longer than 12 weeks to determine the long-term effects and safety of moxibustion. The sample size required for a full-sized RCT can be assumed according to the results of IPSS. When calculated conservatively, the changes in the IG and CG were −3.0 and 0.6, respectively, and the SD was 5.3. Consequently, 35 participants per group would be required (α, 0.05; power, 0.8). Future studies designed with a placebo-control group would require a larger sample size.

Our study had some limitations that are worth mentioning. First, sham intervention was not used in the control group; thus, the placebo effect cannot be eliminated. Participants might have volunteered to participate in this trial with expectations of receiving moxibustion, which might have caused a discrepancy in patient satisfaction between the groups. In addition, it probably caused a higher drop-out rate in the CG than in the IG. Second, heterogeneity was relatively high among the participants as the conventional treatments were not restricted. As possible responders were observed in this trial, future studies should focus on a narrower range of patients to control confounding factors. Third, the results of this study cannot be used as evidence of the efficacy of moxibustion because this was a pilot trial with a small sample size. A full-sized, randomized, sham-controlled trial with a longer duration should be conducted to evaluate the efficacy of moxibustion.

Despite these limitations, to our knowledge, this study is the first to examine the effectiveness and safety of moxibustion treatment as an adjunct for conventional treatment of BPE. Specifically, this is the first trial designed and conducted by UDs, KMDs, and a dual-licensed MD/KMD expert in integrative treatment. The results of this study provide basic data on the effectiveness and safety of moxibustion for LUTS in patients with BPE, together with information about possible responders. We highlight that moxibustion might be beneficial for alleviating LUTS, especially to treat incomplete emptying, straining, and nocturia.

5. Conclusion

Moxibustion treatment might be a beneficial adjunct therapy for LUTS in BPE patients. A full-sized trial with comparator modifications as sham treatment and an extended study period is warranted to confirm the effectiveness of this adjunct therapy. In addition, it would be better if sufficient numbers of participants in subgroups are included to identify effects on patients with atypical symptoms or those who do not respond well to conventional treatment.

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