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Original Article

Moxibustion for prehypertension and stage I hypertension: a pilot randomized controlled trial

Kyung-Min Shin[a], Ji-Eun Park[b], Tae-Han Yook[c], Jong-Uk Kim[c], Ojin Kwon[a], Sun-Mi Choi[d,*]

[a] Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, South Korea
[b] Future Medicine Division, Korea Institute of Oriental Medicine, Daejeon, South Korea
[c] Department of Acupuncture & Moxibustion Medicine, Korean Medicine Hospital of Woosuk University, Jeonju, South Korea
[d] Korea Institute of Oriental Medicine, Daejeon, South Korea

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ABSTRACT

Background: Prehypertension and hypertension are associated with cardiovascular disease, ischemic heart disease, and stroke morbidity. The purpose of this study is to evaluate the effectiveness and safety of moxibustion in patients with prehypertension or hypertension.
Methods: Forty-five subjects with prehypertension or stage I hypertension were randomized into three groups: moxibustion treatment group A (2 sessions/week for 4 weeks), moxibustion treatment group B (3 sessions/week for 4 weeks), and control group (nontreated group). The primary outcome measure was the change in blood pressure after 4 weeks of treatment. Safety was assessed at every visit.
Results: There were no significant differences in systolic blood pressure (SBP) or diastolic blood pressure (DBP) among three groups after 4 weeks of treatment ($p = 0.4798$ and $p = 0.3252$, respectively). In treatment group B, there was a significant decrease in SBP and DBP from baseline to 4 weeks of treatment (mean difference (MD) −9.55; $p = 0.0225$, MD −7.55; $p = 0.0098$, respectively). There were no significant differences among groups in secondary outcome measures after 4 weeks of treatment. Six adverse events (AEs) in the treatment group A and 12 AEs in the treatment group B occurred related to the moxibustion treatment.
Conclusion: In conclusion, the results of this study show that moxibustion (3 sessions/week for 4 weeks) might lower blood pressure in patients with prehypertension or stage I hypertension and treatment frequency might affect effectiveness of moxibustion in BP regulation. Further randomized controlled trials with a large sample size on prehypertension and hypertension should be conducted.
Trial registration: This study was registered with the 'Clinical Research Information Service (CRIS)', Republic of Korea (KCT0000469), and the protocol for this study was presented orally at the 15th International Council of Medical Acupuncture and Related Techniques (ICMART) in Athens, 25–27 May 2012.

1. Introduction

Hypertension is considered one of the prevalent risk factors for coronary heart disease, cardiovascular disease, ischemic heart disease, and cardiac failure.[1,2] The worldwide population of adult patients with hypertension is estimated to increase from 972 million (26.4%) in 2000 to 1.56 billion (29.2%) in 2025.[3] In the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), prehypertension was defined as a systolic blood pressure (SBP) of 120–139 mmHg or a diastolic blood pressure (DBP) of 80–89 mmHg.[4] According to the Korean Nation Health and Nutrition Survey in 2001, the prevalence of hypertension and prehypertension in the adult population was 22.9% and 31.6%, respectively.[5] According to the Framingham Heart Study, 49.5% of people with high normal blood pressure (130–139/85–89 mmHg, defined by JNC-6) in patients 65 years and older progressed to hypertension within four years.[6] Prehypertension is also associated with cardiovascular disease and stroke morbidity.[7,8] Therefore,

* Corresponding author at: Korea Institute of Oriental Medicine, 1672, Yuseong-daero, Yuseong-gu, Daejeon 34054, South Korea.
E-mail address: smchoi@kiom.re.kr (S.-M. Choi).

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in addition to hypertension, prehypertension should be managed appropriately.

Antihypertensive medication is an important treatment for hypertension.[9] Lifestyle modifications such as weight reduction, dietary sodium reduction, and physical activity also help to lower blood pressure (BP).[9] While hypertension is generally well controlled through medications, it can also go uncontrolled for various reasons, such as knowledge deficits, medication costs, and side effects.[10] According to data obtained from the United States National Health Interview Survey (NHIS) in 2002 and 2007, there is a growing interest in complementary and alternative medicine (CAM), including acupuncture, chiropractic, and herbal medicines, to treat diseases such as musculoskeletal problems and hypertension.[11,12]

Moxibustion involves the application of burning of moxa (i.e., *Artemisia vulgaris* or mugwort) directly or indirectly at acupuncture points or other specific parts of the body. Moxibustion is used to treat and prevent various diseases such as breech presentation,[13] menopausal hot flashes,[14] irritable bowel syndrome,[15] knee osteoarthritis,[16] and chronic fatigue.[17] However, according to the systematic reviews, the effectiveness and safety of moxibustion for hypertension were inconclusive due to poor methodological qualities.[18,19] Additionally there are few randomized controlled trials (RCTs) regarding moxibustion for prehypertension. Therefore, rigorously designed trials are needed to establish evidence for effectiveness and safety of moxibustion on prehypertension and hypertension. The purpose of this study is to evaluate the effectiveness and safety of moxibustion in patients with prehypertension or stage I hypertension. In addition, this study compared the moxibustion treatment effects by the treatment frequency.

2. Methods

2.1. Study flow, recruitment, and ethics

This study was a randomized, usual-care controlled, parallel designed trial, and the study protocol has been previously published elsewhere.[20] This trial was conducted at Woosuk Korean Medicine hospital in South Korea from July 2012 to April 2013. Participants were recruited using notices at the hospital and newspaper advertisements.

This study protocol was approved before study onset by the institutional review boards of the Woosuk Korean Medicine hospital (approval no. WSOH IRB 1205-02). Written informed consent was obtained from all of the participants. All participants had the right to withdraw from the trial at any time. The trial was conducted in accordance with the principles of the Declaration of Helsinki.[21]

2.2. Participants

Participants were included if they met the following criteria: (1) age between 19 and 65 years; (2) patients with prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg) or stage I hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg) defined by JNC-7; (3) willingness to volunteer and provide written consent. Participants were excluded if they met the following criteria: (1) use of medications to control BP; (2) secondary hypertension; (3) history of cerebrovascular disease, cardiovascular disease, malignant tumors, kidney disease, liver disease, thyroid gland disease, active tuberculosis, or other infectious disease; (4) presence of diabetes and use of insulin or antidiabetic medications; (5) drug or alcohol dependence; (6) use of hemorrhagic disease and/or anticoagulation medications (excluding aspirin); (7) use of systemic steroid therapy or immunosuppressive therapy; (8) use of medications that could affect BP such as central nervous system depressants or stimulants; (9) pregnancy or the possibility of pregnancy; (10) hypersensitivity reactions following moxibustion; (11) use of traditional Korean Medicine related to hypertension in the past month; (12) classification as unsuitable for the trial, as judged by the person in charge of the clinical trial.

2.3. Sample size, randomization, allocation, and blinding

Given that this is a pilot study, 15 participants were included for each group to fulfill the minimum number of participants necessary to evaluate the effectiveness of moxibustion and to calculate the appropriate sample size for future RCTs in consideration of the 20% dropout rate.[22,23]

Random numbers were generated through computerized block-randomization with the SAS statistical package, version 9.1.3 (SAS Institute Inc., Cary, NC). Randomization was stratified by age and sex in a 1:1:1 allocation ratio. Randomization was performed by a separate statistician using an online centralized randomization service, with allocation concealment.

It was impossible to blind the practitioner and participants to group allocation because participants in the control group did not receive any treatment. As a result, the practitioners, participants, and outcome assessors were not blinded; however, data analysts were blinded to this information.

2.4. Interventions

A total of forty-five participants were randomized into three groups: treatment group A (2 sessions/week), treatment group B (3 sessions/week), and control group (nontreated group) before the first treatment. The treatment was continued for 4 weeks and the follow-up assessments were conducted at weeks 8, 12, 16, 20, and 24 after randomization.

2.5. Treatment group A

In treatment group A, two sessions per week were conducted during a 4-week period for a total of 8 sessions. Eight standard acupuncture points (CV4, CV12, bilateral LI11, ST36 and GB39) were selected by professors and researchers who have an acupuncture and moxibustion specialist license in Korea in a consensus process based on several previous studies.[24–26] During each session, each acupuncture point was treated five times with indirect moxibustion (Manina, Haitnim Co., Korea). The total treatment time of each session was 25 minutes. All participating practitioners have had more than 3 years of clinical experience since completing 6 years of study at the University of Korean Medicine and have received a Korean Medicine Doctor license.

2.6. Treatment group B

The treatment process was exactly the same as those for treatment group A, but in treatment group B, three sessions per week were performed during a 4-week period for a total of 12 sessions.

2.7. Control group

The control group did not receive any moxibustion treatment during the treatment period.

2.8. Permitted and prohibited concomitant treatments

Brochures containing information on diet and exercise that help prevent and alleviate hypertension were provided to all groups. In addition, all participants were asked to maintain their normal

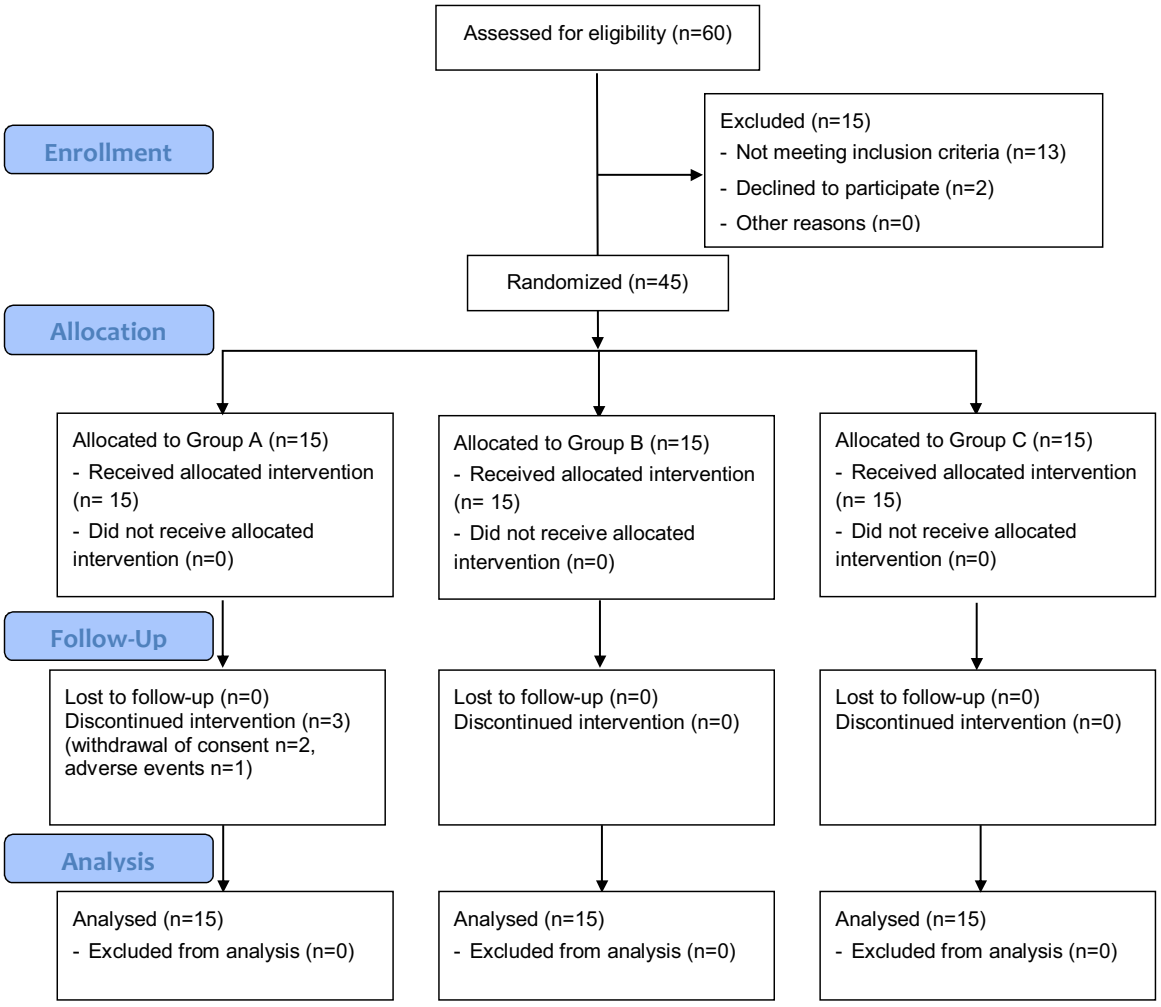

Fig. 1. Study flow chart.

lifestyle, including diet, exercise, and workload, during the study period. All groups were prohibited from undergoing active treatment to lower the BP for the 4-week treatment period. After the completion of the 4-week treatment, the subjects were allowed to decide for themselves whether to receive additional treatment.

2.9. Outcome measures

The primary outcome measurement was the change in SBP and DBP before and after 4 weeks treatment. During the 4-week treatment period, BP was measured using a BP meter (HD-505, Jawon Medical Co., Korea). The secondary outcome measures were the mean pulse pressure, body mass index (BMI), heart rate variability (HRV), neck disability index (NDI), Modified Form of the Stress Response Inventory (SRI-MF), the Fatigue Severity Scale (FSS), the Pittsburgh Sleep Quality Index (PSQI), EuroQol-5 Dimensions (EQ-5D), general assessments, and blood tests including fasting blood sugar (FBS), uric acid, lipid profile, high sensitivity C-reactive protein (hs-CRP), liver function test (LFT), hemoglobin A1c (HbA1C), and complete blood count (CBC). To evaluate safety, the occurrence of adverse events (AEs) and serious adverse events (SAEs) related to moxibustion was assessed during the study period.

2.10. Statistical analyses

Statistical analysis was conducted using intention-to-treat (ITT) analysis. The last observation carried forward (LOCF) method was used for missing data. Interim analysis was not performed. Continuous data were represented by the mean and 95% confidence interval (CI), whereas categorical data were represented by frequency and percentage table. For the comparison of the results among the groups, analysis of covariance (ANCOVA) with baseline as the covariate and group as the fixed factor was used. The Bonferroni test was used for intergroup comparison to compensate for multiple comparisons. Paired *t*-test was used to determine the difference between before and after treatment in each group. In addition, the Fisher exact test was performed for categorical data. The significance levels of the analysis for the primary and secondary outcome assessments were 0.025 and 0.05, respectively. The occurrence of AEs and SAEs was summarized by groups and analyzed by using the Fisher exact test. All statistical analyses were conducted with the SAS statistical package, version 9.4.

3. Results

3.1. Participants

A flow chart of patient enrollment and disposition is shown in Fig. 1, and demographic and baseline characteristics are summarized in Table 1. Of the 60 potential participants contacted, 15 were excluded because they did not meet the inclusion criteria ($n = 13$) or refused to participate ($n = 2$). Forty-five participants were equally allocated into the treatment group A, treatment group B, and control group. Three participants in the treatment group A dropped out during the study. Reasons for discontinuation included withdrawal

Table 1
Baseline Demographics and Characteristics

Characteristics	Treatment group A	Treatment group B	Control group	*p*-value
Age (year)*	42.07 (34.58, 49.55)	40.93 (32.88, 48.98)	40.87 (33.80, 47.93)	0.9639
Sex (M/F)**	9 (60.00%)/6 (40.00%)	9 (60.00%)/6 (40.00%)	11 (73.33%)/4 (26.67)	0.6785
Height (cm)*	165.19 (159.72, 170.65)	165.85 (161.05, 170.64)	166.80 (161.97, 171.63)	0.8879
Weight (kg)*	69.95 (63.38, 76.53)	72.93 (67.58, 78.27)	75.02 (68.30, 81.74)	0.4716
Smoking (Y/N)**	2 (13.33%)/13 (86.67%)	0 (0.00%)/15 (100.00%)	3 (20.00%)/12 (80.00%)	0.3425
Drinking (Y/N)**	8 (53.33%)/7 (46.67%)	7 (46.67%)/8 (53.33%)	9 (60.00%)/6 (40.00%)	0.7650
Exercise (Y/N)**	11 (73.33%)/4 (26.67%)	11 (73.33%)/4 (26.67%)	10 (66.67%)/5 (33.33%)	0.9999
Treatment expectancy*	6.13 (5.33, 6.94)	5.60 (4.31, 6.89)	6.00 (5.09, 6.91)	0.7147

* Analysis of variance (ANOVA).
** Fisher exact test.

Table 2
Primary Outcomes

Outcomes	Time point	Treatment group A	Treatment group B	Control group	*p*-value†
SBP	Baseline	138.44 (131.51, 145.37)	135.55 (129.95, 141.15)	137.57 (132.40, 142.75)	
	Week 4	133.50 (124.89, 142.11)	126.00 (117.56, 134.44)	131.43 (124.29, 138.56)	0.4798
	Diffirence, mean (95% CI)‡	−4.94 (−10.37, 0.49)	−9.55 (−17.55, −1.56)	−6.15 (−12.53, 0.23)	
	p-value§	0.0713	0.0225*	0.0578	
Prehypertention (*n* = 9, 9, and 10, respectively)	Baseline	129.29 (125.80, 132.77)	129.59 (124.31, 134.86)	132.39 (128.07, 136.71)	
	Week 4	123.02 (117.75, 128.30)	120.40 (110.02, 130.78)	127.47 (118.24, 136.70)	
	Diffirence, mean (95% CI)‡	−6.27 (−11.44, −1.09)	−9.18 (−18.73, 0.36)	−4.92 (−13.65, 3.81)	
Stage I hypertention (*n* = 6, 6, and 5, respectively)	Baseline	152.17 (146.50, 157.84)	144.50 (137.00, 152.00)	147.94 (142.13, 153.75)	
	Week 4	149.22 (138.35, 160.09)	134.40 (118.93, 149.87)	139.34 (127.62, 151.06)	
	Diffirence, mean (95% CI)‡	−2.95 (−17.37, 11.47)	−10.10 (−29.34, 9.14)	−8.60 (−22.11, 4.91)	
DBP	Baseline	83.09 (76.39, 89.80)	85.15 (80.51, 89.79)	85.81 (82.58, 89.05)	
	Week 4	81.21 (72.84, 89.58)	77.60 (71.23, 83.97)	80.33 (75.62, 85.05)	0.3252
	Diffirence, mean (95% CI)‡	−1.89 (−7.02, 3.24)	−7.55 (−12.98, −2.13)	−5.48 (−10.80, −0.16)	
	p-value§	0.4433	0.0098*	0.0444*	
Prehypertention	Baseline	76.19 (70.10, 82.28)	79.70 (75.73, 83.67)	82.96 (80.20, 85.72)	
	Week 4	74.90 (64.86, 84.94)	72.26 (65.15, 79.36)	78.83 (72.55, 85.11)	
	Diffirence, mean (95% CI)‡	−1.29 (−9.00, 6.42)	−7.44 (−16.09, 1.20)	−4.13 (−12.06, 3.80)	
Stage I hypertention	Baseline	93.45 (83.18, 103.72)	93.33 (88.63, 98.03)	91.52 (85.32, 97.92)	
	Week 4	90.67 (76.30, 105.04)	85.62 (74.87, 96.37)	83.34 (73.49, 93.19)	
	Diffirence, mean (95% CI)‡	−2.78 (−12.03, 6.46)	−7.72 (−16.26, 0.83)	−8.18 (−15.36, −1.00)	

† *p*-value by Analysis of covariance (ANCOVA).
‡ Mean difference (95% CI) from baseline.
§ *p*-value by paired *t*-test.
* $p < 0.05$. SBP: systolic blood pressure; DBP: diastolic blood pressure; CI: confidence interval.

of consent ($n = 2$) and AEs ($n = 1$) (Fig. 1). There were no significant differences among groups in all demographic characteristics, including age, sex, height, weight, smoking, drinking, exercise, and treatment expectancy (Table 1).

3.2. Primary outcome measures

There were no significant differences in SBP and DBP among groups after 4 weeks of treatment ($p = 0.4798$ and $p = 0.3252$, respectively). In treatment group B, there was a significant decrease in SBP and DBP from baseline to 4 weeks of treatment (mean difference (MD) −9.55; 95% CI −17.55 to −1.56; $p = 0.0225$, MD −7.55; 95% CI −12.98 to −2.13; $p = 0.0098$, respectively). (Table 2 and Fig. 2) The results of SBP and DBP by dividing into patients with prehypertension and stage I hypertension were also presented in Table 2.

3.3. Secondary outcome measures

There were no significant differences among groups in the secondary outcome measures including the mean pulse pressure, BMI, HRV, NDI, SRI-MF, FSS, PSQI, EQ-5D, general assessments, and blood test after 4 weeks of treatment (Table 3).

3.4. Safety

In order to evaluate safety, the occurrence of AEs related to moxibustion were assessed during the study period. Six AEs (blistering 4, headache 1, and itching sensations 1) in the treatment group A and 12 AEs (blistering 12) in the treatment group B occurred related to the moxibustion treatment and the symptom intensity was mild.

4. Discussion

This is a well-designed RCT to evaluate the effectiveness and safety of moxibustion for prehypertension and stage 1 hypertension. In this randomized, 4-week treatment trial, moxibustion might be effective treatment in prehypertension and stage 1 hypertension.

After 4 weeks of moxibustion treatment, treatment group B showed a greater tendency towards decrease in SBP and DBP than did both treatment group A and the control group, although there was no statistically significant difference among the groups. In treatment group B, there was a significant decrease from baseline to the 4th week of treatment in SBP (MD −9.55; 95% CI −17.55 to −1.56; $p = 0.0225$) and DBP (MD −7.55; 95% CI −12.98 to −2.13; $p = 0.0098$). There were no significant differences among groups in

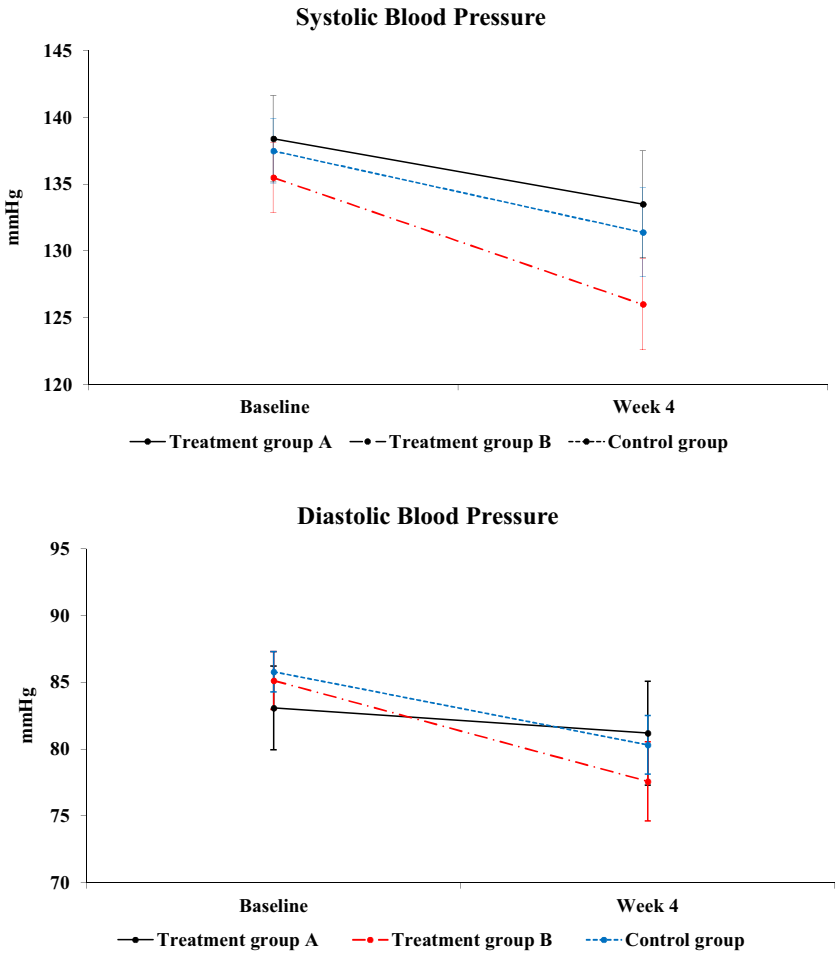

Fig. 2. Primary outcome at endpoint. DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 3
Secondary Outcomes

Outcomes	Treatment group A		Treatment group B		Control group		*p*-value*
	Baseline	Week 4	Baseline	Week 4	Baseline	Week 4	
Pulse pressure	65.89 (60.21, 71.58)	68.28 (61.81, 74.75)	68.00 (62.23, 73.77)	68.65 (63.80, 73.50)	73.77 (67.85, 79.69)	69.79 (64.42, 75.16)	0.2685
BMI	24.85 (22.89, 26.82)	25.51 (24.13, 26.89)	26.56 (24.51, 28.61)	26.31 (24.31, 28.30)	26.31 (24.10, 28.52)	27.14 (24.81, 29.37)	0.3726
NDI	6.44 (3.00, 9.88)	3.52 (1.21, 5.83)	7.87 (3.25, 12.48)	6.27 (1.98, 10.55)	8.93 (4.67, 13.20)	8.67 (3.97, 13.36)	0.1229
SRI-MF	27.53 (24.03, 31.03)	26.73 (23.28, 30.18)	30.13 (25.82, 34.45)	29.80 (25.43, 34.17)	29.80 (27.74, 31.86)	28.87 (25.66, 32.07)	0.8516
FSS	17.80 (12.77, 22.83)	15.47 (1059, 20.35)	20.47 (15.95, 24.98)	17.33 (12.36, 22.31)	21.47 (16.69, 26.25)	19.53 (15.01, 24.06)	0.7550
PSQI	13.80 (12.84, 14.76)	13.20 (11.98, 14.42)	15.20 (13.59, 16.81)	14.33 (12.87, 15.79)	15.07 (13.82, 16.31)	14.80 (13.29, 16.31)	0.4706
EQ-5D	0.942 (0.930, 0.950)	0.932 (0.904, 0.950)	0.933 (0.915, 0.950)	0.928 (0.905, 0.950)	0.931 (0.916, 0.945)	0.934 (0.920, 0.948)	0.6341
hs-CRP	0.49 (0.25, 0.73)	1.54 (0.17, 2.91)	0.74 (0.33, 1.15)	0.82 (0.19, 1.45)	1.06 (0.44, 1.68)	1.09 (0.22, 1.96)	0.5646
HRV							
Mean-RR (ms)	958.8 (869.6, 1047.0)	929.1 (828.6, 1030.0)	901.9 (828.2, 975.7)	896.0 (822.5, 969.5)	882.7 (823.2, 942.3)	901.5 (839.6, 963.5)	0.3613
Mean-HRV (cycle/min)	64.33 (58.13, 70.54)	66.73 (60.07, 73.40)	67.67 (62.85, 72.48)	68.40 (63.17, 73.63)	68.87 (64.05, 73.68)	67.60 (62.65, 72.55)	0.4195
SDNN (ms)	40.33 (32.44, 48.22)	40.80 (34.02, 47.58)	36.20 (29.55, 45.85)	38.20 (30.54, 45.86)	37.80 (31.46, 44.14)	39.00 (30.95, 47.05)	0.9982
Complexity	0.63 (0.54, 0.73)	0.61 (0.52, 0.70)	0.61 (0.53, 0.69)	0.59 (0.50, 0.69)	0.49 (0.38, 0.61)	0.57 (0.47, 0.66)	0.8945
HRV-Index (%)	18.63 (14.33, 22.92)	19.95 (16.26, 23.64)	18.78 (15.20, 22.36)	17.83 (14.36, 21.30)	19.63 (15.61, 23.66)	17.24 (13.47, 21.01)	0.1864
pNN50 (%)	65.14 (56.17, 74.11)	63.35 (55.05, 71.64)	69.01 (60.81, 77.20)	66.87 (57.84, 75.91)	66.05 (58.21, 73.88)	67.21 (58.65, 75.77)	0.7823
RMSSD (ms)	26.73 (19.00, 34.46)	25.73 (18.19, 33.28)	25.00 (15.26, 34.74)	21.80 (15.19, 28.40)	20.07 (13.18, 26.95)	21.60 (15.17, 28.03)	0.6041
SDSD (ms)	33.00 (24.29, 41.71)	32.13 (23.57, 40.69)	30.73 (19.36, 42.11)	27.40 (19.55, 35.25)	25.40 (17.00, 33.80)	27.40 (19.34, 35.46)	0.6282
Ln(TP)	7.13 (6.74, 7.53)	7.19 (6.83, 7.55)	6.86 (6.54, 7.18)	6.98 (6.57, 7.39)	7.08 (6.71, 7.45)	7.11 (6.64, 7.57)	0.9785
Ln(VLF)	6.53 (6.03, 7.04)	6.62 (6.18, 7.06)	6.20 (5.84, 6.56)	6.43 (5.92, 6.93)	6.67 (6.29, 7.05)	6.53 (6.07, 7.00)	0.8822
Ln(LF)	5.59 (5.19, 6.00)	5.70 (5.35, 6.05)	5.46 (5.08, 5.84)	5.47 (5.03, 5.92)	5.18 (4.67, 5.69)	5.60 (5.06, 6.14)	0.1966
Ln(HF)	5.21 (4.76, 5.65)	5.13 (4.63, 5.63)	5.00 (4.48, 5.52)	4.94 (4.43, 5.45)	4.74 (4.08, 5.40)	4.98 (4.32, 5.64)	0.5220
Norm LF (nu)	58.85 (49.06, 68.64)	62.32 (51.50, 73.14)	60.80 (53.37, 68.23)	62.27 (53.46, 71.09)	59.93 (49.90, 69.95)	63.13 (52.93, 73.34)	0.9318
Norm HF (nu)	41.15 (31.36, 50.94)	37.68 (26.86, 48.50)	39.20 (31.77, 46.63)	37.73 (28.91, 46.54)	40.07 (30.05, 50.10)	36.87 (26.66, 47.07)	0.9318

* *p*-value by Analysis of covariance (ANCOVA); BMI: body mass index; NDI: neck disability index; SRI-MF: Modified Form of the Stress Response Inventory; FSS: Fatigue Severity Scale; PSQI: Pittsburgh Sleep Quality Index; EQ-5D: EuroQol-5 Dimensions; hs-CRP: high sensitivity C-reactive protein; HRV: Heart Rate Variability.

secondary outcome measures including mean pulse pressure, BMI, HRV, NDI, SRI-MF, FSS, PSQI, EQ-5D, general assessments, and blood test after 4 weeks of treatment.

With respect to the safety of moxibustion, 6 AEs in treatment group A and 12 AEs in treatment group B occurred related to the moxibustion treatment and the intensity of AEs was mild. All AEs were improved with or without appropriate management during the study period except 1 AE (lost to follow-up). According to the systematic review of AEs of moxibustion, various AEs such as blistering, itching sensations, discomfort due to smoke, general fatigue, headaches, and burns were reported in clinical trials.[27] In this study, blistering, headache, and itching sensations were reported. When performing moxibustion, attention should be paid to these symptoms and appropriate management should be done.

According to systematic review, no confirmatory conclusions could be made regarding the effectiveness and safety of the moxibustion for hypertension because of poor methodological quality.[18,19] There are also few published RCTs concerning moxibustion for prehypertension. Our research team has conducted various RCTs on prehypertension or stage I hypertension from 2011 to 2016. Before conducting the RCTs for hypertension, we reviewed the methodology and results of the clinical trials of acupuncture,[28] moxibustion[29] and Qigong exercise.[30] From 2011 to 2012, we conducted studies to assess the effectiveness and safety of acupuncture,[31] auricular acupuncture,[32] moxibustion,[20] and qigong[33–35] in patients with prehypertension or stage I hypertension. After 8 weeks of acupuncture treatment, there was a significant difference in DBP (−5.7 mmHg, $p = 0.025$) but not SBP (−6.0 mmHg, $p = 0.123$) between the acupuncture group and nontreated control group.[31] After 8 weeks of qigong treatment, significant differences were observed between the qigong group and nontreated control group regarding changes in SBP (−5.19 mmHg, $p = 0.0064$) and DBP (−6.72 mmHg, $p = 0.0003$).[34] After 12 weeks of Dongeui qigong treatment, the difference in the change in BP between the Dongeui qigong group and nontreated control group was 3.58 mmHg ($p = 0.31$) for SBP and 1.73 mmHg ($p = 0.57$) for DBP.[35] The results of these studies indicate that acupuncture and qigong might be an effective intervention in reducing BP in patients with prehypertension or stage I hypertension. From 2013 to 2014, we conducted studies to investigate the effectiveness and safety of acupuncture for prehypertension or stage I hypertension in postmenopausal women.[36,37] After 8 weeks of acupuncture treatment, the acupuncture group showed a significant decrease in DBP, but not SBP, compared to the nontreated control group ($p = 0.032$).[37] The results of this study show that acupuncture might be an effective intervention on prehypertension or stage I hypertension in postmenopausal women. From 2014 to 2016, we conducted a prospective, comparative, randomized, interventional cohort study on prehypertension or stage I hypertension in postmenopausal women.[38] The results are currently being prepared for submission to a peer-reviewed journal.

This study has strengths and limitations. This study was a well-designed RCT for evaluating the effectiveness and safety of moxibustion in reduction of BP in patients with prehypertension or stage 1 hypertension. We employed proper randomization, allocation concealment and blinding of data analysts. In addition, this study compared the moxibustion treatment effects by the treatment frequency. This study has several limitations. First, in this study, practitioners, participants, and outcome assessors were not blinded, although data analyst blinding was conducted. Second, we did not use 24-hour ambulatory blood pressure monitoring (ABPM); therefore, this study did not reflect the various changes in BP during the day. Further studies should be undertaken to clarify the mechanisms of action of moxibustion.

In conclusion, the results of this study show that moxibustion (3 sessions/week for 4 weeks) might lower BP in patients with prehypertension or stage I hypertension, and treatment frequency might affect effectiveness of moxibustion in BP regulation. Further RCTs with rigorous design and a large sample size of patients with hypertension should be conducted to confirm the effectiveness and safety of moxibustion. In addition, the clinical significance in the effect of moxibustion on patients with hypertension should also be confirmed.

Author contributions

KMS contributed to the design of the study and drafted the manuscript. JEP, THY, and JUK participated in the design of the study and contributed to a critical review of the manuscript. OK was involved in statistical analysis of the study. SMC supervised the overall design of the study as the principal investigator. All authors have read, revised, and approved the final manuscript in its current form.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix I. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.imr.2018.11.002.

References

1. Castelli W. Epidemiology of coronary heart disease: the Framingham study. *Am J Med* 1984;76:4–12.
2. Organization WH, Group ISoHW. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypert* 2003;21:1983–92.
3. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217–23.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206–52.
5. Choi KM, Park HS, Han JH, Lee JS, Lee J, Ryu OH, et al. Prevalence of prehypertension and hypertension in a Korean population: Korean National Health and Nutrition Survey 2001. *J Hypert* 2006;24:1515–21.
6. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet* 2001;358:1682–6.
7. Liszka HA, Mainous AG, King DE, Everett CJ, Egan BM. Prehypertension and cardiovascular morbidity. *Ann Fam Med* 2005;3:294–9.
8. Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, et al. Prehypertension and the risk of stroke. A meta-analysis. *Neurology* 2014;82:1153–61.
9. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289:2560–71.
10. Wang TJ, Vasan RS. Epidemiology of uncontrolled hypertension in the United States. *Circulation* 2005;112:1651–62.
11. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Sem Integr Med* 2004;2:54–71.
12. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children; United States 2007. *Natl Health Stat Report* 2008;12:1–23.
13. Cardini F, Weixin H. Moxibustion for correction of breech presentation: a randomized controlled trial. *JAMA* 1998;280:1580–4.
14. Park J-E, Lee MS, Jung S, Kim A, Kang K, Choi J, et al. Moxibustion for treating menopausal hot flashes: a randomized clinical trial. *Menopause* 2009;16:660–5.
15. Shi Y, Chen Y-H, Yin X-J, Wang A-Q, Chen X-K, Lu J-H, et al. Electroacupuncture versus Moxibustion for irritable bowel syndrome: a randomized, parallel-controlled trial. *Evid-Based Complement Altern Med* 2015:2015.

16. Zhao L, Cheng K, Wang L, Wu F, Deng H, Tan M, et al. Effectiveness of moxibustion treatment as adjunctive therapy in osteoarthritis of the knee: a randomized, double-blinded, placebo-controlled clinical trial. *Arthrit Res Therap* 2014;16. R133.
17. Kim HG, Yoo SR, Park HJ, Son C-G. Indirect moxibustion (CV4 and CV8) ameliorates chronic fatigue: a randomized, double-blind, controlled study. *J Altern Complement Med* 2013;19:134–40.
18. Kim J-I, Choi J-Y, Lee H, Lee MS, Ernst E. Moxibustion for hypertension: a systematic review. *BMC Cardiovasc Disord* 2010;10:33.
19. Xiong X, Liu W, Yang X, Feng B, Wang J. Moxibustion for essential hypertension. *Complement Therap Med* 2014;22:187–95.
20. Shin K-M, Park J-E, Liu Y, Jung H-J, Jung S-Y, Lee M-H, et al. Efficacy of moxibustion for pre-or stage I hypertension: study protocol for a pilot randomized controlled trial. *Trials* 2012;13:188.
21. Williams JR. The Declaration of Helsinki and public health. *Bull World Health Organ* 2008;86:650–2.
22. Johanson GA, Brooks GP. Initial scale development: sample size for pilot studies. *Educ Psychol Meas* 2010;70:394–400.
23. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceut Stat* 2005;4:287–91.
24. Kim JI, Choi JY, Lee H, Lee MS, Ernst E. Moxibustion for hypertension: a systematic review. *BMC Cardiovas Disord* 2010;10:33.
25. Lee BH, Kim CH, Seo JC, Youn HM, Jang KJ, Song CH, et al. The effects of decreasement of blood pressure on hypertension patients by moxibustion. *J Korean Acupunct Moxibust Soc* 2001;18:70–6.
26. Liu Y, Park JE, Kim AR, Jung HJ, Choi SM. Review of moxibustion treatment for hypertension in clinical trials. *J Korean Acupunct Moxibust Soc* 2011;28:87–96.
27. Park J-E, Lee S-S, Lee MS, Choi S-M, Ernst E. Adverse events of moxibustion: a systematic review. *Complement Therap Med* 2010;18:215–23.
28. Jung S-Y, Park J-E, Kim J-E, Kim A-R, Choi S-M. Review of acupuncture treatment for hypertension in clinical trials. *J Korean Med* 2012:33.
29. Liu Y, Park J-E, Kim A-R, Jung H-J, Choi S-M. Review of moxibustion treatment for hypertension in clinical trials. *Acupuncture* 2011:28.
30. Jung H-J, Park J-E, Liu Y, Choi S-M. Review of clinical trials using qigong exercise on patients with hypertension. *Korean J Acupunct* 2011;28:177–86.
31. Liu Y, Park J-E, Shin K-M, Lee M, Jung HJ, Kim A-R, et al. Acupuncture lowers blood pressure in mild hypertension patients: a randomized, controlled, assessor-blinded pilot trial. *Complement Therap Med* 2015;23:658–65.
32. Kim J-H, Jung HJ, Kim T-H, Lee S, Kim J-E, Kang K-W, et al. Auricular acupuncture for prehypertension and stage 1 hypertension: study protocol for a pilot multicentre randomised controlled trial. *Trials* 2013;14:303.
33. Park J-E, Liu Y, Park T, Hong S, Kim J-E, Kim T-H, et al. A trial for the use of qigong in the treatment of pre and mild essential hypertension: a study protocol for a randomized controlled trial. *Trials* 2011;12:244.
34. Park J-E, Lee M, Kang K, Jung H, Liu Y, Shin M. Randomized, controlled trial of qigong for treatment of prehypertension and mild essential hypertension. *Altern Therap Health Med* 2014;20:21.
35. Park J-E, Kim J-E, Jung S, Kim A, Park H, Hong S. The effect of dongeui qigong for prehypertension and mild essential hypertension. *Evid-Based Complement Altern Med* 2017:2017.
36. Kim J-E, Choi J-B, Kim H-J, Kang K-W, Liu Y, Jung H-J, et al. Acupuncture for prehypertension and stage 1 hypertension in postmenopausal women: protocol for a randomized controlled pilot trial. *Korean J Acupunct* 2014;31:5–13.
37. Kim J-E, Choi S-M, Choi J-B, Kim H-J, Kwon O, Kim J-H, et al. Acupuncture for prehypertension and stage 1 hypertension in postmenopausal women: a randomized controlled pilot trial. *Korean J Acupunct* 2017;34:116–25.
38. Seo B-N, Park J-E, Kim Y-E, Kang K-W, Seol I-C, Choi S-M. Effects of acupuncture in postmenopausal women with prehypertension or stage 1 hypertension: study protocol for a prospective, comparative, interventional cohort study. *Integr Med Res* 2018;7:95–102.