Original Article: Clinical Investigation

Combination therapy with tamsulosin and traditional herbal medicine for lower urinary tract symptoms due to benign prostatic hyperplasia: A double-blinded, randomized, pilot clinical trial

Chung Lyul Lee,[1,†] Hyeun-Kyoo Shin,[2,†] Ji Yong Lee,[1] Ojin Kwon,[2] Chang-Seob Seo,[2] Ae-Ran Kim,[2] Bok-Nam Seo,[2] Seung Woo Yang,[1] Ki Hak Song,[1] Jae Sung Lim,[1] Jong Mok Park,[1] Yong Gil Na[1] and Ju Hyun Shin[1]

[1]Department of Urology, College of Medicine, Chungnam National University, and [2]Herbal Medicine Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

Abbreviations & Acronyms
ALT = alanine aminotransferase
AST = aspartate aminotransferase
BMI = body mass index
BPH = benign prostatic hyperplasia
BSW = benefit, satisfaction, and willingness to continue
BUN = blood urea nitrogen
DBP = diastolic blood pressure
HJG = Hachimijiogan
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
LUTS/BPH = lower urinary tract symptoms due to benign prostatic hyperplasia
NIH-CPSI = National Institutes of Health-Chronic Prostatitis Symptom Index
PSA = prostate-specific antigen
Q-max = maximum flow rate
QoL = quality of life
RST = Ryutanshakanto
SBP = systolic blood pressure
TURP = transurethral resection of the prostate

Correspondence: Ju Hyun Shin M.D., Department of Urology, College of Medicine, Chungnam National University, 266 Munhwaro, Jung-gu, Daejeon 35015, Republic of Korea. Email: sjh0402@cnu.ac.kr

†These authors contributed equally to this work.

Objectives: To evaluate the efficacy and safety of tamsulosin and Hachimijiogan or Ryutanshakanto in patients with lower urinary tract symptoms due to benign prostatic hyperplasia.

Methods: A prospective, randomized, double-blind method was used to determine the efficacy and safety of the combination or placebo at baseline and 4, 8, and 12 weeks of study. The International Prostate Symptom Score, quality of life index, complete voiding diary, and National Institutes of Health-Chronic Prostatitis Symptom Index were studied. Uroflowmetery and postvoid residual urine volume were measured and compared. Laboratory tests including prostate-specific antigen were performed.

Results: In all groups, International Prostate Symptom Score and quality of life showed improvement, but no significant differences were shown among the groups. Prostate volume increased after treatment, and uroflowmetric parameters showed improvements after treatment without significance among the three groups. The total score of the National Institutes of Health-Chronic Prostatitis Symptom Index showed a significant improvement in all groups, without significant differences among the groups. Only the pain sub-score of the National Institutes of Health-Chronic Prostatitis Symptom Index showed a significant decrease in the tamsulosin with Ryutanshakanto group compared to the control group. A total of 11 adverse reactions occurred, but they were mild and not related to the study drugs.

Conclusion: Ryutanshakanto can provide pain relief in patients with chronic prostatitis and chronic pelvic pain syndrome. If more research is conducted, Hachimijiogan and Ryutanshakanto may be applied as add-on treatments in patients with storage symptoms with alpha-blocker monotherapy.

Key words: benign prostatic hyperplasia, Hachimijiogan, Ryutanshakanto, tamsulosin, traditional herbal medicine.

Introduction

BPH is a common diagnosis of progressive enlargement of the prostate in older men and the prevalence increases with an aging population.[1,2] BPH is one of the leading causes of LUTS, causing significant morbidity and decreasing the QoL of older men.[3]

The first-line treatment for LUTS/BPH is α-blockers alone or with 5α-reductase inhibitors, although they have shown different effects on symptoms and disease progression.[4,5] Moreover, adverse effects have been observed in patients receiving first-line treatment, including dizziness, ejaculatory dysfunction, orthostatic hypotension, headache, dry mouth, and rhinitis.[6]

Traditional herbal medicines, such as HJG and RST, were suggested to improve symptoms of patients with LUTS/BPH. In 2003, Yoshimura *et al.* reported that 41 patients treated with HJG had improved uroflowmetric parameters than patients treated with tamsulosin.[7] Yagi *et al.* suggested that adding HJG to patients with α-blockers was effective in improving the QoL and IPSS of LUTS/BPH patients.[8] Furuya *et al.* reported that RST may have a therapeutic effect on pain and discomfort after TURP.[9] Jin *et al.* studied the effect of HJG on human-kit cytochrome P450 and UDP-glucuronosyltransferase in 2018 and found that the herbal drugs

showed a little suppressive effect on the human microsomal drug-metabolizing enzymes even at high concentrations, suggesting that it does not affect tamsulosin metabolism and lacks any herb–drug interaction.[10]

These results indicate that herbal medicines may have a supplementary effect in improving LUTS/BPH and QoL in patients with adverse effects or in whom conventional medical treatment is ineffective. However, there is insufficient evidence, and the results suggest the low level of recommendations. Detailed, large-scale placebo-controlled clinical trials to compare the efficacy and effectiveness of combination treatment with herbal medicines have not yet been conducted.

The present study is the first to describe the efficacy and safety of combination therapy with tamsulosin, HJG, and RST using prospective, randomized, double-blind methods.

Methods

Chemical preparations

Two traditional herbal medicines, Hachimijiogan (palmijihwang - hwan in Korean; Baweidihuang-wan in Chinese) and Ryutanshakanto (Yongdamsagan-tang in Korean; Longdanxiegan-tang in Chinese) were prepared. High-performance liquid chromatography analysis of the two traditional herbal medicines was conducted according to a previously reported analytical protocol[11,12] to confirm the marker compounds of two medicines and no marker compounds in any of the placebo samples.

Patients

The present study was conducted within the Chungnam National University Hospital between 14 January 2019 and 31 December 2020. The study was approved by the Institutional Review Board (IRB 2018-11-015-025) and was performed after receiving written informed consent from patients.

Men aged 45 years or above with a history of LUTS secondary to BPH of at least 6 months were eligible. The patients agreed not to use BPH medications during the study, except the study medications. The inclusion criteria were as follows: men aged 45 or above, IPSS over 8 points at baseline, Q-max 5–15 mL/s with more than 125 mL voided volume at screening, clinical diagnosis of BPH based on medical history and physical examination, willingness and ability to provide written informed consent, and compliance with study procedures.

The exclusion criteria were immediate necessity for surgery during the study period, previous prostatic or urethral surgery or other invasive procedures to treat BPH; history or evidence of prostate cancer and bladder cancer; clinically significant renal insufficiency (serum creatinine >2.0 mg/dL) or hepatic insufficiency (AST or ALT >100 U/L), history of any adverse effects (syncope or orthostatic hypotension) or hypersensitivity after using alpha-blockers, history of urethral stricture, use of indwelling Foley catheter or clean intermittent catheterization, history of stroke or spinal cord injury that may result in urinary symptoms or changes in flow rate, or ineligible patients based on the judgment of the investigator (Fig. 1).

Study design

This study was conducted as a double-blind clinical study, where both the subjects and investigators (assessors) are blinded. The subjects only know that two different types of drugs are used—the study drug and placebo—but are not informed which is which. Subjects are assigned by block
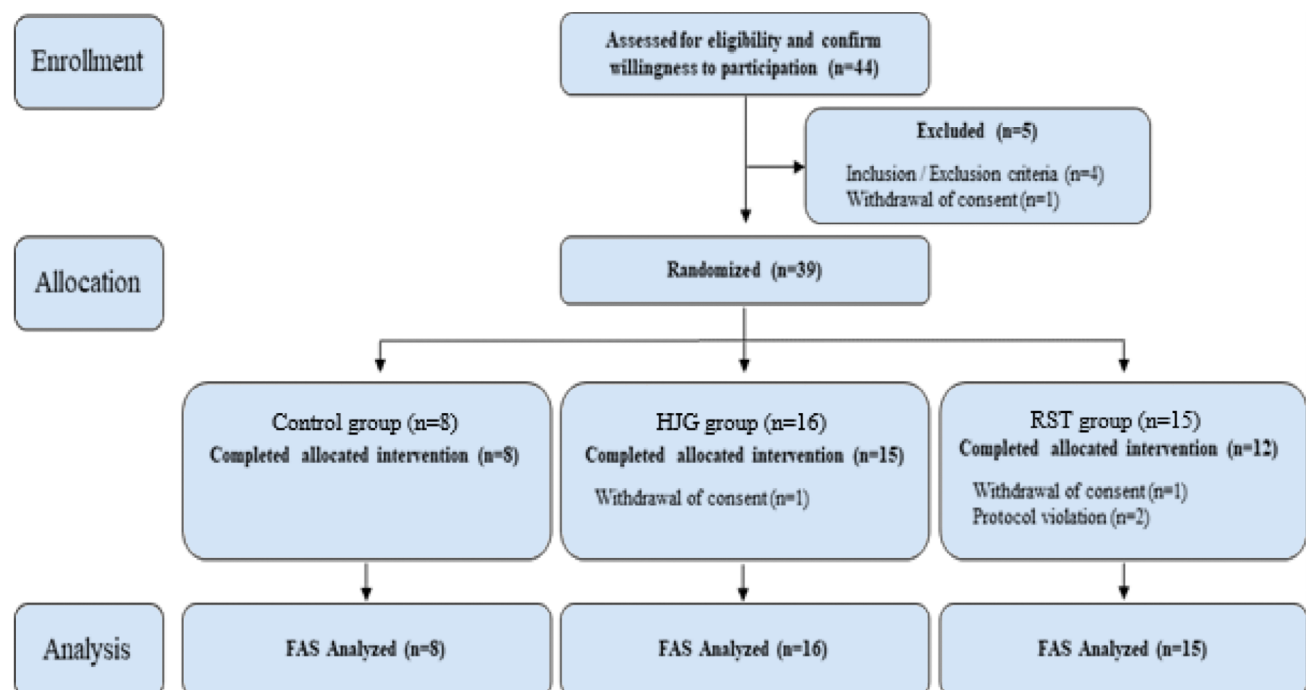

Fig. 1 Flow of study participants: from patient enrollment to analysis.

randomization, without additional stratification and are assigned to the control group or experimental groups according to a pre-generated randomization table, in the order of their subject number. The investigators are not involved in the randomization and remain blinded from group allocation. To maintain blinding, the randomization table and drug assignment are not disclosed until the completion of the trial unless otherwise indicated, such as an emergency.

The sample size was determined based on the investigator's clinical experience by hypothesizing the difference in the effect sizes between the combined therapy and control groups. All calculations were performed at a 5% significance level and 80% power. The two groups had a minimum hypothesized effect size of 0.4, and subjects were allocated at a 2:2:1 ratio. Furthermore, as this is a pilot clinical trial, 10% of the calculated sample size was determined as the final sample size, with reference to a recent recommendation of minimum sample sizes for pilot studies. Based on the above hypothesis, the sample size was calculated to be 36 for each treatment group and 18 for the control group. Considering a dropout rate of 10%, the target sample size set to 100 patients, with 40 patients for each treatment group and 20 patients for the control group.

Two herbal medicines, HJG and RST which are formulated to have nearly identical size and shape and are packed in the same type of packaging with similar scents, were prepared. Double-blindness was maintained by adding the herbal medicinal flavor to the placebo. Eligible patients were then randomized to receive fixed doses of tamsulosin 0.2 mg/day plus HJG (Hanpoong Pharm. and Food Co. Ltd., Seoul, Korea) at a dose of 3.0 g as an oral solution three times daily (Group 1); tamsulosin 0.2 mg/day plus RST (Hanpoong Pharm. and Food Co. Ltd.) at a dose of 3.0 g as an oral solution three times daily (Group 2); or tamsulosin 0.2 mg/day plus three times daily placebo (Group 3). HJG, RST, and placebo were to be taken three times daily immediately before meals or 2 h after meals.

Assessments

Demographics included only the initial of name and age of patients. Personal identifiable information was not collected, including the resident registration number, name, and address of patients.

Efficacy of drugs was observed in three different groups to check whether LUTS/BPH had improved. The IPSS (questions 1 to 7) and QoL index (question 8) were checked at baseline and visits 1 to 3 (4, 8, and 12 weeks). The NIH-CPSI was compared at baseline and visit 3. BSW was checked at baseline and visits 1 to 3. Uroflowmetric values and postvoid residual urine volume were compared at baseline and visit 3. Prostate volume was measured by transrectal ultrasonography at baseline and visit 3. The patients were instructed to complete a voiding diary at the baseline and visit 3. Blood pressure was checked at baseline and at visits 1 to 3. Laboratory tests were conducted to determine PSA, BUN, creatinine, AST and ALT levels; bloody chemistry, complete blood cell count test; and urine microscopy were also conducted. Results of the laboratory tests were compared at the baseline with those at visit 3. All patients completed the physical examination, including height (cm), weight (kg) and BMI (kg/m^2) at baseline. At baseline, detailed clinical history was noted, including medical history of present and past diseases, and other treatments. Patients were also asked to use medications for LUTS/BPH that could interfere with symptoms (alpha-blockers, anticholinergics, sympathomimetic drugs, antihistamines, and herbal preparations), or phosphodiesterase 5 inhibitors (Table S1).

Statistics

All statistical analyses were based on the two-sided significance level at 5% by the statistical programming language, S. Assuming a missing at random, the missing values were replaced by multiple imputations by Markov Chain Monte Carlo. Both full analysis set and per protocol were analyzed. Patients with prostate volumes larger than 30 g were subgrouped and analyzed (Tables S2–S4).

All data are expressed as mean (95% confidence interval). Analysis of covariance was performed to evaluate the efficacy of medications. The analysis of covariance model used the subject groups as fixed effects and baseline values as covariates. We used the paired t-test for comparisons before and after treatment. Repeated ANOVA was used to verify the serial IPSS changes at every visit.

Results

Patient characteristics

Forty-four patients were prospectively enrolled. Eight patients in the tamsulosin + placebo group, 16 patients in the tamsulosin + HJG group, and 15 patients in the tamsulosin + RST group were randomly assigned.

There were no significant differences in age, height, weight, BMI, and vital signs among patients of all three groups (Table 1).

Prostate volume change

Patients with higher mean total prostate volumes and transitional zones were assigned to the herbal medicine group, but the difference was not statistically significant (Table 2). In all three groups, prostate volume increased after treatment compared to that before treatment. Moreover, the transitional volume of the prostate, which is known as a predictor of acute urinary retention,[13] also increased after treatment compared to that before treatment. Concomitant herbal medicines have no effect on volume reduction in BPH.

IPSS

After drug administration, patients in all three groups showed significant improvement in IPSS and QoL index without significant differences among the groups (Fig. 2).

Uroflowmetric parameters

There was no difference before and after treatment in uroflowmetric parameters and postvoid residual urine volume.

Table 1 Baseline clinical profile of the study subjects

Demographic	Control group (*n* = 8)	HJG group (*n* = 16)	RST group (*n* = 15)	*P*-value†
Age (years)	66.13 (59.21, 73.04)	60.94 (56.61, 65.27)	67.73 (62.52, 72.95)	0.0942
Height (cm)	168.4 (165.0, 171.8)	169.0 (166.8, 171.3)	166.5 (162.9, 170.0)	0.3761
Weight (kg)	69.08 (64.23, 73.92)	72.59 (68.16, 77.02)	70.31 (64.86, 75.76)	0.5932
BMI (kg/m^2)	24.45 (22.08, 26.82)	25.39 (24.03, 26.74)	25.33 (23.84, 26.82)	0.6914
Vital sign				
SBP	135.0 (126.2, 143.8)	137.5 (129.9, 145.1)	136.0 (130.0, 142.0)	0.8851
DBP‡	76.63 (67.65, 85.60)	84.31 (78.47, 90.16)	81.33 (75.70, 86.96)	0.2583

†*P*-value were analyzed by Analysis of variance (ANOVA).

Table 2 Comparison of prostate volume, PSA, and uroflowmetric parameters in the study groups

	Control group (*n* = 8)			HJG group (*n* = 16)			RST group (*n* = 15)		
	Baseline	Week 12	*P*-value§	Baseline	Week 12	*P*-value	Baseline	Week 12	*P*-value
Prostate volume (gm)	33.38	34.5	0.5256	37.75	41.76	0.0163*·§ 0.3610†	41.53	43.93	0.0649§ 0.7126‡
PSA (ng/mL)	1.5	1.63	0.6219	1.08	1.16	0.3746§ 0.8706†	1.89	2.22	0.7316§ 0.1481‡
Micturition volume (mL)	278.6	281	0.9713	274.3	261.4	0.6943§ 0.8035†	253.8	270.2	0.6142§ 0.8222‡
Postvoid residual urine volume (mL)	70.13	47.5	0.4015	43.56	53	0.4970§ 0.4980†	65	78.03	0.3858§ 0.2004‡
Q-max (mL/s)	10.35	16.45	0.9716	11.43	13.79	0.7999§ 0.2275†	10.85	11.54	0.8316§ 0.5632‡

*Indicates $P < 0.05$. †Least squares mean difference and *P*-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group (Control or HJG) as the fixed factor. ‡Least squares mean difference and *P*-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group (Control or RST) as the fixed factor. §Mean difference and *P*-value were analyzed using a paired t-test for the baseline value and week 12.

No statistical improvement is observed in all three groups (Table 2).

NIH-CPSI

The NIH-CPSI significantly decreased in all three groups before and after treatment, but there was no significant difference among the groups. By subdividing and analyzing the group of patients with more than 80% adherence to medication, the average value of moderate pain in the sub-score showed a significant average decrease in the tamsulosin + RST group compared to the average decrease in the control group before and after treatment. As the drug is better tolerated, treatment-associated prostatic pain further improved with RST treatment (Table 3). Furthermore, by analyzing the group of patients with prostate volume over 30 gm, a significant average decrease in the study group compared to the average decrease in the control group before and after treatment (Table S3).

Laboratory tests

Regarding the hematologic chemistry tests, urinalysis, and BSW questionnaire analysis, there were no significant differences among the groups before and after treatment, and stable laboratory results were observed after treatment. In the case of PSA, which increased and decreased according to the size of the prostate, an increase in overall prostate volume was observed after 12 weeks, but it was not significant in all three groups and showed a slight increase (Table 2).

Adverse events

A total of 11 adverse reactions occurred, but they were all mild (grade 1) and were not related to the study drugs.

Discussion

Despite advances in medicine, the number of patients with LUTS/BPH is increasing, and thus either is the number of patients who are both irresponsive to medical treatment and ineligible for surgical intervention. Several studies have been conducted to determine the efficacy of traditional herbal medicine, but the sample sizes have been small.[14] This study is the first to identify the efficacy and safety of the combination therapy of alpha-blockers and traditional herbal medicines for LUTS/BPH.

Prostate volume usually correlates with the severity of LUTS, and transitional zone volume is the main contributor
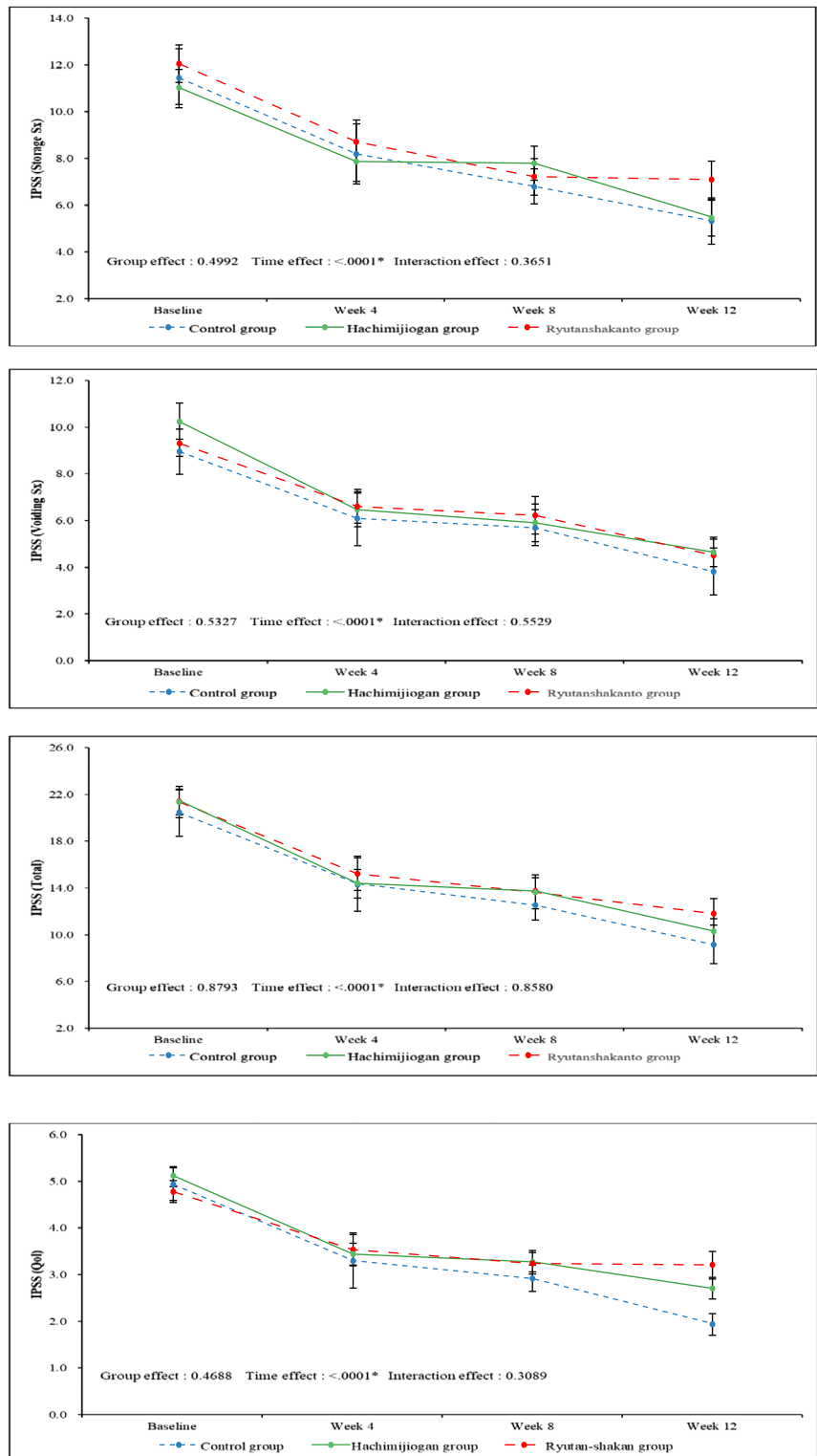
Fig. 2 IPSS sub-score and total score changes and QoL index changes in the study groups: patients in all three groups showed significant improvement in all IPSS and QoL scores over time, however, showed no significant differences among the groups.

to the total prostate volume growth, which is suggested to be closely related to the severity of LUTS/BPH.[15,16] Although the assigned patients in the study group had a higher average prostate volume, the comparable effectiveness was shown in IPSS and QoL index with the control group scores. This result suggests that the HJG and RST combination do not exhibit inferior efficacy to alpha-blocker monotherapy. However, in future, statistical analysis will be required to verify drug efficacy by comparing patients with similar prostate size or dividing subgroups for patients with mild prostatic hyperplasia suitable for medical treatment, accompanied by a long-term study with more patients.

Table 3 NIH-CPSI score changes in the study groups

	Control group (n = 8)			HJG group (n = 16)			RST group (n = 15)		
	Baseline	Week 12	P-value§	Baseline	Week 12	P-value	Baseline	Week 12	P-value
Pain	2.5	0.38	0.2102	1.23	0.92	0.8078§ 0.6126†	4.7 *P*	0	0.0008*·§ 0071*·‡
Urinary	6.13	2.88	0.0009*	6.69	3	0.0001*·§ 0.9692†	6.9	3.7	0.0034*·§ 0.5226‡
QoL	8.38	2.75	<0.0001*	7.62	3.92	<0.0001*·§ 0.0354*·†	8.2	4.6	0.0011*·§ 0.0492*·‡
Total	17	6	0.0005*	15.54	7.85	0.0012*·§ 0.3356†	19.8	8.3	<0.0001*·§ 0.3585‡

*Indicates $P < 0.05$. †Least squares mean difference and P-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group (Control or HJG) as the fixed factor. ‡Least squares mean difference and P-value were analyzed by analysis of covariance (ANCOVA) with the baseline scores as covariates and group (Control or RST) as the fixed factor. §Mean difference and P-value were analyzed using a paired t-test for the baseline value and weak 12.

In a previous study in Japan, the combination of an alpha-blocker and HJG had a positive effect on improving the detrusor overactivity induced by cold environment, which is mediated through a sensitive C-fiber sensory nerve pathway involving α1-adrenergic receptors.[17] Lee *et al*. reported that in patients with ketamine-induced cystitis, HJG could improve overactivity by inhibiting neuroreceptor upregulation and reducing inflammatory mediators.[18] Yoshimura *et al*. also reported that low-dose HJG significantly improves dysuria in LUTS/BPH patients, while improving Q-max and voiding scores of the IPSS.[7] In the present study, even though the change in IPSS was inferior to that in the control group, the HJG group also showed a comparable decrease in storage symptom score of IPSS, which was comparable to the control group. These results suggest that HJG may affect bladder afferent sensory receptors and improve the storage symptoms of LUTS/BPH patients. In another study in Japan, RST administration was suggested to improve the severity and frequency of postoperative pain and discomfort after TURP.[9] In the present study, RST also showed a significant effect on improving the pain score in NIH-CPSI. Moreover, as the drug is better tolerated, the treatment effect on prostatic pain shows further improvement. As a result, this suggests that the combination of HJG and RST can be added to patients with chronic pelvic pain syndrome who are not responsive to conventional medical treatment.

Park *et al*. suggested that RST water extract may decrease the volume of prostate in a rat model induced by testosterone and that the extract had an inhibitory effect on the proliferation of BPH-1 cells by cell-cycle arrest and anti-inflammatory activities in a dose-dependent manner.[19,20] In another study, the administration of HJG was suggested to decrease serum testosterone levels, especially at low dosages.[21] Based on these studies, we initially expected to reduce the volume of the prostate with the herbal medicine combination. However, the prostate volume and transitional volume of all patients increased in this study. To identify for herbal medicines to have effect on reducing prostate volume, an optimal dosage adjustment will be needed in the future study.

Dizziness, ejaculatory dysfunction, and impotence are the major adverse events associated with tamsulosin. In a 4-year study to establish the safety of tamsulosin, up to 26% of patients experienced some drug-related adverse events.[6] Mirabegron, a β3-adrenoceptor agonist that is usually added to tamsulosin for patients with OAB, also showed 3.9% of adverse events.[22] In the present study, a total of 11 adverse events occurred, three in the control group and five and three in the HJG and RST groups, respectively. However, they were not drug-related adverse events without severe adverse events, but only with grade 1 events. Therefore, HJG and RST add-on to tamsulosin can be safe supplements for patients with adverse events on taking other medications or high operation risk.

This study has limitations. The number of patients was small, and some assigned patients had a relatively large prostate, with less response to treatment and requiring surgery. Although this study provides meaningful results, in future, long-term studies with large number of patients with prostate volumes of 35 gm or less which the previously reported best cutoff value for small prostate volume in 2003,[23] will be required to verify drug efficacy to use as add-on treatments to patients previously treated by alpha-blocker monotherapy.

Acknowledgments

Author contributions

Chung Lyul Lee: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review and editing;. Hyeun-Kyoo Shin: Conceptualization; Funding acquisition; Investigation; Methodology; Supervision; Validation. Ji Yong Lee: Conceptualization; Writing – original draft; Writing – review and editing. Ojin Kwon: Data curation; Formal analysis; Software; Validation. Chang-Seob Seo: Data curation; Formal analysis; Investigation; Software; Supervision; Validation. Ae-Ran Kim: Data curation; Investigation; Resources; Software. Bok-Nam Seo: Data curation; Investigation. Seung Woo Yang: Investigation; Supervision. Ki Hak Song: Conceptualization; Supervision. Jae Sung Lim: Conceptualization; Supervision.

Jong Mok Park: Investigation; Supervision. Yong Gil Na: Conceptualization; Project administration; Supervision. Ju Hyun Shin: Conceptualization; Data curation; Project administration; Supervision.

Conflict of interest

None declared.

Approval of the research protocol by an Institutional Reviewer Board

IRB 2018-11-015-025.

Informed consent

All patients provided written informed consent before enrollment.

Registry and the Registration No. of the study/trial

Korea Food and Drug Administration 1AA-1902-197854: 2019-02-28.

Animal studies

Not applicable.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Timeline of clinical visits and assessments.
Table S2. Sub-analysis with the prostate volume over 30 gm of prostate volume and uroflowmetric parameters.
Table S3. NIH-CPSI score changes in the sub-analysis group with the prostate volume over 30 gm.
Table S4. IPSS changes in the sub-analysis group with the prostate volume over 30 gm.