Int J Clin Exp Med 2014;7(9):2744-2753
www.ijcem.com /ISSN:1940-5901/IJCEM0001629

Original Article

Efficacy and safety of Baweidihuang-wan in women with overactive bladder: a randomized, double blind, placebo controlled trial

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Received July 31, 2014; Accepted August 26, 2014; Epub September 15, 2014; Published September 30, 2014

Abstract: The aim of this study was to identify the efficacy and safety of Baweidihuang-wan (BWDH) in women with overactive bladder (OAB) and to investigate whether BWDH is more effective in OAB diagnosed as kidney yang deficiency pattern by the Korean medical pattern identification. The design of this study was a randomized, double blind, placebo controlled trial. One hundred eighty-six women with OAB were randomized to treatment (n=93) or control group (n=93). Participants received BWDH or placebo three times a day for eight weeks. Efficacy was assessed by overactive bladder symptom score and 3-day bladder diary. Subgroup analysis was conducted between kidney yang deficiency pattern and other patterns according to the Korean medical pattern identification. One hundred sixty-four participants completed this trial. The treatment group has improved in OABSS score, Total micturitions per 24 hr, Daytime micturitions per 24 hr, Total count of urgency, and Total urgency score over the control group, but differences were not statistically significant. By a subgroup analysis, OABSS score, total micturitions per 24 hr, total count of urgency and total urgency score improved most in the treatment group with the kidney yang deficiency pattern but this was also not statistically significant. No obvious adverse events were found in the use of BWDH. In conclusion, this trial did not show significant difference between BWDH and placebo in women with OAB. However BWDH tended to improve urinary frequency and urgency in OAB, especially diagnosed as kidney yang deficiency pattern. Further additional research will be needed.

Keywords: Overactive bladder, herbal medicine, randomized controlled trial

Introduction

According to the International Urogynecological Association (IUGA)/the International Continence Society (ICS), overactive bladder (OAB) syndrome is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTI) or other obvious pathology [1]. OAB is a chronic condition affecting 12~17% of adult population in Europe and North America [2-4]. The prevalence of OAB in Korea is similar to that in Western countries [5].

OAB is a highly prevalent disorder which increases with age in both sexes and has a profound impact on quality of life [2-4]. Current therapy for OAB is only partially effective. Behavioral therapies such as lifestyle modification, bladder training and pelvic floor muscle training, and pharmacotherapy such as antimuscarinic agents are usually primary treatments. However, many patients do not respond to these antimuscarinic agents or discontinue therapy because of adverse effects such as dry mouth, constipation and dry eyes [6, 7].

In Korea, herbal medicine and acupuncture have traditionally been used to treat OAB symptoms. Several systematic reviews support acupuncture as an effective and safe treatment of OAB, but evidence of the efficacy of herbal medicine for OAB is not sufficient [8, 9]. Recent randomized controlled clinical studies undertaken in China show that both Traditional Chinese

Medicine and Integrated Traditional Chinese/Western Medicine are effective for OAB [10-13]. But the trials were small in size, and there were no trials evaluating efficacy using a placebo control.

In Traditional Korean Medicine (TKM), lower urinary tract symptoms such as abnormal storage urinary frequency, OAB, and urinary incontinence are diagnosed as kidney yang deficiency, causing dysfunction of qi transformation in bladder [13]. Baweidihuang-wan (BWDH) consists of eight herbs, Shudihuang (*Rehmanniae Radix Preparata*), Shanyao (*Dioscorea Rhizome*), Shanzhuyu (*Corni Fructus*), Baifuling (*White Poria Cocos Wolf*), Mudanpi (*Moutan Cortex*), Zexie (*Alismatis Rhizoma*), Fuzi (*Aconiti Lateralis Preparata Radix*), Rougui (*Cinnamomi Cortexs*), which treats the overall symptoms caused by kidney yang deficiency. It is especially effective in treating urinary symptoms due to kidney yang deficiency and is thus a typical prescription for OAB [14].

We undertook a randomized, double blind, placebo controlled trial to identify the efficacy and safety of BWDH in women with OAB. The primary objective of this study was to evaluate the efficacy and safety of BWDH on OAB. A secondary objective was to investigate whether BWDH is more effective in OAB diagnosed as kidney yang deficiency pattern by the Korean medical pattern identification.

Materials and methods

Study design

This study was designed as a two-center, randomized, double blind, placebo controlled trial. It was performed at department of obstetrics & gynecology of Korean medicine of the Dongguk University Ilsan Korean Medical Hospital and Wonkwang University Gwangju Korean Medical Hospital in South Korea between February 2011 and December 2012. This study was approved by both hospitals' Institutional Review Boards (DGIRB SR-20 and WKIRB 10-1) before study initiation. All participants signed written informed consent before the start of the study. The study was monitored by Contract Research Organization (PharmaCRO Co.).

Participants

Participants were recruited through outdoor and hospitals website advertising. The inclusion criteria were women: 1) over 40 years of age without the possibility of pregnancy; 2) with symptoms of urinary frequency and urgency lasting more than three months; 3) who fit the diagnostic criteria for OAB, with a total score more than three points in Korean version overactive bladder symptom score (OABSS); 4) who have average urinary frequency of more than eight times per day and urgency which is defined as urgency rating scale (URS) on bladder diary is more than two points and/or UUI on 3-day bladder diary during one week screening period; 5) who agreed to this clinical study after sufficient explanation.

The exclusion criteria were women: 1) diagnosed with UTI by urine examination; 2) with stress urinary incontinence without symptoms of OAB; 3) with suspected of having voiding dysfunction induced by neurological damage; 4) with a medical history of cystocele, uterine prolapse or similar; 5) with a medical history of obstructive uropathy such as urinary stones and urinary tumors; 6) with a surgical history of urethra or bladder; 7) with a medical history of malignant tumors of urinary tract; 8) with a medical history of neurologic disease or psychiatric illness; 9) whom the researchers had determined hard to be involved in this study because of the following diseases: uncontrolled high blood pressure, diabetes, thyroid disease and who are on medications for that, acute or chronic hepatitis/cirrhosis, severe hyperlipidemia, severe cardiovascular disease, tuberculosis, and other infectious diseases; 10) with hypersensitivity or allergies to the study drug; 11) who are unable to take BWDH because is diagnosed as fire due to yin deficiency pattern, characterized by symptoms such as dry mouth, redness of tongue, thirst, hot flash and redness of the eyes, night sweat, or floating and speedy pulse; 12) who participated in another clinical trial within the past three months; 13) who have taken therapeutic drugs that may affect bladder function within one month of the start of this study; 14) unable to take herbal medicine because of systemic disease, determined by researcher; 15) with inadequate literacy to complete study documents.

Sample size

Sample size was estimated using the results by Tseng et al. [15] whose primary endpoint was bladder diary. It reported that urge incontinence per 24 hr was 1.8±0.7 before, and

1.5±0.5 after tolterodine therapy. Assuming an alpha error to 5% and power of 80%, sample size was calculated by the equation:

$$n \geq 2\frac{(z_\alpha + z_\beta)^2 s^2}{\delta^2} = \frac{2 \cdot (1.96 + 0.84)^2 \cdot 0.37}{0.3^2} = 64.5$$

Where S^2 is pooled variance and δ is difference in mean between groups; those were borrowed from Tseng; S^2=0.37, δ=0.3 ($s^2 = \frac{0.7^2 + 0.5^2}{2} = 0.37$, $\delta = 1.8 - 1.5 = 0.3$). Thus the minimum size considering 30% drop-out rate was 93 per group.

Intervention

Participants took BWDH or placebo for eight weeks. Those in the treatment group took BWDH, three capsules (500 mg/capsule) per dose, three times a day, for eight weeks. The ingredient of one dose of BWDH included Shudihuang (*Rehmanniae Radix Preparata*) 2 g, Shanyao (*Dioscorea Rhizome*) 1 g, Shanzhuyu (*Corni Fructus*) 1 g, Baifuling (*White Poria Cocos Wolf*) 1 g, Mudanpi (*Moutan Cortex*) 1 g, Zexie (*Alismatis Rhizoma*) 1 g, Fuzi (*Aconiti Lateralis Preparata Radix*) 0.33 g, Guizhi (*Cinnamomi Ramulus*) 0.33 g, lyophilized and extracted. Participants in the control group took placebo for eight weeks at the same dosage. Placebo was manufactured into capsules containing brown granules. The placebo material was carefully prepared to match the appearance, volume, weight, color, flavor, and taste of BWDH. One dose of placebo consisted of lactose hydrate (50%), cornstarch (48.3%), caramel color, artificial shuanghe-tang flavor, and herbal flavor. BWDH and Placebo were manufactured by Kyung-Bang Pharmaceutical Co.

Randomization

According to the sample size, the table of random numbers was produced by statistical software R ver 2.15.2. One hundred eighty-six participants were randomly allocated to the treatment group and control group based on the table of random numbers in a ratio of 1:1.

Blinding

Manufacturing and packaging were performed by Kyung-Bang Pharmaceutical Co. People involved in the manufacturing and package of medication were not allowed to contact the participants or the research personnel.

Efficacy assessment

Efficacy was assessed by OABSS and 3-day bladder diary. Changes in Total score of OABSS, Total micturitions per 24 hr, Daytime micturitions per 24 hr, Nocturnal micturitions per 24 hr, Total count of urgency (sum of urgency episodes defined as URS ≥ 3 for three days), Total urgency score (sum of urgency score for three days), Total count of UUI (sum of UUI episodes for three days) were assessed.

Participants completed the Korean version of OABSS [16] before and after treatment. The OABSS, an assessment tool for OAB symptoms, was developed and validated in Japanese populations in 2006 [17]. The OABSS consists of four questions regarding OAB symptoms; daytime frequency, nocturia, urgency, and UUI. The sum of the four scores runs between 0 and 15. The diagnostic criteria for OAB is a total OABSS of ≥ 3 with an urgency score for Question 3 of ≥ 2 [18].

Participants completed a 3-day bladder diary before and after treatment. Participants recorded the time of every micturition and rated the intensity of urgency using the five-point URS (1=no urgency, 2=mild urgency, 3=moderate urgency, 4=severe urgency, 5=UUI).

To assign the Korean medical pattern identification, participants completed a pattern identification questionnaire of 12 questions representing symptoms of kidney yang deficiency and kidney yin deficiency at baseline. This pattern identification questionnaire was developed through in-depth discussions among researchers based on Korean medical texts such as Dong Ui Bo Gam [19], Bang Yak Hap Pyeon [14], Sin Gye Nae Gwa Hak [20]. Finally, a specialist in internal medicine of Korean medicine who is one of researchers in this study diagnosed participants as kidney yang deficiency, kidney yin deficiency and others, according to the results of the pattern identification questionnaire and physical examination. Additionally, subgroup analysis was conducted between kidney yang deficiency pattern and other patterns according to the Korean medical pattern identification.

Safety assessment

Laboratory blood tests were conducted before and after treatment to assess general health

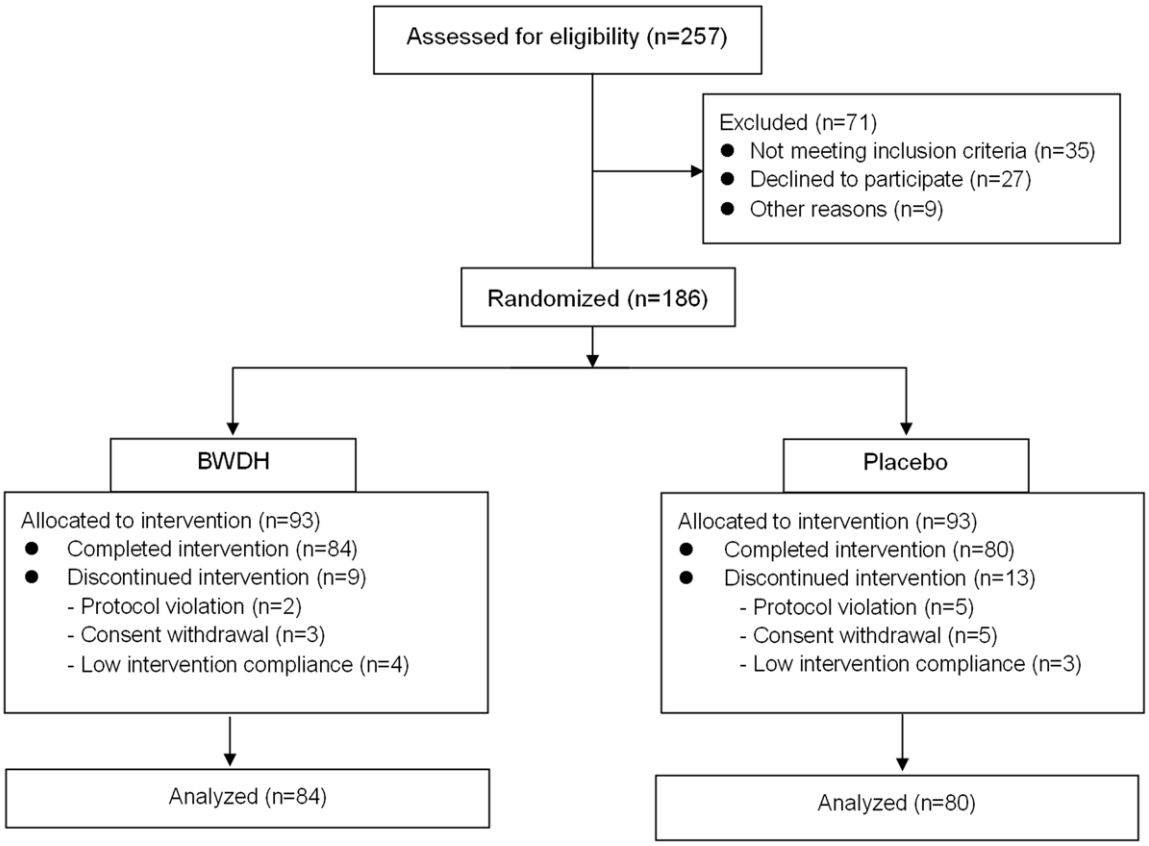

Figure 1. Flow diagram. BWDH: Baweidihuang-wan.

status and to confirm the safety of BWDH. Blood tests included white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), blood urea nitrogen (BUN), Creatinine.

All participants were monitored for adverse events during the study. An adverse event was defined as symptoms and signs newly appearing after dosing. The Korean medical doctor in charge graded the severity of adverse events as mild, moderate, severe and serious adverse event (SAE) and all were recorded.

Statistical analysis

Values were given as mean±SD or n (%). Analyses were performed with PP group (per-protocol group), because there were no significant differences with results of analysis of FA group (full analysis group). Independent t test, chi-square test, linear model with random intercepts (linear mixed effect analysis; LME) and Friedman test were used to compare differences between groups as appropriate. All analyses were performed using R ver 2.15.2 (R Development Core Team (2012). R: A language and environment for statistical computing, reference index version 2.15.2. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org). $P < 0.05$ was regarded as statistically significant.

Results

Participants flow

Two hundred and fifty-seven participants were screened, one hundred eighty-six participants who met criteria were enrolled and randomized. One hundred sixty-four participants completed this trial (**Figure 1**).

Demographic and clinical characteristics

Baseline demographic and clinical characteristics of the study participants are presented in **Table 1**. There were no statistically significant

Table 1. Demographic and clinical characteristics

		BWDH (n=93)	Placebo (n=93)	*P*-value
Age, yr (mean±SD)		53.3±9.1	54.0±8.9	0.586
Duration of OAB symptoms, months (mean±SD)		107.3±118.3	94.3±110.4	0.440
Previous treatment for OAB, n (%)		36 (38.7)	24 (25.8)	0.084
Smoking, n (%)		0 (0)	1 (1.1)	1.000
Drinking, n (%)		21 (22.6)	18 (19.4)	0.719
Caffeine, n (%)		67 (72.0)	70 (75.3)	0.739
Amount of Day Water intake, cup (mean±SD)		5.9±3.4	6.1±3.1	0.670
BMI, kg/m^2 (mean±SD)		23.5±3.0	23.6±3.1	0.62
BDI (mean±SD)		11.2±8.2	10.1±7.7	0.35
Married, n (%)		92 (98.9)	92 (98.9)	1.000
No. of parity (mean±SD)		2.1±1.0	2.2±0.8	0.307
Menopause, n (%)		54 (58.1)	52 (55.9)	0.882
Hysterectomy, n (%)		13 (14.0)	7 (7.5)	0.219
Korean medical pattern Identification n (%)	Kidney yang deficiency	61 (65.6)	62 (66.6)	0.358
	Kidney yin deficiency	17 (18.2)	13 (14.0)	
	Spleen and lung qi deficiency	11 (11.8)	13 (14.0)	
	Liver qi stagnation	4 (4.4)	2 (2.2)	
	Unidentified	0 (0)	3 (3.2)	

Note: Statistical significance tested by independent t test and chi-square test ($P < 0.05$). BWDH: Baweidihuang-wan; OAB: overactive bladder; SD: standard deviation; BMI: body mass index; BDI: Beck Depression Inventory.

Table 2. Comparison of OABSS before and after treatment in the two groups

	Baseline (mean±SD)	8 weeks (mean±SD)	*P*-value
BWDH	6.62±2.66	4.63±2.87	1.00
Placebo	6.38±2.51	4.84±2.52	

Note: Statistical significance tested by a linear model with random intercepts ($p < 0.05$). BWDH: Baweidihuang-wan.

differences between the two groups in age, duration of symptoms of OAB, drinking, smoking, caffeine intake, parity, menopausal status and body mass index et al. Also there was no statistically significant difference in the Korean medical pattern identification.

OABSS

After eight weeks of treatment, the OABSS score of the treatment group was more reduced than in the control group, but there was no statistically significant difference (**Table 2**).

3-day bladder diary

After eight weeks of treatment, the treatment group showed more reduction in Total micturitions per 24 hr, Day time micturitions per 24 hr, Total count of urgency, Total urgency score than the control group, although without statistically significant differences. Nocturnal micturitions per 24 hr and Total count of UUI reduced more in the control group, Nocturnal micturitions per 24 hr revealed a significant difference between the two groups (**Table 3**).

Efficacy by the Korean medical pattern identification

Fifty-five participants (65.48%) in the treatment group and fifty-one participants (63.75%) in the control group were diagnosed as kidney yang deficiency pattern. Following reanalysis of subgroups divided into kidney yang deficiency pattern and the other patterns, the treatment group with kidney yang deficiency pattern improved the most in OABSS score and Total micturitions per 24 hr, Total count of urgency and Total urgency score showed a wide variation of reduction. However, we found no statistically significant differences between kidney yang deficiency pattern and the other patterns (**Table 4**).

Safety assessment

For safety in the ITT group (intend-to-treat group) (n=186), there was no SAE. The treatment group had mild adverse events such as

Table 3. Comparison of 3-day bladder diary variables before and after treatment in the two groups

		Baseline (mean±SD)	8 weeks (mean±SD)	*P*-value
Total micturitions, per 24 hr	BWDH	11.95±2.88	10.13±2.79	0.19
	Placebo	12.52±3.83	11.17±4.49	
Daytime micturitions, per 24 hr	BWDH	10.67±2.59	9.17±2.55	0.50
	Placebo	10.88±3.52	9.91±4.22	
Nocturnal micturitions, per 24 hr	BWDH	1.30±1.09	0.96±0.84	0.01*
	Placebo	1.64±1.28	1.25±1.05	
Total count of urgency	BWDH	29.22±12.45	23.93±12.23	0.15
	Placebo	30.75±12.66	28.54±14.11	
Total urgency score	BWDH	81.48±40.20	66.26±37.48	0.13
	Placebo	87.37±42.54	79.90±44.98	
Total count of UUI	BWDH	0.84±3.30	0.81±2.95	0.157[a]
	Placebo	1.27±3.38	0.35±1.32	

Note: Statistical significance tested by linear model with random intercepts ($p < 0.05$). [a]Statistical significance of total count of UUI tested by Friedman test ($p < 0.05$). BWDH: Baweidihuang-wan; UUI: urgency urinary incontinence. *$P < 0.05$.

abdominal discomfort, dyspepsia, or diarrhea, and there was no significant difference with the control group.

Discussion

OAB is a common female urinary dysfunction with gradually increasing prevalence. In a survey of OAB prevalence in adults over the age of eighteen in Korea, the male prevalence was 10.0%, female prevalence was 14.3%, and total prevalence was 12.2% [5]. We estimate that actual prevalence of OAB is much higher if we include those hiding in shame of symptoms, or unawareness of disease because of mild symptoms. Most OAB occurs in chronic form and has a tendency to cycle through mitigation and aggravation. This heavily affects the quality of life of patients. According to one study, OAB has much more impact on the quality of life than chronic diabetes and hypertension [21].

Herbal medicine and acupuncture is a typical and common treatment for OAB in Korea. Significant improvement effect in OAB symptoms by herbal medicine and acupuncture is reported mainly in Korea and China [8-10, 12, 22-24]. However, studies to identify these effects objectively are still lacking.

Therefore, we conducted a primary two-center, randomized, double blind, placebo controlled trial to assess efficacy and safety of BWDH, an herbal medicine typically prescribed for OAB.

We found that OAB symptoms were improved in the treatment and control groups. And except for Nocturnal micturitions per 24 hr, there were no statistically significant differences between the two groups. Nocturnal micturitions per 24 hr was reduced more in the control group, with statistically significant differences. However, it does not seem to be clinically significant as difference of mean values between the two groups is very small in degree. By the way especially the OABSS score, Total micturitions per 24 hr, Daytime micturitions per 24 hr, Total count of urgency and Total urgency score improved more in the treatment group, we found that BWDH tended to improve urinary frequency and urgency, main symptoms of OAB, although without statistically significant differences.

In the analyses of subgroups by the Korean medical pattern identification, both treatment and control groups also improved in urinary symptoms, regardless of Korean medical pattern. But with regards to OABSS score, Total micturitions per 24 hr, Total count of urgency and Total urgency score, treatment group diagnosed as kidney yang deficiency pattern showed the greatest improvement, also not statistically significant differences. This implies that more valid results can come out if a clinical trial is implemented on larger numbers of OAB patients diagnosed as kidney yang deficiency pattern, because BWDH is suitable for kidney yang deficiency pattern in Korean medical pattern identification.

It is usually known that the placebo effect is very strong in clinical trials of OAB. The effect of

Table 4. Comparisons of OABSS and 3-day bladder diary variables by the Korean medical pattern identification in the two groups

	PI	BWDH (mean±SD)		Placebo (mean±SD)		*P*-value	
		Baseline	8 weeks	Baseline	8 weeks	BWDH vs. Placebo	KYD vs. Others
OABSS	KYD	6.69±2.55	4.55±2.87	6.34±2.19	4.98±2.61	1.00	0.18
	Others	6.48±2.90	4.79±2.91	6.44±3.07	4.59±2.38		
Total micturitions, per 24 hr	KYD	11.89±3.00	9.82±2.53	12.15±3.32	10.52±3.75	0.19	0.08
	Others	12.08±2.67	10.71±3.19	13.22±4.64	12.30±5.45		
Daytime micturitions, per 24 hr	KYD	10.74±2.80	9.50±2.35	10.61±2.87	8.89±3.26	0.50	0.10
	Others	10.53±2.15	9.70±2.86	11.41±4.52	10.64±5.51		
Nocturnal micturitions, per 24 hr	KYD	1.18±0.97	0.93±0.87	1.55±1.29	1.03±1.00	0.01*	0.14
	Others	1.55±1.26	1.01±0.78	1.81±1.26	1.66±1.05		
Total count of urgency	KYD	28.40±12.64	22.76±11.13	30.51±10.65	27.18±11.43	0.15	0.20
	Others	30.84±12.09	26.14±14.02	31.22±15.99	30.93±17.86		
Total urgency score	KYD	78.29±39.22	62.11±32.46	86.95±35.22	76.71±36.85	0.13	0.09
	Others	87.87±42.01	74.14±45.09	88.16±54.49	85.52±56.85		
Total count of UUI	KYD	0.85±3.46	0.80±2.97	1.21±3.47	0.25±1.07	0.79	0.49
	Others	0.81±3.02	0.83±2.95	1.38±3.25	0.52±1.68		

Note: Statistical significance tested by linear model with random intercepts ($p < 0.05$). PI: Pattern Identification; BWDH: Baweidihuang-wan; KYD: Kidney Yang Deficiency; UUI: urgency urinary incontinence. *$P < 0.05$.

antimuscarinics as primary treatment of OAB is broadly recognized, and several studies found improvements that were statistically significant, but the difference with placebo was not large [25-27]. Additional studies of the placebo effect of antimuscarinics on OAB are underway in Western Medicine. Lee et al. [28] meta-analyzed placebo effect based on urinary frequency, urinary incontinence frequency, averaged urine output as a primary endpoint in 36 RCT studies comparing antimuscarinics with placebo. The changes in three endpoints in placebo group were substantial and also statistically significant. They concluded that these findings result from a strong placebo effect of urogenital disorders, thus in order to manage placebo response, further clinical trials have attempted to enroll larger numbers of participants and more severely affected patients to offset the placebo effect, which showed a statistically significant difference in the treatment groups.

Mangera et al. [29] meta-analyzed the placebo effect in 62 clinical trials comparing antimuscarinics with placebo on OAB. They noted statistically significant improvement in incontinence episodes per day, micturition episodes per day and mean micturition volume in the placebo groups. They explained that this placebo effect may be related to factors such as expectations of patients and physicians, experimental subordination not to disappoint the doctors, the use of subjective scales like bladder diary, a response to the additional attention and concern afforded by trial protocols, additional effect of bladder training resulting from the use of bladder diary and recording and recall bias in the process of writing a bladder diary. Furthermore they noted that the brain's role in OAB pathophysiology is important in the mechanism of the placebo effect in OAB, especially as urgency is related to the central nervous system (CNS) components and a placebo 'expectation effect' can affect outcome parameters by modulating the CNS component of OAB. Thus, given that the placebo effect is very strong in clinical trials of OAB, it can be regarded that placebo effect was somewhat appeared in this study.

This study has some methodological limitations of clinical trials in addition to placebo effects associated with disease characteristics of OAB. First, using only subjective assessment scales such as 3-day bladder diary and OABSS can be a limitation. Objective evaluations such as urodynamic test and urine volume measurement used in other OAB trials are necessary in consideration of strong placebo effect seen with urogenital disorders. Second, this study enrolled every woman diagnosed as OAB with more than three points of OABSS score to ensure a sufficient number of participants. While the study was able to enroll the target number of participants within the trial period, there is a possibility of the actual treatment effect and the placebo effect did not differ clearly because of inclusion of milder cases of OAB. If participants were chosen with only severe OAB, as Lee et al. [28] suggested, significant differences between groups might have been seen. Third, the short treatment period was another limitation of the study. Optimal treatment period was set at eight weeks considering drug compliance of participants. However, antimuscarinics are clinically recommended to be taken for three to six months, and clinical trials usually applied 12 weeks of treatment [27, 30-32]. If this study had secured more than 12 weeks of treatment, a significant effect of BWDH on OAB might have been observed.

Comprehensively reviewing the results of this study, BWDH had no statistically significant effect on OAB symptoms improvement. But BWDH tended to improve urination symptoms in most evaluation scales more than the placebo, especially in kidney yang deficiency pattern, and intensity and frequency of urgency which is major symptom of OAB were more improved than other symptoms.

Therefore, if the limitations of this study are overcome, such as securing more than 12 weeks of treatment period, targeting severe OAB patients diagnosed as kidney yang deficiency pattern for better clinical trial methodology, significant results can be expected. Further additional research will be needed.

Acknowledgements

This study was supported by a grant of the Traditional Korean Medicine R & D Project, Ministry of Health & Welfare, Republic of Korea (B100044).

Disclosure of conflict of interest

None.

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