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Minagawa T[1], Gotoh M[2], Yokoyama O[3], Sugaya K[4], Kikuchi T[5], Yamanishi T[6], Kawahara K[7], Kaga K[6], Uno E[5], Yamashiro K[5], Nishizawa O[8]

1. *Department of Urology, Shinshu University,* ***2.*** *Department of Urology, Nagoya University,* ***3.*** *Department of Urology, University of Fukui Faculty of Medical sciences,* ***4.*** *Department of Urology, Kitakami Central Hospital,* ***5.*** *Translational Research Informatics Center,* ***6.*** *Department of Urology, Continence Center, Dokkyo Medical University,* ***7.*** *Kawahara Urological Clinic Medical corporation,* ***8.*** *Department of Urology, NorthAlps Medical center Azumi Hospital*

THERAPEUTIC EFFECT OF PROPIVERINE HYDROCHLORIDE ON MIXED-TYPE URINARY INCONTINENCE IN FEMALE; THE FEMALE URGENCY AND STRESS URINARY INCONTINENCE STUDY OF PROPIVERINE HYDROCHLORIDE (FRESH) TRIAL

Hypothesis / aims of study

Propiverine hydrochloride (PH) is one of anticholinergic drugs for patients with urgency urinary incontinence (UUI). Moreover, the efficacy of PH on stress urinary incontinence (SUI) in mixed-type urinary incontinence (MUI) was reported whereas tolterodine, which is also an anticholinergic drug, did not affect on SUI in the MUI patients. [1, 2] PH may increase urethral closing pressure and extend functional urethral length resulting in the improvement of SUI. [3]

SUI is one of the most common problems faced by aging female, impairing the quality of life. Although surgical treatments are reported to be effective for SUI, only a few medications are available. Considering the mechanism of action of PH, it can be a prospective drug for SUI. Therefore, this clinical trial is especially interested in therapeutic effect of PH for SUI. Our hypothesis in this study is thus that PH can decrease the frequency of SUI in the patients among MUI.

Study design, materials and methods

This study was conducted as a multicenter single-arm prospective clinical trial and carried out by 64 institutions in Japan. The participants were female patients aged 20 years or older who had been complaining of MUI for more than 3 months. Patients who had UUI more than 1 time/week and SUI more than 3 times/week were enrolled this study. Before enrolling this study, a bladder diary was used to determine the frequency of urinary incontinence. The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was also used to confirm the urinary incontinence at the entry of this study. All participants were required to record the daily counts of urinary incontinence in a pre-specified bladder diary during this study. The following patients were excluded: urethral stricture, bladder stone, bladder tumor, urinary tract infection, pregnancy, and pelvic organ prolapse. Patients who had severe bladder dysfunction such as urinary retention or lack of urine sensation were also excluded in this study. PH (20 mg once daily) was given for 12 weeks to patients with MUI. If the response was not favorable, the dose of PH was allowed to increase to 30 or 40 mg. The frequency and decreasing rate of SUI, UUI, and unclassified urinary incontinence per a week were evaluated at baseline, 4, 8, and 12 weeks. Average of urinary frequency (/day), frequency of urgency (/week), and number of used incontinence pad (/week) were also evaluated. Residual urine was measured using transabdominal ultrasonography before and 12 weeks after PH administration. Moreover, subjective symptoms were evaluated using the overactive bladder symptoms score (OABSS) and ICIQ-SF. Wilcoxon singed rank test was used to compare the difference between the baseline and the observation periods at 4, 8, and 12 weeks.

Results

In total, 62 MUI patients were enrolled in this study. The disposition of the patients through this study was shown in Figure.

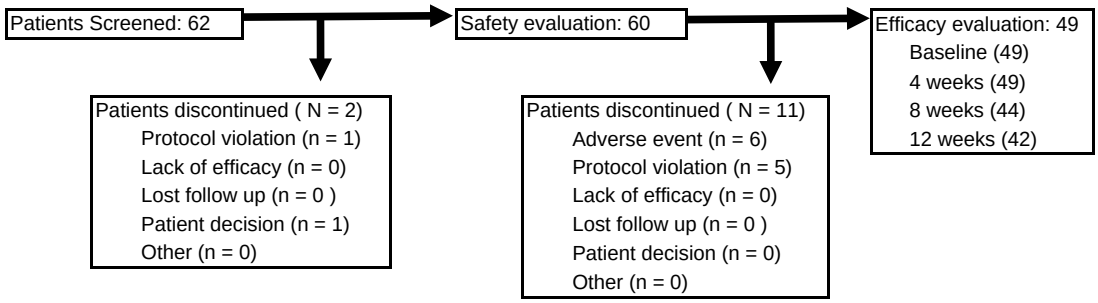

Figure . Disposition of patients through the study.

The clinical characteristics of the enrolled patients for safety and efficacy were shown in Table I. Adverse events were reported in 20 patients (33.3%; oral thirst 6, constipation 4, and other 10). The efficacy of PH on the MUI patients were shown in Table II.

Table I. Characteristics of the patients for safety and efficacy evaluation.

		Safty evaluation		Efficacy evaluation	
		N	Mean ± S.D.	N	Mean ± S.D.
Age	(y.o.)	60	67.7 ± 9.9	49	68.0 ± 10.5
Body weight	(kg)	54	55.1 ± 8.3	46	54.3 ± 7.5
Height	(m)	54	1.5 ± 0.6	46	1.5 ± 0.1
BMI	(kg^2/cm)	54	23.7 ± 3.4	46	23.5 ± 3.3
Number of childbirth	(case)	59	2.2 ± 0.9	45	2.2 ± 0.7
Menopause	(case)	Yes	51		41
		No	6		6
		Missing	3		2
Postmenopausal period	(month)	40	212.9 ± 112.2	31	218.3 ± 120.4
Complication	(case / %)				
Hypertension		59	28 / 46.7	31	21 / 42.9
Diabetes mellitus		59	7 / 11.7	31	5 / 10.2
Others		60	27 / 45.0	31	21 / 42.9

Table II. Therapeutic effect of propiverine hydrochloride on the patients with mixed-type urinary incontinence.

		Baseline	4W		8W		12W	
	N	49	49		44		42	
Urinary incontinence (total)	(/week)	28.7 ± 17.5	19.8 ± 18.3	(<.0001)	17.7 ± 18.9	(<.0001)	15.8 ± 17.1	(<.0001)
	(-%baseline)	0.0	28.1 ± 71.6		40.0 50.5		49.3 41.7	
Urgency urinary incontinence	(/week)	11.9 ± 10.8	7.2 ± 11.2	(0.0001)	4.5 ± 7.2	(<.0001)	4.4 ± 7.7	(<.0001)
	(-%baseline)	0.0	33.0 ± 104.4		63.9 ± 49.0		65.7 ± 69.9	
Stress urinary incontinence	(/week)	16.8 ± 11.6	12.6 ± 14.4	(0.0002)	13.2 ± 16.6	(0.0159)	11.4 ± 14.0	(0.0002)
	(-%baseline)	0.0	24.6 ± 83.2		30.3 ± 64.1		37.7 ± 66.7	
Unclassified urinary incontinece	(/week)	4.9 ± 9.3	3.1 ± 8.1	(0.0064)	2.6 ± 5.5	(0.1181)	1.5 ± 3.8	(0.0001)
Average of urinary frequency	(/day)	69.3 ± 17.1	62.4 ± 17.4	(<.0001)	58.5 ± 14.9	(<.0001)	56.5 ± 12.5	(<.0001)
Frequency of urinary urgency	(/week)	23.8 ± 19.4	16.3 ± 18.0	(0.0004)	11.2 ± 14.5	(<.0001)	10.3 ± 15.7	(<.0001)
Number of used incontinence pad	(/week)	28.9 ± 22.6	21.6 ± 20.2	(<.0001)	19.6 ± 21.2	(0.0007)	18.2 ± 19.3	(<.0001)
OABSS		8.8 ± 3.1	6.4 ± 4.4	(<.0001)	5.0 ± 3.9	(<.0001)	5.1 ± 3.8	(<.0001)
ICIQ-SF		14.1 ± 3.8	10.0 ± 4.9	(<.0001)	9.2 ± 4.8	(<.0001)	8.8 ± 5.4	(<.0001)
Residual urine	(ml)	11.5 ± 15.9					8.5 ± 21.0	(0.0732)

Mean ± SD (*p* value) Wilcoxon singed rank test was used for stastical analysis comparing with baseline value.

Urinary incontinence was expressed in times per week and in percentage of decline from the baseline value.

Interpretation of results

PH decreased the frequency of SUI and UUI per week after PH administration in a time-dependent manner, which is statistically significant. Moreover, urinary frequency, frequency of urgency, and number of used pad were similarly decreased after PH administration. These results of this study indicated that PH may improve both of UUI and SUI. In addition, subjective symptoms evaluated by the OABSS and ICIQ-SF were also improved. However, residual urine did not increase after PH administration. These results indicate that PH can be a prospective treatment option for SUI patients without severe adverse events.

Concluding message

PH can be an effective therapeutic option in management for SUI patients among MUI patients. However, a placebo controlled and randomized trial is necessary for the conclusion since the evaluation of our study depended on self-descriptive bladder diary written by the patients.

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Disclosures

Funding: FRESH study (Funded by Taiho Pharma. Co.; under the study contract) Funding/Support: Taiho Phama. Co. **Clinical Trial:** Yes **Registration Number:** The University Hospital Medical Information Network - Clinical Trials Registry registration number was UMIN000011491. **RCT:** No **Subjects:** HUMAN **Ethics Committee:** The Ethics Committee of Shinshu University School of Medicine (Permission No. 2339, 2013) **Helsinki:** Yes **Informed Consent:** Yes