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Efficacy and Safety of Pilocarpine Hydrochloride in the Treatment of Voiding Difficulty in Patients with Detrusor Underactivity

*Kanya Kaga[1], Tomohiko Kamasako[1], Mayuko Kaga[1], Miki Fuse[1], Mitsuru Ishizuka[2] and Tomonori Yamanishi[1]**

[1]Department of Urology, Continence Center, Dokkyo Medical University, Tochigi, Japan

[2]Department of Surgery, Continence Center, Dokkyo Medical University, Tochigi, Japan

Abstract

Background and Objective: We previously examined the contractile effect of pilocarpine on pig and human isolated bladder smooth muscle. The present study exploratorily investigated the efficacy and safety of pilocarpine for the treatment of voiding difficulty due to detrusor underactivity.

Methods: Patients with voiding symptoms, maximum urinary flow rate (Qmax) ≤ 10 mL/s, and Post-Void Residual urine volume (PVR) ≥ 50 mL, and diagnosed with detrusor underactivity in a pressure-flow study, were treated with pilocarpine (a dose of 5 mg 3 times daily) for 8 weeks. The primary endpoint was the change in Qmax *vs.* baseline. The secondary endpoints were changes in the International Prostate Symptom Score (IPSS; total IPSS, voiding symptoms including sensation of incomplete emptying), Quality of Life (QOL) score, and average urinary flow rate (Qave).

Results: In uroflowmetry, significant changes were demonstrated (Qmax, 9.1 ± 4.6 to 12.9 ± 5.5 ml/s, P=0.0313; Qave, 6.1 ± 5.3 to 8.8 ± 6.3 ml/s, P=0.0039; voided volume, 158.8 ± 114.5 to 186.8 ± 110.0 ml, P=0.0273; and PVR, 222.7 ± 122.3 to 102.4 ± 92.9 ml, P=0.0020). IPSS total score and IPSS voiding symptom score were significantly decreased after the treatment (IPSS total score, 15.8 ± 9.4 to 12.1 ± 9.0 points, P=0.0039; voiding symptom subtotal score, 9.3 ± 6.1 to 7.3 ± 5.7 points, P=0.0469).

Conclusion: Pilocarpine improved voiding symptoms scores and urinary flow rates, decreasing PVR. Pilocarpine appeared to be safe and effective for the treatment of detrusor underactivity in patients with voiding difficulty due to detrusor underactivity.

Keywords: Pilocarpine; Muscarinic receptor; Detrusor underactivity, Voiding difficulty; Urinary flow

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Correspondence:
Tomonori Yamanishi, Department of Urology, Continence Center, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi, 321-0293, Japan, Tel: +81 282 86 1111; Fax: +81 282 86 5105;
E-mail: yamanish@dokkyomed.ac.jp

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Introduction

Voiding (emptying) difficulty can be caused by Bladder Outlet Obstruction (BOO) or by voiding dysfunction due to detrusor underactivity. Alpha1-adrenoceptor antagonists, phosphodiesterase 5 inhibitors, and 5α-reductase inhibitors are reported to be effective for the treatment of BOO due to Benign Prostatic Hyperplasia (BPH) [1-5]. On the other hand, voiding dysfunction caused by detrusor underactivity is treated with distigmine bromide and bethanechol chloride, with which the treatment outcomes have been less than satisfactory [6], leaving new treatment drugs awaited. It is estimated that many patients have comorbid detrusor underactivity and BOO.

Pilocarpine is a cholinergic drug for which oral formulations were approved in recent years for the improvement of dry mouth symptoms accompanying radiotherapy for the head and neck and for dry mouth symptoms in patients with Sjogren's syndrome, and it is expected to be effective in improving lower urinary tract dysfunctions due to detrusor underactivity, similarly to bethanechol chloride [7-10]. In a previous basic study, we examined the contractile effect of pilocarpine on pig and human isolated bladder smooth muscle, and compared it with other muscarinic agonists to evaluate its potential as a therapeutic drug for underactive bladder (*in press*).

In the present study, the efficacy and safety of pilocarpine for the treatment of voiding dysfunction were exploratorily investigated in patients with voiding difficulty due to detrusor underactivity, based on the findings from the basic study.

Materials and Methods

This was an open label study to investigate the efficacy and safety of pilocarpine for the treatment of detrusor underactivity.

Inclusion criteria were male and female patients aged 20 years or older with voiding symptoms, maximum urinary flow rate (Qmax) ≤ 10 mL/s, and Post- Void Residual urine volume (PVR) ≥ 50 mL, and who had been confirmed to have detrusor underactivity in a pressure-flow study.

Patients were excluded if they had prostatic cancer, urethral stricture, neurogenic bladder with acontractile detrusor due to acute phase of spinal cord injury, after pelvic surgery such as rectal cancer cervical uterine cancer, and with detrusor-sphincter dyssynergia, those with urinary retention requiring urinary catheterization. Patients with a severe cardiac or cerebrovascular disorder, hepatic disorder, or renal dysfunction were also excluded. Patients who were being treated with an anticholinergic, or a β-adrenergic receptor agonist or antagonist discontinued that treatment at least 2 weeks prior to the study. Patients with comorbid prostatic hyperplasia or neurogenic bladder were allowed to take α1 blockers concomitantly. However, the dosage and method of administration for these drugs remained unchanged for the entire duration of both the observation period and the study period. No patients were taking anti-androgen medication. Urinalysis was performed for all patients, and patients with cystitis or bacterial prostatitis were treated with antibiotics accordingly.

Lower Urinary Tract Symptoms (LUTS) were assessed in terms of the International Prostate Symptom Score (IPSS) and Quality of Life (QOL) score. The IPSS sub-scores were assessed as individual scores, storage symptom scores (frequency, urgency, and nocturia), voiding symptom scores (intermittency, decreased urinary stream, and straining), and a post-micturition symptom score (a feeling of incomplete voiding).

Free urinary flow rate and PVR were evaluated at the end of the observation period and after the therapy. Post-Void Residual urine volume (PVR) was measured using ultrasonography.

Urodynamic studies, including a Pressure-flow study, were performed. A 6-Fr double-lumen catheter was inserted transurethrally, and a water cystometrogram was recorded at an infusion rate of 50 ml/min with the patient in a supine position. Simultaneously, rectal pressure was measured with a balloon catheter. Detrusor pressure was calculated by subtracting the abdominal pressure from the intravesical pressure, electronically. At maximum cystometric capacity, patients assumed a sitting or standing position, and the pressure/flow study was performed.

In the International Continence Society report on terminology, detrusor underactivity is defined as "low detrusor pressure or short detrusor contraction time, usually in combination with a low urine flow rate resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span [11]." In our study, detrusor underactivity was defined as Qmax ≤ 10 mL/sec, Abram's Bladder Contractility Index (BCI) = detrusor pressure at time of maximum urinary flow (pdet Qmax) + 5 Qmax < 100, and weak or very weak class in Shafer's nomogram (linear Passive Urethral Relation: PURR) in males, and/or pdet Qmax ≤ 20 cm H_2O, with straining pattern, in females [12,13].

Data were expressed as mean and standard deviation. Pre- and post-treatment data were analyzed using the Wilcoxon matched-pairs signed-ranks test. P-values of less than 0.05 were regarded as statistically significant.

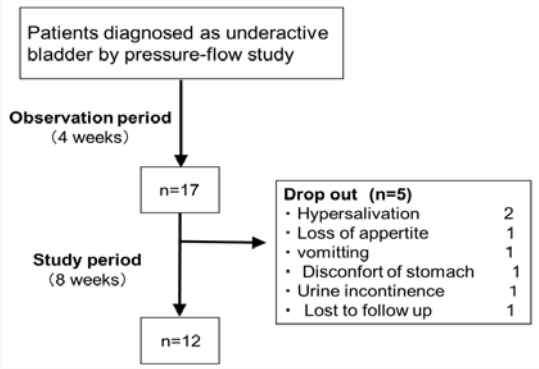

Figure 1: Flow chart of patient selection.

Pilocarpine (Salagen®) containing 5 mg of the test substance per tablet was used as pilocarpine. One tablet of Salagen® was to be orally administered 3 times daily, after each meal, for 8 weeks.

Endpoints

The primary endpoint was the change in Qmax compared with the baseline. The secondary endpoints were changes in IPSS (total IPSS, voiding symptoms subscore including sensation of incomplete emptying), QOL score, and average urinary flow rate (Qave). The efficacy endpoints were evaluated in terms of the change from pre- to post-administration of the drug assessed using a one-sample t-test. In certain cases, differential analysis by patient background may have been performed. All adverse events were recorded.

The study was conducted in accordance with the Declaration of Helsinki. The approval of the Institutional Review Board (No. 2083) and informed consent from all subjects were obtained before the start of the study.

Results

Initially, 17 patients were enrolled. Four patients discontinued because of adverse events such as hypersalivation or discomfort of the stomach, and one patient did not come to the hospital, for unknown reason. Finally, 12 patients completed the study (Figure 1). The mean age was 64.3 ± 17.9 years; the most common complication was neurogenic bladder (n=5). Seven patients were administered α1 blockers as concomitant medication (Table 1).

The results of IPSS and uroflowmetry, and PVR before and after the treatment are summarized in (Table 2). IPSS total score and IPSS voiding symptom score were significantly decreased after the treatment (IPSS total score, 15.8 ± 9.4 to 12.1 ± 9.0 points, P=0.0039; voiding symptom subtotal score, 9.3 ± 6.1 to 7.3 ± 5.7 points, P=0.0469). In uroflowmetry, significant changes were also demonstrated (Qmax, 9.1 ± 4.6 to 12.9 ± 5.5 mL/s, P=0.0313; Qave, 6.1 ± 5.3 to 8.8 ± 6.3 ml/s, P=0.0039; voided volume, 158.8 ± 114.5 to 186.8 ± 110.0 ml, P=0.0273; and PVR, 222.7 ± 122.3 to 102.4 ± 92.9 ml, P=0.0020).

Pre- treatment IPSS total score in the α1-blocker users and non-users (13.4 ± 10.5 *vs.*19.2 ± 7.2, P=0.2903), and that in post-treatment (12.1 ± 9.0 *vs.*10.7 ± 10.6, P=0.5691) were comparable, and changes in pre- and post-treatment were not different between the groups.

Table 1: Background characteristics of patients.

Age (mean ± SD)	64.3 ± 17.9 years old	
Sex (Male/Female)	4/8	
BMI (mean ± SD)	22.4 ± 2.8 kg/m^2	
Complications (Number of Subjects)	Neurogenic Bladder (NB)	5
	Benign Prostatic Hyperplasia (BHP)	2
	None	2
	Multiple System Atrophy (MSA)	1
	Diabetes Mellitus (DM)	1
	Hypertension (HT)	1
	Disk herniation (Central type)	1
	Guillan-Barre syndrome	1
	Endometriosis	1
	Cerebral Infraction and HT	1
	Post operation of lumber spinal canal stenosis	1
	Frontotemporal dementia	1
Orally administration of α1-blocker	Urapidil	5
	Silodosin	2
	None	5

Table 2: IPSS, uroflowmetry, and postvoid residual urine volume before and after the treatment.

		Pre	Post	P value	Mean change
IPSS	Total Score	15.8 ± 9.4	12.1 ± 9.0	***0.0039***	-3.8
Voiding symptom score	Subtotal	9.3 ± 6.1	7.3 ± 5.7	***0.0469***	-2.0
	Q3 Intermittency	3.0 ± 2.4	2.8 ± 2.0	0.7656	-0.8
	Q5 Weak stream	3.5 ± 2.0	2.6 ± 2.0	0.0625	-0.8
	Q6 Straining	2.8 ± 2.2	1.8 ± 2.0	0.0781	-0.5
Storage symptom score	subtotal	5.3 ± 4.5	4.1 ± 4.6	0.0859	-1.3
	Q2 Frequency	2.3 ± 1.9	1.5 ± 1.9	0.1563	-0.8
	Q4 Urgency	1.3 ± 1.8	0.8 ± 1.4	0.5000	-0.5
	Q7 Nocturia	1.8 ± 1.5	1.8 ± 1.9	1,0000	0
Post micturition symptom score	Q1 Incomplete emptying	1.3 ± 1.4	0.8 ± 0.9	0.1253	-0.5
IPSS QOL index		3.6 ± 1.8	2.7 ± 2.0	0.0625	-0.9
Qmax (mL/s)		9.1 ± 4.6	12.9 ± 5.5	***0.0313***	3.9
Qave (mL/s)		6.1 ± 5.3	8.8 ± 6.3	***0.0039***	2.6
Voided volume (mL)		158.8 ± 114.5	186.8 ± 110.0	***0.0273***	49.7
Residual urine volume (mL)		222.7 ± 122.3	102..4 ± 92.9	***0.0002***	-120.3

P value compared to pre status: Wilcoxson signed-rank test, n=12
Abbreviation: IPSS: International Prostate Symptom Score; Q: Question
The data were presented in mean ± SD

Changes in IPSS voiding symptom scores were not different between the two groups (Table 3).

Six adverse events were noted in 4 patients, including hypersalivation in 2 cases, and loss of appetite, vomiting, discomfort of stomach, and urinary incontinence in 1 case each (Figure 1). All adverse events were mild or moderate, although 4 patients withdrew due to adverse events.

Discussion

LUTS have been divided into storage, voiding and post-micturition symptoms [11]. Among these symptoms, the pathophysiology and the treatment of storage symptoms such as overactive bladder have been well established. Overactive bladder is a symptom syndrome that is suggestive of urodynamically demonstrable detrusor overactivity, and anticholinergic drugs and/or β3-adrenoceptor antagonists have been the treatment of choice. On the contrary, underactive bladder has been termed as a symptom complex suggesting of detrusor underactivity that is urodynamically determined as reduced urinary flow rate and/or increased of post-void residual with low detrusor pressure during voiding [14]. Recently, many researchers have been investigating the pathophysiology and treatment of underactive bladder. However, there has been no established definition of underactive bladder nor detrusor underactivity, because of the difficulty in defining these conditions [12,13]. Therefore, we included patients with detrusor

Table 3: IPSS before and after the treatment by α1-blocker use status.

α1-blocker use status			n	Pre	Post	Intragroup P value
IPSS	Total score		12	15.8 ± 9.4	12.1 ± 9.0	***0.0039***
	α1-blocker	Users	7	13.4 ± 10.5	10.7 ± 10.6	
		Non users	5	19.2 ± 7.2	14.0 ± 6.9	0.5691
Between-group P value				0.2903	0.5691	
Voiding symptom score						
Q1,Q3,Q5,Q6 subtotal			12	10.5 ± 6.6	8.0 ± 6.2	***0.0156***
	α1-blocker	Users	7	8.4 ± 7.5	7.4 ± 7.0	0.7500
		Non users	5	13.4 ± 4.4	8.8 ± 5.5	0.0625
				0.4135	0.7423	

P value compared to pre status: Wilcoxson signed-rank test
Abbreviation: IPSS: International Prostate Symptom Score; Q: Question
The data were presented in mean ± SD

underactivity defined as low urinary flow (Qmax ≤ 10 mL/sec, PVR ≥ 50 and BCI < 100, and weak or very weak class in Shafer's nomogram in males, and/or pdet Qmax ≤ 20 cm H_2O, with straining pattern, in females [12,13].

For the management of voiding difficulty in patients with an underactive detrusor, clean intermittent catheterization is used as the first choice of treatment. However, complications can occur in clean intermittent catheterization, and there are many patients who want to urinate by themselves even if it requires straining or the Credé maneuver, or because they reject self-catheterization due to pain, etc. Drug therapy can enable natural voiding and is ideal for increasing the patient's quality of life, provided the risk of upper urinary tract deterioration or infection can be avoided.

Bethanechol chloride, a choline ester, acts on muscarinic receptors with only a feeble nicotinic effect, while distigmine bromide, a choline esterase inhibitor, sustains acetylcholine activity. These drugs have been considered to enhance detrusor contractility and promote bladder emptying in patients with underactive bladders. Oral administration of bethanechol and distigmine has been empirically used for underactive bladder dysfunction in the hope of reducing residual urine, but the use of these drugs has not been standardized, due to lack of efficacy and serious side effects. The main reasons for these side effects may likely be due to their nicotinic effects.

Pilocarpine promotes physiological salivation by binding the muscarinic M3 receptor in the salivary glands, and has been used to treat dry mouth [15]. In a previous basic study in vitro, we found that pilocarpine increased contraction of the pig and human bladder through activation of M3-muscarinic receptor (on submission). Based on the findings, here we performed a clinical pilot study to evaluate the efficacy and safety of pilocarpine for the treatment of detrusor underactivity. In the present study, pilocarpine was found to be effective in improving voiding symptoms scores, urinary flow rates, and decreasing PVR. These effects were unrelated to the concomitant use of α-blockers. As to adverse events, hypersalivation and gastrointestinal effects may be the most frequent side effects. These adverse events, however, were mostly mild, and thus the safety profile of pilocarpine may be more favorable compared with cholinergic drugs.

Limitations of the present study were that the number of patients was small, there were no controls, and pressure flow studies were not used in the analysis of the effects. Because this was a pilot study, we could not obtain informed consent to perform invasive urodynamic studies both before and after the treatment. A randomized, controlled study with large number of patients should be performed to verify the effects of pilocarpine for the treatment of underactive bladder in the future.

In conclusion, pilocarpine appeared to be safe and effective for the treatment of detrusor underactivity.

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