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ORIGINAL ARTICLE

Naftopidil and propiverine hydrochloride for treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder: A prospective randomized controlled study

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Abstract

Objective. To assess the efficacy and safety of propiverine hydrochloride (antimuscarinic), naftopidil (α_1-adrenoceptor antagonist) or both in patients with male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia and concomitant overactive bladder (OAB). *Material and methods*. Men aged at least 50 years who had a total International Prostate Symptom Score (IPSS) of 8 or higher and bladder dairy documenting micturition frequency (more than eight micturitions/24 h) and urgency (more than one episode/24 h), with or without urgency urinary incontinence were randomized into three groups: group N, naftopidil (50 mg once daily) only; group P, propiverine hydrochloride (20 mg once daily); and group NP, naftopidil (50 mg once daily) plus propiverine hydrochloride (20 mg once daily) for a 4-week treatment regimen. *Results*. A total of 66 men, including 20 in group N, 23 in group P and 23 in group NP, were treated and 58 (87.9%) completed the 4 weeks of treatment. IPSS improved significantly in groups N and NP. Urinary frequency improved significantly in groups P and NP. Postvoid residual urine volume increased significantly in groups P and NP. Significant improvements in urgency episodes were noted in each group. One patient in group P required catheterization owing to acute urinary retention and another stopped medication because of difficulty in voiding. *Conclusion*. These results suggest that each treatment showed effectiveness for male LUTS with OAB. However, there are some possibilities of adverse effects with propiverine hydrochloride monotherapy.

Key Words: *α1-Adrenoceptor antagonist, antimuscarinics, benign prostatic hyperplasia, lower urinary tract symptoms, naftopidil, overactive bladder, propiverine*

Introduction

Lower urinary tract symptoms (LUTS) are a major health problem. LUTS are common among elderly men and are therefore usually considered synonymous with benign prostatic hyperplasia (BPH). The pathophysiology of male LUTS could be bladder dysfunction [weak detrusor or detrusor overactivity (DO)], bladder outlet obstruction (BOO) due to BPH, or a combination of these etiologies [1]. In male LUTS both storage and voiding symptoms exist and the complication rate of overactive bladder (OAB) has been reported at 50–70% [2,3]. Considering the high prevalence of storage symptoms in patients with male LUTS, the severe impact on patients' quality of life, and the availability of drugs acting on OAB, it may be logical to administer anticholinergic drugs. However, in patients with male LUTS suggesting of BPH, it remains unclear whether α_1-adrenoceptor antagonist or anticholinergic drug monotherapy or combination therapy is the best option.

Propiverine hydrochloride is the most popularly administered anticholinergic drug in Japan, and

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efficacy has been reported against urinary incontinence and high urinary frequency such as in unstable bladder or bladder irritation. While caution must be exercised when administering anticholinergic drugs to patients with BOO, Abrams et al. reported that even when administering anticholinergic drugs for BOO with OAB, BOO was not exacerbated [4].

Naftopidil is an α_1-adrenoceptor antagonist for the treatment of BPH that was approved in December 1998 in Japan. According to recent clinical studies, naftopidil improves not only voiding symptoms, but also urinary urgency and nocturia in patients with BPH [5].

The present study compared and analyzed the usefulness of naftopidil and propiverine hydrochloride combination therapy, propiverine hydrochloride monotherapy and naftopidil monotherapy in patients with male LUTS suggestive of BPH and concomitant OAB.

Material and methods

Subjects comprised 66 consenting patients with male LUTS and OAB who visited Kawasaki Medical University Hospital or Okayama University Hospital between June 2004 and March 2007 and satisfied the following conditions: age $\geq$50 years, International Prostate Symptom Score (IPSS) $\geq$8, 2-day frequency volume chart showing $\geq$1 episode/day of urinary urgency, day-time voiding frequency $\geq$8 episodes/day, night-time voiding frequency $\geq$1 episode/day and postvoid residual urine volume (PVR) $\leq$50 ml. Patients who had an elevated serum prostate-specific antigen (PSA) level ($>$10 ng/ml) were confirmed as having BPH before the treatment by transrectal ultrasound-guided prostate sextant biopsies.

Transabdominal ultrasonography was performed to determine prostate volume.

Methods

This study was conducted with the approval of the Institutional Review Board of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. After written informed consent had been obtained, subjects were registered through the study's website and divided according to daily urinary urgency episodes into three groups: naftopidil monotherapy group (group N), receiving 50 mg of naftopidil once daily after dinner; propiverine hydrochloride and naftopidil combination therapy group (group NP), receiving 20 mg of propiverine hydrochloride and 50 mg of naftopidil once daily after dinner; and propiverine hydrochloride monotherapy group (group P), receiving 20 mg of propiverine hydrochloride once daily after dinner.

The duration of administration was 4 weeks. Before and after administration, subjective symptoms were assessed using the International Prostate Symptom Score (IPSS) and Quality of Life (QoL) index, and urinary urgency was assessed in four grades by referring to the Urgency Perception Scale [6]: 4 = "Unable to hold urine"; 3 = "Able to hold urine until I reach the toilet if I go immediately"; 2 = "Able to finish what I am doing before going to the toilet"; and 1 = "No urinary urgency". Subjects were instructed to keep frequency–volume charts, and voiding frequency, daily void volume, urinary urgency and urinary incontinence were assessed. Furthermore, uroflowmetry was performed to measure voided volume and maximum flow rate (Q_{max}), and PVR was measured by transabdominal ultrasonography. Every PVR was measured by a doctor just after uroflowmetry. The PVR was calculated as height $\times$ width $\times$ length $\times$ 0.52 [7].

Using preadministration severity as assessed by the IPSS and preadministration night-time voiding frequency as stratification factors, Zelen's method was used to correct intergroup variations among hospitals.

Statistical analysis

Based on the characteristics of the data, mean $\pm$ standard deviation (SD) was calculated. The paired *t* test was performed to compare data before and after administration in each group. One-way analysis of variance (ANOVA) was used to compare data among the three groups. When significance was detected, Scheffé's test was used to ascertain intergroup significance. Values of $p < 0.05$ were considered statistically significant.

Results

Assessments

Of the 66 patients who registered online, valid data were obtained from 58 patients. Two patients who did not make a second visit, four patients who stopped taking the assigned drug owing to adverse events and two patients for whom final data could not be obtained were excluded. Table I shows preadministration background factors for the 58 patients.

Clinical assessment

The IPSS showed that incomplete emptying, frequency, urgency and nocturia were significantly improved after therapy for group N; incomplete

Table I. Preadministration background factors of patients in the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup[a]
Age (years)	69.1±8.3	69.1±8.3	68.7±7.5	70.9±6.7	0.6276
Prostate volume (ml)	26.6±12.3	26.6±12.3	27.1±9.3	25.3±7.7	0.8495
Frequency–volume chart					
24 h voiding frequency (times)	12.0±2.4	11.1±1.7	12.4±2.9	12.4±2.9	0.0872
24 h voided volume (ml)	1912±561	1839±513	1892±642	2015±523	0.6787
Mean voided volume/void (ml)	166.0±51.0	153.6±51.0	174.3±56.5	168.8±43.9	0.4818
Urgency incontinence (times)	0.6±1.1	0.8±1.3	0.5±0.7	0.6±1.3	0.7775
Urinary urgency (times)	2.7±1.3	2.6±1.2	3.1±1.4	2.4±1.3	0.2449
Subjective symptoms					
IPSS storage symptom	9.7±2.4	10.3±2.1	9.3±2.6	9.6±2.6	0.4284
IPSS voiding symptom	6.1±4.0	5.9±3.8	6.4±4.3	6.1±4.0	0.9304
Total IPSS	18.1±6.3	18.2±5.7	17.9±6.4	18.2±7.0	0.9818
IPSS QoL index	4.7±0.8	4.5±0.8	4.9±0.7	4.8±0.8	0.3509
Objective symptoms					
Voiding volume (ml)	110.6±57.3	112.8±60.1	109.0±64.3	109.9±48.0	0.9783
Maximum flow rate (ml/s)	9.8±3.6	9.8±4.0	10.2±3.7	9.5±3.1	0.8031
Postvoiding residual urine volume (ml)	13.3±15.5	16.7±13.5	12.3±16.9	10.8±15.9	0.4911

Data are shown as mean±SD.
Group N = naftopidil monotherapy; NP = propiverine hydrochloride and naftopidil combination therapy; P = propiverine hydrochloride monotherapy; IPSS = International Prostate Symptom Score; QoL = quality of life.
[a]Preadministration background factors were compared by one-way ANOVA.

emptying, frequency, urgency, weak stream and nocturia were improved for group NP; and frequency and urgency were improved for group P. IPSS storage symptom subscores were significantly improved in all three groups, but voiding symptom subscores were not improved in any of the three groups. Total score was significantly improved for groups N and NP. QoL scores were significantly improved after therapy in all three groups. However, no significant differences existed in the degree of change in seven items of IPSS score and total score among the three groups. Severity of urgency improved significantly after therapy in all three groups, and there was no significant difference in the degree of change among the three groups (Tables II and III). With regard to frequency volume chart data, night-time voiding frequency and urgency episodes improved significantly for group N; day-time/night-time/24 h voiding frequency, day-time/24 h average voided volume/void, urgency incontinence and urgency episodes improved significantly for group NP; and day-time/24 h voiding frequency and urgency episodes improved significantly for group P (Tables IV–VI).

Comparing the degree of change among the three groups, no significant differences existed in day-time/night-time/24 h voiding frequency, night-time average voided volume/void or urgency incontinence episodes, but the degree of change in day-time/24 h average voided volume/void for group N was −10.4±35.8 ml/–6.2±34.0 ml, while that for group NP was significantly larger at 28.2±38.7 ml/–23.5±34.9 ml, respectively. In addition, the degree of change in urgency episodes for group N was −1.0±1.0 and that for group NP was significantly larger at −2.0±1.3 (Table IV–VI).

PVR decreased for group N, and both PVR and voided volume for group NP were significantly increased, while PVR for group P increased significantly. Among the three groups, the degree of change in PVR was significantly lower for group N than for groups NP and P (Table VII, Figure 1).

Safety

Of the 66 patients for whom safety was analyzed, five patients experienced adverse events. Three group NP patients (13.0%) experienced staggering, rash and blurred vision, and the patients with staggering and rash stopped taking the drug. Two group P patients (10.0%) developed difficulty on voiding and transient urinary retention (urethral catheterization was needed once, and the patient was able to urinate spontaneously after he stopped taking the drug). None of the patients in group N experienced adverse events.

Discussion

In the treatment of LUTS suggestive of BPH, α_1-adrenoceptor antagonists are in wide use because

Table II. Change in seven items on the International Prostate Symptom Score from pre- to postadministration and comparisons of the degree of change among the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup
Incomplete emptying					
Pre	2.2±1.7	2.0±1.6	2.1±1.7	2.5±1.9	0.2861
Post	1.7±1.5	1.3±1.1	1.4±1.4	2.3±1.8	
Intragroup	0.0013	0.0190	0.0097	0.6044	
Frequency					
Pre	3.6±1.3	3.7±1.3	3.3±1.4	3.7±1.2	0.7299
Post	2.7±1.3	2.8±1.2	2.3±1.3	3.0±1.4	
Intragroup	<0.0001	0.0250	0.0052	0.0482	
Intermittency					
Pre	1.8±1.8	1.6±1.7	2.0±1.8	1.8±1.9	0.3599
Post	1.5±1.5	1.1±1.2	1.6±1.6	1.8±1.7	
Intragroup	0.0774	0.1257	0.1861	0.8162	
Urgency					
Pre	3.4±1.3	3.4±1.4	3.5±1.2	3.2±1.2	0.1505
Post	2.2±1.4	2.5±1.3	1.9±1.6	2.2±1.4	
Intragroup	<0.0001	0.0149	<0.0001	0.0124	
Weak stream					
Pre	2.9±1.8	2.6±1.8	3.2±1.8	2.8±1.8	0.6023
Post	2.3±1.6	2.2±1.7	2.3±1.7	2.4±1.5	
Intragroup	0.0089	0.3306	0.0081	0.3313	
Straining					
Pre	1.4±1.5	1.6±1.6	1.1±1.5	1.5±1.3	0.1395
Post	1.5±1.4	1.3±1.6	1.3±1.3	1.9±1.5	
Intragroup	0.6664	0.2175	0.4787	0.1492	
Nocturia					
Pre	2.8±1.3	3.2±1.3	2.5±1.2	2.7±1.3	0.0504
Post	2.1±1.1	2.1±1.0	1.8±1.1	2.4±1.1	
Intragroup	<0.0001	0.0003	0.0027	0.3105	

Data are shown as mean±SD.
Group N = naftopidil monotherapy; NP = propiverine hydrochloride and naftopidil combination therapy; P = propiverine hydrochloride monotherapy.
Intragroup: paired *t* test; intergroup: change between pre- and postadministration was compared in each group (one-way ANOVA).

of their fast-acting properties and safety. The affinity of naftopidil towards α_{1d} is about three to 17 times greater than that towards α_{1a} and α_{1b}, and α_{1d} receptor is believed to be involved with storage symptoms as well as voiding symptoms [8]. However, α_1-adrenoceptor antagonist monotherapy is often insufficient to improve OAB symptoms. Several studies have been published on α_1-adrenoceptor antagonist monotherapy and anticholinergic agent combination therapy using for BOO accompanied by OAB. Athanasopoulos et al. prescribed either 0.4 mg of tamsulosin hydrochloride or 0.4 mg of tamsulosin hydrochloride and 4 mg of tolterodine tartrate for 50 patients with urodynamically proven mild-to-moderate BOO and DO for 3 months. The results showed that QoL improved and bladder volume significantly increased for combination therapy compared with tamsulosin monotherapy. Furthermore, combination therapy did not cause acute urinary retention (AUR) in any patients [9].

Lee et al. examined 211 patients who were diagnosed with BOO with OAB, and 4 mg of doxazosin was administered to 69 patients and 4 mg of doxazosin and 20 mg of propiverine hydrochloride were administered to 142 patients for 2 months. Compared with the monotherapy group, voiding frequency, mean voided volume/void, IPSS storage symptom subscores and patient satisfaction improved significantly in the combination group. PVR increased significantly for the combination group, but none of the patients demonstrated AUR [10]. Lee et al. administered 4 mg of doxazosin to patients with BOO and DO for 3 months, then 4 mg of tolterodine tartrate was added to the regimen for 2 months when symptoms did not improve. They revealed that doxazosin monotherapy improved symptoms in only 35% of BOO + DO patients, and doxazosin and tolterodine combination therapy improved symptoms in 73% of patients. As to adverse events, two of the 60 patients on combination therapy (3.3%) experienced

Table III. Change in International Prostate Symptom Score (IPSS), Quality of Life (QoL) index and severity of urgency from pre- to postadministration and comparisons of the degree of change among the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup
IPSS storage symptoms					
Pre	9.7±2.4	10.3±2.1	9.3±2.6	9.6±2.6	0.2942
Post	6.9±2.8	7.4±2.6	5.9±2.8	7.7±2.8	
Intragroup	<0.0001	0.0004	<0.0001	0.0175	
IPSS voiding symptoms					
Pre	6.1±4.0	5.9±3.8	6.4±4.3	6.1±4.0	0.3146
Post	5.3±3.7	4.6±3.4	5.2±3.9	6.1±3.7	
Intragroup	0.0273	0.0801	0.0571	0.9999	
Total IPSS					
Pre	18.1±6.3	18.2±5.7	17.9±6.4	18.2±7.0	0.1437
Post	13.9±6.5	13.3±6.0	12.5±6.3	16.1±7.1	
Intragroup	<0.0001	0.0019	<0.0001	0.1398	
IPSS QoL index					
Pre	4.7±0.8	4.5±0.8	4.9±0.7	4.8±0.8	0.1567
Post	3.5±1.2	3.6±1.2	3.1±1.3	3.8±1.2	
Intragroup	<0.0001	0.0149	<0.0001	0.0041	
Severity of urgency					
Pre	2.7±1.0	2.8±1.0	2.8±0.9	2.4±1.1	0.1201
Post	1.4±1.2	1.7±1.1	1.1±0.9	1.4±1.5	
Intragroup	<0.0001	0.0007	<0.0001	0.0030	

Data are shown as mean±SD.
Group N=naftopidil monotherapy; NP=propiverine hydrochloride and naftopidil combination therapy; P=propiverine hydrochloride monotherapy.
Intragroup: paired *t* test; intergroup: change between pre- and postadministration was compared in each group (one-way ANOVA).

transient urinary retention [11]. These reports are correlated with the present results. In this study, combination therapy was more effective than α_1-adrenoceptor antagonist monotherapy; however, the difference was small. Although PVR was significantly increased after combination therapy, AUR was not demonstrated.

Kaplan et al. conducted the first large-scale randomized double-blind study on patients with male LUTS diagnosed with a questionnaire [12]. In total, 876 male LUTS patients with OAB ≥40 years old were divided into four groups using the double-blind method: placebo group, tolterodine group, tamsulosin group, and tolterodine plus tamsulosin group.

Table IV. Frequency–volume chart (1): change in average voiding frequency from pre- to postadministration and comparisons of the degree of change among the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup
Day-time					
Pre	9.2±2.0	9.6±2.1	8.6±1.9	9.5±2.1	0.4477
Post	8.1±2.2	8.9±2.3	7.4±2.1	8.0±2.0	
Intragroup	0.0001	0.3077	0.0010	0.0028	
Night-time					
Pre	2.8±4.0	3.1±3.8	2.5±4.3	2.8±4.0	0.3570
Post	2.1±1.2	2.3±1.2	1.7±1.0	2.5±1.5	
Intragroup	<0.0001	0.0039	0.0002	0.1879	
24 h					
Pre	12.0±2.4	12.7±2.5	11.1±1.7	12.4±2.9	0.7761
Post	10.2±2.4	11.3±2.2	9.1±2.2	10.4±2.4	
Intragroup	<0.0001	0.0772	0.0002	0.0042	

Data are shown as mean±SD.
Group N=naftopidil monotherapy; NP=propiverine hydrochloride and naftopidil combination therapy; P=propiverine hydrochloride monotherapy.
Intragroup: paired *t* test; intergroup: change between pre- and postadministration was compared in each group (one-way ANOVA).

Table V. Frequency–volume chart (2): change in average voided volume/void from pre- to postadministration and comparisons of the degree of change among the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup
Day-time					
Pre	152.3±47.7	139.9±43.5	159.4±54.4	156.5±43.3	0.0072[†]
Post	164.0±56.5	129.5±49.6	187.6±60.5	171.5±38.8	
Intragroup	0.0507	0.2640	0.0052	0.1174	
Night-time					
Pre	224.0±98.0	213.0±92.7	237.7±125.3	173.0±42.4	0.3467
Post	226.4±86.4	224.2±90.9	246.6±86.0	183.3±35.4	
Intragroup	0.9379	0.5545	0.5735	0.1476	
24 h					
Pre	166.0±51.0	153.6±51.0	174.3±56.5	173.0±42.4	0.0340[‡]
Post	177.2±54.5	147.4±50.9	197.8±59.8	83.3±35.4	
Intragroup	0.0452	0.4894	0.0088	0.1476	

Data are shown as mean±SD.
Group N = naftopidil monotherapy; NP = propiverine hydrochloride and naftopidil combination therapy; P = propiverine hydrochloride monotherapy.
Intragroup: paired *t* test; intergroup: change between pre- and postadministration was compared in each group (one-way ANOVA). Scheffé's test: [†]N vs NP $p=0.0072$, [‡]N vs NP $p=0.0340$.

After 12 weeks of administration, patient satisfaction, urgency, day-time frequency and night-time frequency were significantly improved for the combination therapy group compared with the placebo group. Urinary retention requiring urethral catheterization was seen in one patient in the tolterodine group (0.5%) and one patient in the combination therapy group (0.5%).

In the present study, even with a low number of patients and no placebo group, usefulness was highest for the combination therapy. In all groups, IPSS storage symptoms improved significantly, but voiding symptoms were unchanged between before and after therapy. Even naftopidil administration did not significantly improve voiding symptoms, probably because of the low number of patients and the fact that many patients had storage symptoms rather than voiding symptoms.

As reported in the past, anticholinergic agents significantly increased PVR. In group P, a 79-year-old patient with a prostate volume of 51 ml experienced urinary retention requiring urethral catheterization, despite residual urine was not found before therapy. Another 79-year-old patient, with a preadministration residual urine of 30 ml, complained of difficulty on voiding after treatment. Abrams et al. reported the safety of monotherapy with tolterodine, an anticholinergic agent for patients with urodynamically proven BOO and DO [4]. However, caution must be exercised when administering anticholinergic agents alone, especially to elderly men who may have DO with

Table VI. Frequency–volume chart (3): change in urgency incontinence and urgency episodes from pre- to postadministration and comparisons of the degree of change among the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup
Urgency incontinence (times)					
Pre	0.6±1.1	0.8±1.3	0.5±0.7	0.6±1.3	0.4877
Post	0.2±0.6	0.6±0.9	0.1±0.4	0.1±0.2	
Intragroup	0.0012	0.1489	0.0093	0.0735	
Urinary urgency (times)					
Pre	2.7±1.3	2.6±1.2	3.1±1.4	2.4±1.3	0.0157[†]
Post	1.2±1.2	1.6±1.1	1.0±1.0	1.1±1.5	
Intragroup	<0.0001	0.0003	<0.0001	<0.0001	

Data are shown as mean±SD.
Group N = naftopidil monotherapy; NP = propiverine hydrochloride and naftopidil combination therapy; P = propiverine hydrochloride monotherapy.
Intragroup: paired *t* test; intergroup: change between pre- and postadministration was compared in each group (one-way ANOVA). Scheffé's test: [†]N vs NP $p=0.0242$.

Table VII. Change in uroflowmetry parameters from pre- to postadministration and comparisons of the degree among the three groups.

	All ($n=58$)	Group N ($n=19$)	Group NP ($n=21$)	Group P ($n=18$)	Intergroup
Voiding volume (ml)					
Pre	110.6±57.3	112.8±60.1	109.0±64.3	109.9±48.0	0.0676
Post	136.2±74.8	138.2±78.5	158.0±80.7	108.7±56.8	
Intragroup	0.0062	0.1472	0.0090	0.9024	
Maximum flow rate (ml/s)					
Pre	9.8±3.6	9.8±4.0	10.2±3.7	9.5±3.1	0.1555
Post	10.7±4.7	10.7±4.5	12.2±5.1	9.0±3.8	
Intragroup	0.1050	0.3305	0.0617	0.5135	

Data are shown as mean±SD.
Group N = naftopidil monotherapy; NP = propiverine hydrochloride and naftopidil combination therapy; P = propiverine hydrochloride monotherapy.
Intragroup: paired *t* test; intergroup: change between pre- and postadministration was compared in each group (one-way ANOVA).

impaired contractility, even if little PVR was demonstrated before treatment.

Based on the above findings on safety and efficacy, in patients with male LUTS with OAB who are ≥50 years old, an α_1-adrenoceptor antagonist may be administered first, and if that drug is ineffective, an anticholinergic agent should be added to the drug regimen.

The efficacy and safety of long-term anticholinergic agent administration to patients with male LUTS suggestive of BPH and concomitant OAB need to be clarified in future studies.

In conclusion, in patients with male LUTS suggestive of BPH and concomitant OAB, naftopidil monotherapy was the safest, while combination therapy with naftopidil and anticholinergic agent was the most effective treatment. Anticholinergic agent monotherapy was the least effective and safe. As a result, α_1-adrenoceptor antagonists should be administered initially. More cases need to be studied in the future.

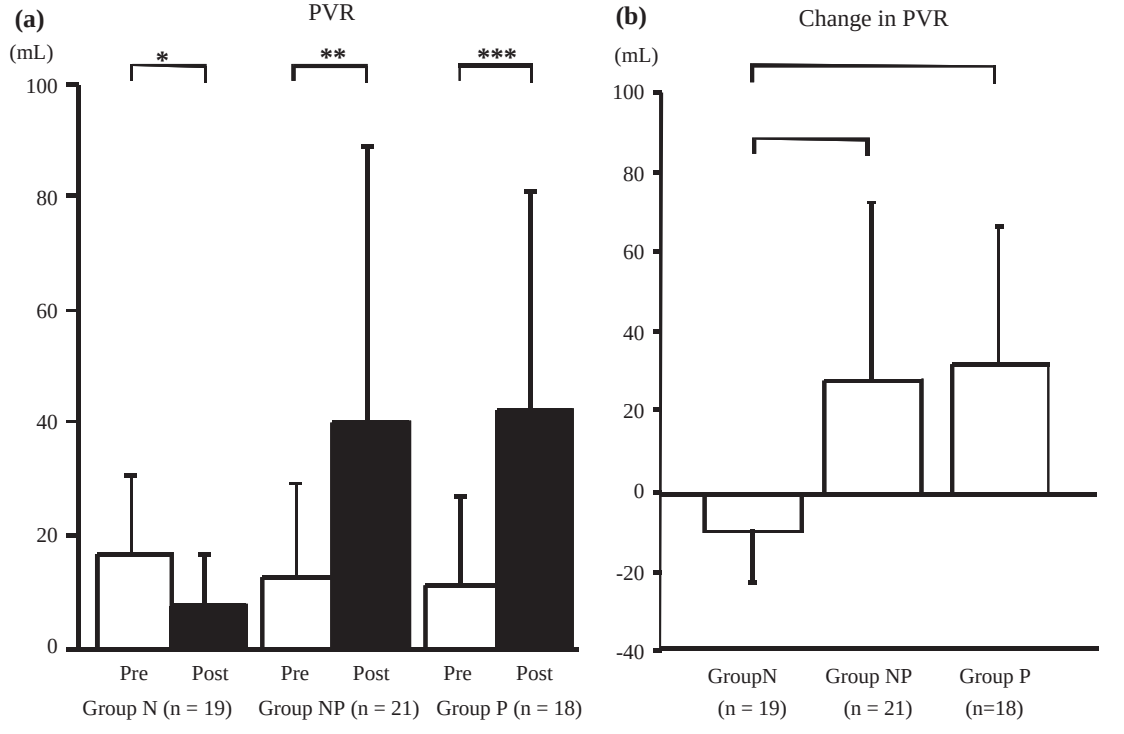

Figure 1. (a) Change in postvoid residual urine volume (PVR) from preadministration to postadministration (mean±SD), and (b) comparisons of the degree among the three groups (mean±SD). Group N = naftopidil monotherapy; NP = propiverine hydrochloride and naftopidil combination therapy; P = propiverine hydrochloride monotherapy. (a) $^{\star}p=0.0085$, $^{\star}p=0.0102$, $^{\star\star\star}p=0.0012$ (paired *t* test). (b) The change between pre- and post-treatment was compared in each group: $p=0.0242$ (one-way ANOVA); †N vs NP $p=0.0058$, ‡N vs P $p=0.0031$ (Scheffé's test).

Conflicts of interest: None declared.

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