Efficacy of propiverine hydrochloride for urinary incontinence after robot-assisted or laparoscopic radical prostatectomy

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Introduction: *To clarify the efficacy and safety of propiverine hydrochloride for incontinence after robot-assisted laparoscopic prostatectomy (RALP)/laparoscopic radical prostatectomy (LRP), along with changes in the urethral pressure profile (UPP) and quality of life in patients treated with propiverine hydrochloride.*
Materials and methods: *In this randomized, comparative study, 104 patients who were aware of urinary incontinence after RALP or LRP were assigned to receive propiverine hydrochloride (treatment group) or not (controls). Pad test results, International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) scores, and UPP results [including maximum urethral closure pressure (MUCP) and functional urethral length (FUL)], were recorded immediately and at 6 months postoperatively.*
Results: *No serious intraoperative complications or adverse events were caused by propiverine hydrochloride. The pad-test negative rate was significantly greater in the treatment group than in controls (89.1% vs. 73.2%, p = 0.044). Changes in ICIQ-SF scores and MUCP were significantly greater in the treatment group than in controls [-6.5 vs. -4.5 points (p = 0.021), and +49.5 vs. +28.7 mmHg (p = 0.038), respectively]. FUL change did not significantly differ between groups [+4.5 vs. +3.8 mm (p = 0.091)]. In univariate logistic regression analyses, body mass index (BMI), MUCP, and treatment with propiverine hydrochloride were significantly associated with continence status. In multivariate analyses, BMI and MUCP were independently associated with continence status [odds ratio (OR), 1.266; 95% confidence interval (CI), 1.047–1.530 (p = 0.015), and OR, 0.986; 95% CI, 0.973-0.999 (p = 0.042), respectively].*
Conclusions: *Treatment with propiverine hydrochloride alleviated urinary incontinence while improving patient symptoms and quality of life after RALP or LRP.*

Key Words: propiverine hydrochloride, quality of life, radical prostatectomy, urethral pressure profile, urinary incontinence

Introduction

Urinary incontinence is an important complication in patients who have undergone radical prostatectomy (RP), which is the standard treatment for localized prostate cancer. The traditional surgical procedure is retropubic RP, which is open surgery performed via midline abdominal incision. In 1997, laparoscopic radical prostatectomy (LRP) using an extraperitoneal approach was reported, and RP has since been further developed.[1] Recently, robot-assisted laparoscopic prostatectomy (RALP) has evolved rapidly and its usage is expanding worldwide.[2] RALP and LRP allow the performance of delicate surgery, which can preserve urethral function. Although both procedures provide clearer operative fields than retropubic RP, they are associated with high incidences of postoperative urinary incontinence. Many studies have reported that urinary incontinence after RP is caused by reduced urethral pressure[3,4] and improves gradually over time, regardless of surgical approach.[5,6] However, until improvement occurs, urinary incontinence remains a frustrating side effect of RP that impairs patients' quality of life. As a countermeasure, several drugs are used for the medical treatment of urinary incontinence after RP.

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Propiverine hydrochloride is an anticholinergic agent[7] that increases plasma noradrenaline and dopamine levels without changing heart rate or blood pressure.[8] This mechanism presumably involves the inhibition of noradrenaline reuptake.[9] Several studies have reported that increased catecholamine levels after propiverine hydrochloride administration stimulate the smooth muscle of the bladder neck and proximal urethra through α1-adrenergic receptors.[10] In a clinical trial (i.e., the FRESH study), propiverine hydrochloride was found to be an effective therapeutic option for stress urinary incontinence.[11] Additionally, propiverine hydrochloride was reported to improve female stress urinary incontinence by increasing the maximum urethral closure pressure (MUCP) and functional urethral length (FUL).[12] Given these prior observations, we hypothesized that decreased urethral pressure resulting from surgical damage contributes to incontinence after RP and that propiverine hydrochloride could increase urethral pressure in these patients. However, no studies have assessed the effect of propiverine hydrochloride on urinary incontinence after RP.

The main aim of this study was to clarify the efficacy of propiverine hydrochloride treatment after RALP/LRP. We evaluated the improvement in incontinence and changes in the urethral pressure profile. We also investigated patients' quality of life and the safety of propiverine hydrochloride treatment after RALP/LRP.

Materials and methods

This single-center, randomized prospective study was performed in accordance with the ethical principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Nagasaki University Hospital (approval number: 13052792-3). All patients provided written informed consent before enrollment in this study.

The study participants were 104 patients who underwent RALP or LRP performed by a single surgeon at our hospital from April 2013 to December 2017, all of whom experienced postoperative urinary incontinence, defined as pad gain ≥ 1 g during the 1-hour pad test. Patients were excluded if they had neurogenic bladder dysfunction, overactive bladder, stress urinary incontinence, urinary tract infection, urethral stricture, glaucoma, severe cardiac disease, renal dysfunction, and/or hepatic dysfunction. Patients were also excluded if they had received radiation therapy and/or oral treatment with anticholinergic agents, antidepressants, or anxiolytics. Patients were randomized into two groups at a ratio of 1:1 using computer-generated random numbers. Randomization was stratified by surgical procedure (LRP/RALP): patients in the treatment group received propiverine hydrochloride at a dose of 20 mg/day for 6 months, while patients in the control group did not. This dosage of propiverine hydrochloride is approved in Japan. Subjective symptoms at baseline were evaluated by using the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF). Patients also completed pad tests and urodynamic studies, including uroflowmetry, MUCP measurement, and FUL measurement.

The urodynamic studies were performed in accordance with the standard methods defined by the International Continence Society.[13] A transurethral catheter was inserted into the bladder and removed by an electronic puller at 1 mm/s, with a perfusion rate of 2 mL/min to measure the urethral pressure profile (e.g., MUCP and FUL). Data from the urodynamic studies were independently analyzed by two of our research group members who were not involved in the collection of the data. The efficacy of treatment was assessed by comparing these baseline parameters to measurements at 3 and 6 months postoperatively.

The primary endpoint was the pad-test negative rate. The secondary endpoints were the changes from baseline in the ICIQ-SF score, MUCP, and FUL. Safety was assessed based on adverse events, uroflowmetry, and residual urine volume. Continuous variables that demonstrated normal distributions were represented as mean ± standard deviation; continuous variables that did not demonstrate normal distributions were represented as median and range. Categorical variables were represented as number and percentage (%). Statistical analyses were performed with the Mann–Whitney U test or Student's t-test for continuous variables; the chi-squared test was used to analyze categorical variables. Univariate and multivariate logistic regression analyses were used to identify variables significantly associated with postoperative urinary continence. All statistical analyses were performed with SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). All tests of significance were two-sided; p values α 0.05 were considered statistically significant. This study was estimated to require at least 98 participants for 80% power with an effect size of 0.5.

Results

Patient characteristics

In total, 104 patients were enrolled in this study; two patients were excluded from analysis because of loss to follow up. The remaining 102 patients were allocated

TABLE 1. **Demographics and baseline characteristics of patients in this study**

	Mean (± SD) or n		
	Treatment group	**Control group**	**p value**
Age (y.o)	68.8 ± 5.8	69.3 ± 6.4	0.576
BMI (kg/m^2)	23.8 ± 2.7	24.4 ± 2.9	0.290
Prostate volume (mL)	32.9 ± 13.9	34.0 ± 10.9	0.220
PSA (ng/mL)	10.4 ± 6.3	10.4 ± 8.6	0.362
RALP/LRP	24/26	27/25	0.320
Nerve sparing	13	14	0.900
Pathological			
EPE1	16	17	0.675
RM1	10	13	0.859

BMI = body mass index; EPE1 = extraprostatic extension-positive; LRP = laparoscopic radical prostatectomy; PSA = prostate-specific antigen; RALP = robot-assisted laparoscopic prostatectomy; RM1 = resection margin-positive; SD = standard deviation

as follows: 50 patients in the treatment group and 52 patients in the control group. The characteristics of patients in each group are summarized in Table 1. Fifty-one patients underwent LRP and 51 patients underwent RALP. The nerve-sparing technique was performed in 14 patients who underwent LRP and in 13 patients who underwent RALP. There were no statistically significant differences in patient characteristics between the two groups at baseline.

Primary endpoint: efficacy of propiverine hydrochloride

Changes in the pad-test negative rates in each group are shown in Figure 1a. At 6 months postoperatively, the pad-test negative rate was significantly greater in the treatment group than in the control group (89.1% vs. 73.2%, respectively; p = 0.044). Furthermore, there was greater improvement in the amount of urinary incontinence in the treatment group than in the control group (improvement by 8.0 g [−7.2 to 326.0 g] vs. 1.5 g [−14.0 to 217.0 g], respectively; p = 0.050) at 6 months postoperatively. In contrast, there were no differences between groups in the pad-test negative rates at baseline and 3 months.

Secondary endpoint

Nearly all patients in both the treatment and control groups showed improved ICIQ-SF scores at 3 and 6 months postoperatively. Over time, the MUCP and FUL increased significantly (immediately vs. 3 months vs. 6 months: MUCP, 78.3 ± 41.1 vs. 100.8 ± 48.9 vs. 114.8 ± 45.4 cmH_2O, respectively [p = 0.001]; FUL, 15.9 ± 5.4 vs. 17.5 ± 5.9 vs. 20.5 ± 9.6 mm, respectively [p = 0.008]). The changes in these parameters in each group are shown in Figure 1b–d and Table 2. At 6 months postoperatively, changes in ICIQ-SF scores and MUCP were significantly greater in the treatment group than in the control group. There were no significant associations between the change in MUCP and either the use of nerve-sparing technique, surgical procedure, or body mass index (BMI). There was no significant difference in the change in FUL between the two groups, although the change tended to be greater in the treatment group.

To identify factors involved in postoperative urinary continence, univariate and multivariate logistic regression analyses were performed; the results are shown in Table 3. In univariate analysis, BMI at baseline, MUCP at 6 months postoperatively, and treatment with propiverine hydrochloride were significantly associated with continence status at 6 months postoperatively, whereas MUCP at baseline was not associated with postoperative urinary continence (p = 0.269). Conversely, use of the nerve-sparing technique was not a significant predictive factor in this analysis, although it is believed to be important for urinary continence after RP.[14] Therefore, use of the nerve-sparing technique was included in multivariate analysis. Notably, multivariate analysis showed that BMI at baseline was a significant predictive factor, while MUCP at 6 months postoperatively was independently associated with urinary continence after RP.

In this study, there were no serious intraoperative complications; none of the patients discontinued propiverine hydrochloride treatment. Although mild constipation and dry mouth occurred in several patients, there were no severe adverse events caused

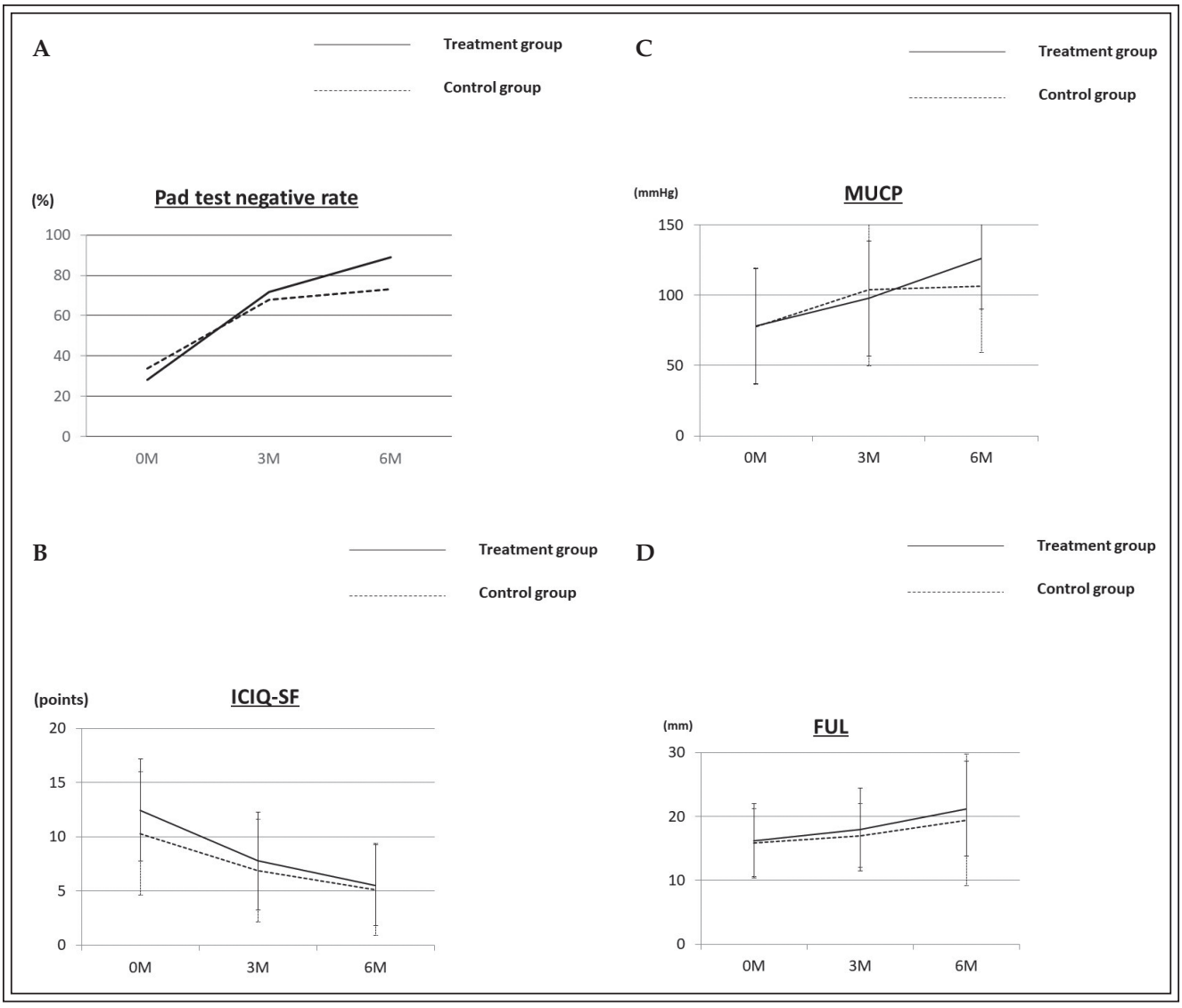

Figure 1. Changes in subjective symptoms and urodynamic evaluations at each time point. **A)** Pad-test negative rate. **B)** International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) score. **C)** Maximum urethral closure pressure (MUCP). **D)** Functional urethral length (FUL).

TABLE 2. **Improvements (changes) in parameters at 6 months postoperatively**

	Median (range)		
	Treatment group	**Control group**	**p value**
ICIQ-SF	6.5 (0-15)	4.5 (-2-18)	0.021
MUCP	49.5 (-26-132)	28.7 (-109-122)	0.038
FUL	4.5 (-8.0-20.4)	3.8 (-10.1-13.5)	0.091

FUL = functional urethral length; ICIQ-SF = International Consultation on Incontinence Questionnaire–Short Form; MUCP = maximum urethral closure pressure

TABLE 3. **Univariate and multivariate logistic regression analyses of factors associated with urinary continence after radical prostatectomy**

	Univariate p value	OR	Multivariate 95%CI	p value
Age	0.116	-	-	-
BMI	0.008	1.266	1.047-1.530	0.015
Nerve sparing	0.999	0.868	0.255-2.959	0.822
Propiverine	0.049	0.482	0.148-1.570	0.226
MUCP	0.022	0.986	0.973-0.999	0.042
FUL	0.160	-	-	-
LRP/RALP	0.455	-	-	-

BMI = body mass index; FUL = functional urethral length; LRP = laparoscopic radical prostatectomy; MUCP = maximum urethral closure pressure; RALP = robot-assisted laparoscopic prostatectomy

by propiverine hydrochloride. Constipation (seven patients, 14%), dry mouth (five patients, 10%), and gastritis (one patient, 2%) were noted as adverse events in the treatment group. None of the patients had increased residual urine or deteriorated uroflow.

Discussion

The present study is the first randomized clinical trial to show that treatment with propiverine hydrochloride improved urinary incontinence after LRP or RALP. The etiology of urinary incontinence after RP is multifactorial. However, the main cause is reportedly urethral sphincter dysfunction,[15] which is caused by neuromuscular injury during surgery. There have been several reports regarding the improvement of voiding function with drug treatments. Honda et al reported the efficacy of tadalafil, a phosphodiesterase type 5 inhibitor, for recovery of lower urinary tract symptoms after RALP.[16] However, tadalafil did not improve the rate of postoperative urinary incontinence. Furthermore, in the early postoperative period, tadalafil may exhibit a negative effect on urinary continence.[17] One study demonstrated that solifenacin succinate, an antimuscarinic drug, improved lower urinary tract symptoms after RP;[18] however, the type of incontinence was not determined in that study, and surgical manipulation of the urethra might have been inconsistent due to differences in surgical procedures (e.g., open surgery vs. laparoscopy). In the present study, we hypothesized that propiverine hydrochloride might increase MUCP and extend FUL, which could result in postoperative improvement of urinary incontinence via urethral contraction. We found that postoperative MUCP was significantly greater in the treatment group than in the control group. However, FUL did not significantly differ between the two groups. These results suggest that the excitatory effect of propiverine hydrochloride is limited to the proximal urethra. However, the results regarding FUL may have been biased because this parameter is affected by many factors, such as surgical technique and anatomical differences.

In this study, we assessed incontinence objectively by using the pad test and subjectively by using a questionnaire related to urinary incontinence, the ICIQ-SF. In many studies, urinary incontinence was assessed based on self-reported pad use;[19] many investigators have included safety-pad use in their definition of continence. Notably, Ficarra et al proposed a standardized classification to distinguish patients not using pads (C0) from those using a single safety pad (C1) and those using multiple pads (C2).[20] However, patient usage of pads is variable, and some might not present with pad use as a sign of incontinence. For such patients, the use of subjective findings to assess urinary incontinence might be inaccurate. In the present study, we performed pad tests for the assessment of urinary incontinence. Because pad tests measure the amount of urinary incontinence after the addition of stress common to all patients, this is presumably an accurate method of assessment. For supportive data, we used the ICIQ-SF to assess the subjective postoperative continence status.[21] Because this questionnaire can evaluate subjective symptoms, it is an important patient-rated assessment tool. In this study, treatment with

propiverine hydrochloride resulted in improvement in the ICIQ-SF score, although the score at baseline tended to be slightly greater in the treatment group than in the control group. This result showed that patients with postoperative incontinence experienced a noticeable effect of propiverine hydrochloride treatment.

This study also considered risk factors for postoperative urinary incontinence. Studies of potential predictors showed that patient age, BMI, lower urinary tract symptoms, and prostate volume were related to the recovery of urinary continence.[19] Some studies showed that patient age was a significant predictor of the recovery of urinary continence after RP.[22-24] Others reported that preoperative erectile function and nerve-sparing technique usage were important in the recovery of urinary continence.[14,22,23] Regarding BMI, improvement in urinary continence was reported to be significantly worse for obese men than for non-obese men.[25] However, another study found that the recovery of urinary function was similar across all BMI categories.[26] Among preoperative patient characteristics, prostate volume greater than 50 mL was found to correlate with urinary incontinence after RP.[27] In terms of surgical procedures, the use of RALP resulted in improved urinary function outcome, compared with the use of retropubic radical prostatectomy.[25] However, it is controversial whether the use of RALP results in superior urinary functional outcome, compared with the use of LRP.[28-30] Multivariate analysis in the present study showed that patient BMI and MUCP were independently associated with improvement in postoperative incontinence. However, propiverine hydrochloride treatment was not independently associated with improvement in postoperative incontinence. The weight of visceral fat may limit increases in MUCP, which may be affected by many factors in addition to propiverine hydrochloride. In addition, we found no association between use of the nerve-sparing technique and changes in MUCP ($p = 0.824$). The finding that the nerve-sparing technique did not affect postoperative incontinence is presumably attributable to the small number of patients in the present study.

Adverse events were noted in patients who received propiverine hydrochloride treatment. In our country, propiverine hydrochloride has been used for more than 20 years, and there is sufficient information available regarding its safety. A systematic review revealed that the major adverse events caused by propiverine hydrochloride are dry mouth and constipation.[31] In the present study, constipation, dry mouth, and gastritis were noted as adverse events in the treatment group. Because all of these symptoms were mild and within a range similar to that of previous reports, they were considered treatable.

A notable limitation of this study was that no pressure flow studies were performed. There is general agreement that many factors contribute to the pathological mechanism of post-prostatectomy incontinence. In this study, urethral function-related parameters and patients' backgrounds (e.g., age and BMI) were evaluated, whereas bladder function, injury to the urethral sphincter, and detrusor activity were not. However, as shown in Table 1, there were no significant differences between groups in RP difficulty-related factors (such as prostate volume), surgical method (including nerve-sparing technique), or pathological features of prostate cancer. In addition, these variables were not significantly associated with changes in MUCP after RP. Therefore, we speculate that changes in bladder function resulting from RP were comparable between the two groups. Moreover, our study population did not include patients with overactive bladder and/or stress urinary incontinence and was divided into control and treatment groups by randomization. Thus, although we did not examine bladder capacity by means of urodynamic studies, we presume that differences in bladder function between groups had minimal influence on our results. Another limitation of this study was that it included a relatively small number of patients. For example, it was unclear why use of the nerve-sparing technique did not affect the recovery from post-prostatectomy incontinence in this study. To address this point, we attempted various statistical analyses of clinicopathological features, surgical methods, FUL, and MUCP. However, the number of patients was insufficient to allow such analyses. More detailed clinical studies that evaluate bladder function-related parameters and injuries (e.g., to the urethral sphincter, urethra-supporting structures, and related nerves) by means of multivariate analyses in larger study populations are needed to confirm the clinical usefulness of propiverine hydrochloride treatment after RP.

Conclusion

Propiverine hydrochloride alleviated urinary incontinence, evaluated by means of the pad-test negative rate, and improved both patient symptoms and quality of life after RP. Postoperative MUCP was increased by treatment with propiverine hydrochloride, which may have a favorable effect on urinary continence after RP. □

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