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Phosphodiesterase type 5 inhibitor administered immediately after radical prostatectomy temporarily increases the need for incontinence pads, but improves final continence status

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Purpose: To evaluate the effects of phosphodiesterase type 5 inhibitor (PDE5i) on urinary continence recovery after bilateral nerve-sparing radical prostatectomy (BNSRP).

Materials and Methods: Between 2002 and 2012, 137 of 154 consecutive patients who underwent BNSRP in our institution retrospectively divided into 3 groups that included patients taking PDE5i immediately after surgery (immediate PDE5i group, n=41), patients starting PDE5i at an outpatient clinic after discharge (PDE5i group, n=56), and patients taking no medication (non-PDE5i group, n=40). Using self-administered questionnaires, the proportion of patients who did not require incontinence pads (pad-free patients) was calculated preoperatively and at 1, 3, 6, 12, 18, and 24 months after BNSRP. Severity of incontinence was determined based on the pad numbers and then compared among the 3 groups.

Results: Proportions of pad-free patients and severity of incontinence initially deteriorated in all of the groups to the lowest values soon after undergoing BNSRP, with gradual improvement noted thereafter. The deterioration was most prominent in the immediate PDE5i group. As compared to the non-PDE5i group, both the PDE5i and immediate PDE5i groups exhibited a better final continence status.

Conclusions: PDE5i improves final continence status. However, administration of PDE5i immediately after surgery causes a distinct temporary deterioration in urinary incontinence.

Keywords: Incontinence pads; Phosphodiesterase inhibitors; Prostatectomy; Recovery of function; Urinary incontinence

INTRODUCTION

Although radical prostatectomy (RP) provides an effective cure for localized prostate cancer, RP entails several complications [1,2]. Both urinary incontinence and erectile dysfunction are common complications observed after RP [3,4]. In dealing with the recovery of postoperative sexual function, rehabilitation programs has been advocated

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and is attracting attention. Phosphodiesterase type 5 (PDE5) inhibitor (PDE5i) reportedly acts to prevent fibrosis and apoptosis of the corporal smooth muscles [5,6], and has been considered one of the first-line treatment options for rehabilitation programs that promote recovery of sexual function after RP [7,8]. PDE5 has recently been reported to be expressed in urethra and bladder tissues [9,10]. and recent studies that examined PDE5i prescribed for recovery of sexual function have found it to be beneficial and able to affect the recovery of postoperative urinary continence [11,12].

Although the effects of PDE5i on the recovery of urinary functions after RP have been confirmed in some cases, we demonstrated in one of our recent basic experimental animal model studies that PDE5i had potentially unfavorable effects that worsened stress urinary incontinence (SUI) [13]. This study examined whether the reflex contractions of the external urethral sphincter that maintains the urinary continence would be decreased after an administration of PDE5i in rats. The study results raised concerns about possible deterioration of urinary incontinence in humans when using PDE5i.

The current study was designed to elucidate the effects of PDE5i on urinary continence status after RP. All retrospectively assessed data were collected for analysis from self-administered questionnaires that had been completed pre- and postoperatively.

MATERIALS AND METHODS

Between August 2002 and February 2012, which was prior to our implementation and use of robotic-assisted RP in our institution, 364 patients underwent radical retropubic prostatectomy by 6 well-experienced staff urologists or under their supervision using virtually the same technique. There were 154 consecutive patients who underwent bilateral nerve-sparing radical retropubic prostatectomy (BNSRP). All patients were preoperatively explained about a rehabilitation program using PDE5i that promotes recovery of sexual function, and a PDE5i (sildenafil, vardenafil, or tadalafil) had been prescribed when patients requested pharmacotherapy. The patients who asked to be given pharmacotherapy were instructed to regularly take the medicine once or twice a week [14]. For our analysis, we divided the 154 patients into 3 groups that included, patients taking PDE5i soon after surgery during urethral catheter indwelling (immediate PDE5i group, n=51), starting PDE5i at an outpatient clinic after discharge (PDE5i group, n=58), and taking no medication (non-PDE5i group, n=45). Patients who refused to continue taking the medication on several occasions due to economic reasons or the adverse effects of PDE5i, such as headache or dyspepsia, were excluded from the study. For all of the patients who subsequently started taking anticholinergic drugs or had hormonal therapy for cancer recurrence, their data were only used up until the date when they first began taking these drugs. After the exclusions a total of 147 patients remained and were used for the analysis.

Urinary continence was estimated from incontinence pad usage numbers. These were obtained preoperatively and at 1, 3, 6, 12, 18, and 24 months after surgery from Item 3 of the University of California Los Angeles Prostate Cancer Index survey [15], which was used until March 2006, and subsequently from Item 5 of the Extended Prostate Cancer Index Composite questionnaire [16]. Both questionnaires have already been translated into Japanese and the validity and reliability have been tested previously [17,18]. Patients who returned the questionnaire ≥3 times were included in the study.

In the first step of our analysis, we initially calculated the proportion of patients who did not use incontinence pads (pad-free patients) at any time before or after the surgery. Pad-free status was defined as a response of "no pads" on the questionnaire. Severity of incontinence was then compared using the pad numbers from the subjects in the immediate PDE5i, PDE5i, and non-PDE5i groups. In order to conduct an accurate comparison when using data from 2 different questionnaires, we used a 3-point scale to rate the number of pads required per day: 3, no pads; 2, one or two pads per day; and 1, three or more pads per day. Pad usage scores in each group were then compared preoperatively and at 1, 3, 6, 12, 18, and 24 months after surgery.

For the statistical analyses, two-tailed Mann-Whitney tests were used to compare the pad usage scores, clinical T stage, pathological T stage and the Gleason score for RP. Student t-test was used to compare the age, levels of prostate specific antigen, body mass index and excised prostate weight. Statistical analysis was performed using JMP Pro ver. 11 (SAS Institute, Cary, NC, USA). Values of $p<0.05$ were considered significant. This study was approved by the Ethics Committee at Tohoku University.

RESULTS

From the overall total of 154 patients, 137 (89.0%) had returned self-administered questionnaires ≥3 times, including 41 of 51 patients in the immediate-PDE5i group, 56 of 58 patients in the PDE5i group and 40 of 45 patients in the non-PDE5i group. Response rates for these 137 total

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Table 1. Demographic characteristics of patients

Characteristic	Immediate-PDE5i group (n=41)	PDE5i group (n=56)	Non-PDE5i group (n=40)	p-value		
				Immediate-PDE5i group vs. PDE5i group	Immediate-PDE5i group vs. non-PDE5i group	PDE5i group vs. non-PDE5i group
Age (y)	62.0±5.4	62.7±6.0	66.7±6.1	0.96	0.002*	0.001*
PSA (ng/mL)	7.4±4.6	7.0±4.5	7.7±4.4	0.24	0.56	0.49
BMI (kg/m^2)	24.4±0.4	24.0±0.4	24.7±0.4	0.54	0.64	0.33
Excised prostate weight (g)	47.0±2.6	44.6±2.5	45.2±2.6	0.51	0.63	0.87
cT				0.60	0.35	0.13
1	35	50	31			
2	6	5	8			
3	0	1	1			
pT				0.18	0.62	0.42
2	32	50	33			
3	9	3	7			
4	0	3	0			
RP-GS				0.81	0.14	0.06
6	9	12	3			
7	28	38	32			
8	2	3	4			
9	2	1	1			
ND	0	2	0			

Values are presented as mean±standard deviation or number.

PDE5i, phosphodiesterase type 5 inhibitor; PSA, prostate-specific antigen; BMI, body mass index; cT, clinical T stage; pT, pathological T stage; RP-GS, radical prostatectomy Gleason score; ND, not determined.

*p<0.05, significant difference.

patients at the preoperative and 1, 3, 6, 12, 18, and 24 months after surgery time points were 92.2%, 85.0%, 94.2%, 93.7%, 96.5%, 81.4%, and 81.0%, respectively. The median period from the time of the surgery to starting the PDE5i therapy in the immediate PDE5i group and the PDE5i group was 1 day (range, 1–3 days) and 92 days (range, 27–372 days), respectively. The mean duration of medication in the immediate PDE5i group and the PDE5i group was 12 months (range, 2–24 months) and 16 months (range, 1–24 months), respectively. The mean number of oral use in the immediate PDE5i group and the PDE5i group was 3.7 times a month (range, 1–10 times a month) and 3.6 times a month (range, 1–12 times a month), respectively. Table 1 presents the background factors. Except for age, none of the parameters differed significantly among the 3 groups. The non-PDE5i group consisted of elderly patients compared with the immediate PDE5i group and PDE5i group.

1. Effects of PDE5i administration after RP on the proportion of pad-free patients

At 1 month after BNSRP, the proportion of pad-free patients decreased from the very high initial scores to nadir values for the immediate PDE5i (97% to 26%), PDE5i (98% to 49%) and non-PDE5i (100% to 31%) groups. The decrease of the proportion in the immediate PDE5i group was distinct even when it was compared with that in the non-PDE5i group composing significantly elderly patients. Subsequently, all of the patients exhibited gradual improvements so that by 12 months, the proportions of pad-free patients in the immediate PDE5i and PDE5i groups had recovered to the almost preoperative levels. The proportions in the immediate PDE5i group were 88%, 96%, and 96% at 12, 18, and 24 months, postoperatively, while in the PDE5i group they were 92%, 94%, and 92% at 12, 18, and 24 months after surgery, respectively. In the non-PDE5i group, the proportions remained under approximately 80% even after 12 months postoperatively (78%, 77%, and 74% at 12, 18, and 24 months after surgery, respectively) (Fig. 1).

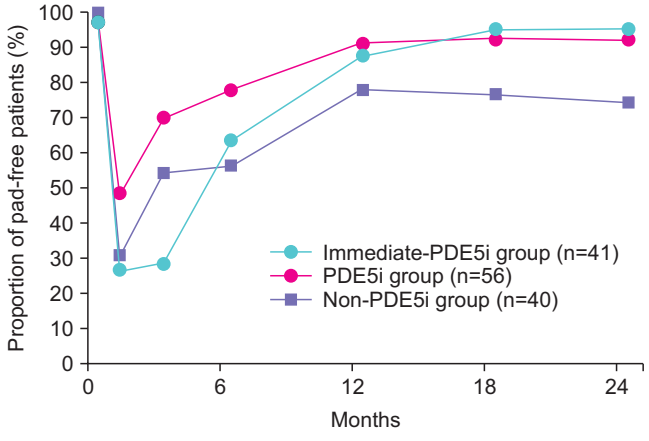

Fig. 1. In all groups, the proportions of pad-free patients decreased to a nadir at 1 month after surgery, after which all patients showed a gradual improvement. At 12 months postoperatively, the proportions of pad-free patients in the phosphodiesterase type 5 inhibitor (PDE5i) and immediate PDE5i groups recovered to levels that were almost the same as those for the preoperative levels, while levels in the non-PDE5i group remained under approximately 80%.

2. Comparison of the urinary continence after RP based on the number of pads used among the immediate PDE5i, PDE5i, and non-PDE5i groups

In all groups, pad usage scores worsened at 1 month after the surgery. Subsequently, the scores then gradually returned to better levels. Postoperative deterioration was most prominent in the immediate PDE5i group, which exhibited significantly worse scores as compared to the PDE5i group at 1 and 3 months and to the non-PDE5i group at 3 months after surgery. Despite this deteriorated state at 1 and 3 months after the surgery, the immediate PDE5i group showed good recovery thereafter, with pad usage scores finally returning to the same or better than those seen in the PDE5i group (Fig. 2).

The PDE5i and immediate PDE5i groups exhibited better pad usage scores than the non-PDE5i group after 6 months

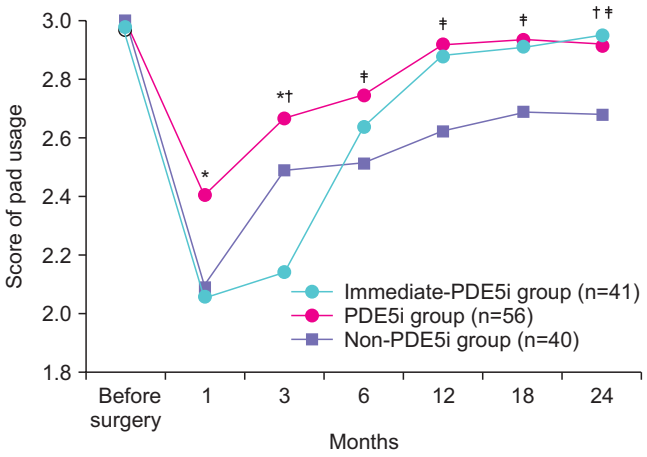

Fig. 2. In all groups, pad usage scores worsened at 1 month after the surgery, and then gradually improved. The deterioration at 1 month after the surgery was most prominent in the immediate phosphodiesterase type 5 inhibitor (PDE5i) group. Better pad usage scores were seen after 6 months postoperatively for the PDE5i and immediate PDE5i groups versus the non-PDE5i group. Asterisks (*) indicate statistical significance between the immediate PDE5i and PDE5i groups. The dagger (†) indicates statistical significance between the immediate PDE5i and non-PDE5i groups. Double daggers (‡) indicate statistical significance between the PDE5i and non-PDE5i groups. Score of pad usage: 3, no pads; 2, one or two pads per day; 1, three or more pads per day.

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postoperatively. Significantly higher scores were seen at 6, 12, 18 and 24 months after surgery for the PDE5i versus the non-PDE5i group and at 24 months after surgery for the immediate PDE5i group versus the non-PDE5i group.

DISCUSSION

To investigate the administration of PDE5i after RP and its effect on the recovery of urinary continence, the present study analyzed data on incontinence pad usage that was obtained from pre- and postoperatively self-administered questionnaires. While our results demonstrated that PDE5i improved the final continence status, there was a transient, but distinct, deterioration of the postoperative urinary continence that occurred when PDE5i was administered immediately after surgery.

Although a number of reports have described the effectiveness of PDE5i on the recovery of sexual function after RP, few reports have assessed the effects of PDE5i on the recovery of postoperative urinary function. Gacci et al. [11] reported the first and only randomized trial that examined the effects of PDE5i on urinary continence recovery after RP. Their study followed 39 patients who had undergone BNSRP and were then assigned in a double-blinded manner to one of 3 arms, which included vardenafil nightly (10 mg of vardenafil every night starting at 2 weeks after surgery), vardenafil on demand, or placebo. After monitoring the level of continence recovery from 1 to 12 months, the authors reported that the patients who took vardenafil nightly achieved significantly better recovery of urinary function compared with the other groups. Gandaglia et al. [12] retrospectively analyzed 341 incontinent patients after BNSRP and concluded that patients taking PDE5i starting from the first month after the surgery exhibited higher rates of urinary continence recovery as compared with patients left untreated after the surgery. While the precise mechanism of the urinary continence recovery remains unclear, PDE5i might improve the pelvic floor blood and oxygen supply [12]. Although the timing for the initiation of the PDE5i therapy and the dosage schedule that we used in our study differed from that of other studies, our findings that both the PDE5i and immediate PDE5i groups exhibited good recovery of the urinary continence are consistent with the previously reported effects for PDE5i.

The most notable point in the present study was the distinct temporary deterioration in urinary incontinence after BNSRP that occurred when PDE5i was administered immediately after the surgery. The postoperative deterioration in the immediate PDE5i group was prominent even when it was compared with that in the non-PDE5i group consisting of comparatively elderly patients (Figs. 1, 2). The immediate PDE5i group showed a significant decline in pad usage scores compared with the PDE5i and non-PDE5i groups (Fig. 2). Gacci et al. [11] reported that administration of PDE5i every night tended to result in a substantial decline in the urinary function score at 1 month after BNSRP compared with the on-demand and placebo groups, although these differences were not significant. In our study, we confirmed that an immediate administration of PDE5i after surgery induced a temporary, but significant deterioration of the urinary incontinence.

The precise mechanisms underlying the temporary deterioration in the postoperative urinary incontinence induced by immediate PDE5i treatment have yet to be explained. One possibility is that PDE5i administration inhibits reflex contractions of the external urethral sphincter that normally maintains urinary continence during a sudden increase in intra-abdominal pressure, such as that caused by coughing or sneezing [13]. We recently demonstrated the inhibitory effects of PDE5i on the urethral continence reflex in a rat model. Our results showed that the reflex contractions of the external urethral sphincter during sneezing were dose-dependently decreased by PDE5i administration [13]. It is likely that the inhibitory effect of PDE5i on the external urethral sphincter is probably similar in humans with urinary incontinence after RP. Thus, this might be the reason why there is a higher rate of urinary incontinence under the postoperative conditions with surgical damage during the immediate postoperative period. In addition to the inhibitory effect of PDE5i on the urethral continence reflex, it is also possible that this effect could be due to PDE5i causing a decreased urethral pressure. Since PDE5i acts by producing relaxation of the urethral smooth muscles [10], this may increase urinary leakage immediately after the RP.

No convincing evidence has been accumulated regarding when PDE5i should be started after RP. From the standpoint of rehabilitation programs for sexual functions, several reports have recommended starting PDE5i administration for erectile function recovery as early as possible, because postoperative degeneration of cavernous tissues starts immediately after RP [19,20]. From the perspective of rehabilitation programs for urinary continence, our results showed sustained efficacy of PDE5i in recovery of postoperative urinary continence, although our findings also indicate the possibility of temporary deterioration of urinary incontinence when PDE5i is administered immediately after RP. For patients who prioritize urinary continence

over sexual function, immediate PDE5i therapy may not be warranted. Starting PDE5i approximately 1 month after RP may be adequate in such cases. However, to clarify the optimal treatment strategy with PDE5i, accumulating data on recovery of both sexual and urinary functions when PDE5i is administered immediately after surgery are necessary in the future.

When interpreting the results of our study, there are several limitations that must be considered. Both the nonrandomized nature of the study and the small numbers of patients represent major limitations. In addition, over time there has been a trend noted in which the prescribed medical agents has changed from sildenafil to vardenafil or tadalafil. However, we believe that our data correctly represent the effects of the PDE5i therapy on urinary continence after BNSRP, as all the data on urinary continence status were collected prospectively using self-administered questionnaires, and for which the response rates remained high throughout the study period. Even so, randomized prospective studies that introduce PDE5i treatments at different time points would be of benefit for further elucidating definitive treatment strategies with PDE5i after RP.

Another limitation of our study involved the dosage schedule. We did not include a daily administration of PDE5i in this study. Since PDE5i is not covered by health insurance in Japan, the dosage schedule is limited by economics of the drug cost that can be covered by the patient. However, our results did show that there were significant changes in the urinary continence after surgery, even with the limited dosage schedule that was applied.

CONCLUSIONS

In conclusion, based on information collected on incontinence pad usage obtained from pre- and post-operatively self-administered questionnaires, our results indicated that PDE5i administered after RP can improve final continence status. However, we also found that there is a transient deterioration of the postoperative urinary continence that occurs when PDE5i is administered immediately after surgery.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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