The Effect of Phosphodiesterase 5 Inhibitor on Biochemical Recurrence Following Radical Prostatectomy in Patients with Prostate Cancer

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Purpose: Recently, controversy exists regarding the oncologic outcomes associated with the use of phosphodiesterase 5 inhibitor (PDE5i). Therefore, we attempted to verify the effect of PDE5i on biochemical recurrence (BCR) following radical prostatectomy (RP) in patients with prostate cancer (PCa).

Materials and Methods: From January 2011 to May 2016, 351 patients who had undergone bilateral neurovascular bundle saving and who were confirmed as having pT2N0M0 disease were included in the present study. We divided these patients into three groups: no PDE5i use, PDE5i use on demand , and PDE5i use for rehabilitation. We retrospectively analyzed the effect of PDE5i on BCR of PCa. Mean follow-up period was 34.4 months and mesurement of outcome was whether the patients developed BCR during regular follow-up.

Results: 25 (7.1%) patients showed BCR and univariate analysis found no significant differences in BCR between the three groups (5 (6.9%) in no PDE5i use, 8 (9.5%) in PDE5i use on demand, 12 (6.2%) in PDE5i use for rehabilitation). Multivariable analyses showed that treatment type was not a significant factor for BCR between the groups with no PDE5i use and PDE5i use (HR = 1.34 [0.49–3.70]; P = .573) and between the groups with on demand and rehabilitation use (HR = 1.37 [0.35–5.37]; P = .646). Kaplan-Meier survival curves show that there were no significant differences in PSA recurrence-free survival in three groups (P > .05).

Conclusion: Use of PDE5is was not associated with any adverse effects on BCR after RP in patients with PCa.

Keywords: phosphodiesterase 5 inhibitor; prostate cancer; prostatectomy; recurrence

INTRODUCTION

Prostate cancer (PCa) is the most common solid malignancy and remains the second leading cause of death from cancer in men, with approximately 233,000 new diagnoses and 29,480 deaths from the disease in the United States in 2014.[1] There has been a rapid rise in the incidence of PCa in several Asian countries, with PCa steadily becoming one of the leading cancers in Asian men.[2] Similarly, in Korea, the incidence rate of PCa has rapidly increased during the past decade.[3]
Radical prostatectomy (RP) is the gold standard for surgical treatment for patients with localized prostate cancer. Erectile dysfunction (ED) following RP for PCa is a common complication reported to urologists.[4-7] ED leads to severe economic and psychological problems that increase distress and decrease quality of life after RP for patients with PCa. Following the determination that the main mechanism of postoperative ED was the injury of neurovascular bundles, nerve-sparing RP has been widely performed.[8] Since the introduction of phosphodiesterase 5 inhibitor (PDE5i), these agents have been widely used for the treatment of ED following RP in patients with PCa. Numerous studies have demonstrated the safety and efficacy of PDE5i.[9,10]
However, controversy has recently arisen regarding oncologic outcomes associated with the use of PDE5i. [11-14] Gallina et al. reported that the use of PDE5i was not associated with an increased risk of biochemical recurrence (BCR).[11] On the other hand, Michl et al. reported that postoperative use of PDE5i may adversely impact BCR.[14] Since these two studies have shown contrary outcomes with PDE5i use following RP, additional evaluation of the potential effects of postoperative PDE5i use is thought to be clinically important in the field of oncology. Therefore, we attempted in the present study to verify the effect of PDE5i on BCR after RP in patients with PCa.

PATIENTS AND METHODS

Study population

From January 2011 to May 2016, a total of 750 patients were diagnosed with PCa and underwent RP. We included patients who underwent bilateral neurovascular bundle saving and who were confirmed as having pT2N0M0 disease so as to choose the patients who have the similar chance of BCR before the exposure of PDE5i. On the other hand, we excluded patients who did not undergo regular follow-up, who underwent non- or unilateral neurovascular bundle saving, who received neoadjuvant or adjuvant hormone/radiation therapy, whose pathologic reports showed pT3 or 4 or pTanyN1 disease, or who experienced distant metastasis. Finally,

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351 patients were included in the study. This study was approved by the Ethics Committee of the Kyungpook National University School of Medicine (IRB Number KNUH 2016-08-017).

Study design

This study was a retrospective single center trial. We divided these patients into three groups: no PDE5i use, PDE5i use on demand, and PDE5i use for rehabilitation. The patients were allocated for each group according to the age, sexual activity and economic status. The rehabilitation group was defined on the basis of daily PDE5i use for more than 3 months. We retrospectively analyzed the effect of PDE5i on BCR of PCa (defined as two consecutive prostate-specific antigen [PSA] levels ≥ 0.2 ng/mL). Mean follow-up period was 34.4 months and measurement of outcome was whether the patients developed BCR during regular follow-up. 176 patients (176/279, 63.1%) started PDE5i intake within 4 weeks after surgery.

Statistical analysis

Patient characteristics were analyzed using the Chi-square test (surgical technique, pathologic Gleason score, surgical margin status, type of PDE5i, BCR), Student's t-test (number of pills taken, period of PDE5i use, time to first intake of PDE5i after RP) and Kruskal-Wallis test for the method of post hoc analysis (age, body mass index (BMI), preoperative PSA, follow-up period). In addition, multivariable Cox regression was used for analysis of the impact of PDE5i on BCR, and Kaplan-Meier curves via a log-rank test were used for analysis of BCR-free survival. Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

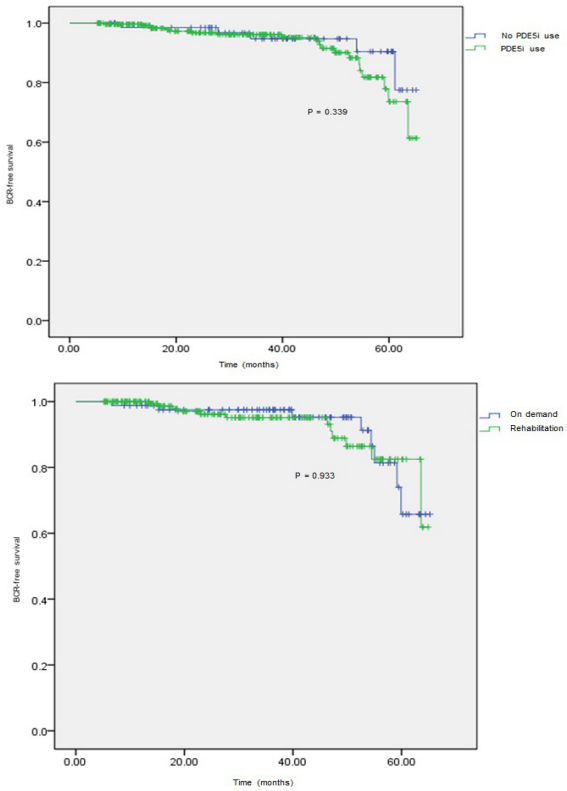

Figure 1. Probability estimates of biochemical recurrence-free survival in all patients stratified by use of phosphodiesterase type 5 inhibitors (no PDE5i use versus PDE5i use).
Probability estimates of biochemical recurrence-free survival in all patients stratified by use of phosphodiesterase type 5 inhibitors (on demand versus rehabilitation).

Table 1. Descriptive characteristics of 351 patients according to use of phosphodiesterase 5 inhibitors.

Variables[a]	Overall	No PDE5i use	PDE5i use on demand	PDE5i use for Rehabilitation	*P* value
Patients, n (%)	351 (100.0)	72 (20.5)	84 (23.9)	195 (55.6)	-
Age, years	65.4 ± 6.6	67.8 ± 6.9	66.1 ± 5.7	64.2 ± 6.6	< .001
BMI, kg/m2	23.8 ± 2.8	24.0 ± 2.9	24.1 ± 3.0	23.7 ± 2.6	.326
Preoperative PSA, ng/mL	9.1 ± 9.1	11.2 ± 15.1	8.1 ± 4.1	8.9 ± 7.6	.094
Surgical technique, n (%)					.322
Robotic	247 (70.4)	40 (11.4)	59 (16.8)	148 (42.2)	
Open	104 (29.6)	32 (9.1)	25 (7.1)	47 (13.4)	
Pathologic Gleason score, n (%)					.509
≤ 6	66 (18.8)	19 (5.4)	13 (3.7)	34 (9.7)	
7	239 (68.1)	44 (12.5)	61 (17.4)	134 (38.2)	
8	34 (9.7)	7 (2.0)	9 (2.6)	18 (5.1)	
9	12 (3.4)	2 (0.6)	1 (0.3)	9 (2.6)	
Surgical margin status, n (%)					.599
Negative	210 (59.8)	44 (12.5)	48 (13.7)	118 (33.6)	
Positive	141 (40.2)	28 (8.0)	36 (10.3)	77 (21.9)	
Type of PDE5i					.121
Udenafil	136 (48.7)	-	35 (12.5)	101 (36.2)	
Non-udenafil	143 (51.3)	-	49 (17.6)	94 (33.7)	
Number of pills taken, n	132.9 ± 138.9 (10-1680)	-	47.4 ± 40.9	169.8 ± 149.7	< .001
Period of PDE5i use, months	11.8 ± 11.1 (3-56.8)	-	6.7 ± 8.4	13.9 ± 11.4	< .001
Time to first intake of PDE5i after RP	2.7 ± 4.1(1-33)	-	4.9 ± 6.6	1.8 ± 1.7	< .001
Follow-up period, months	34.4 ± 17.7(5.2-65.2)	41.1 ± 16.4	40.2 ± 15.8	29.4 ± 17.5	< .001
BCR, n (%)					.317
No	326 (92.9)	67 (19.1)	76 (21.7)	183 (52.1)	
Yes	25 (7.1)	5 (1.4)	8 (2.3)	12 (3.4)	

[a]Data are presented as mean ± SD or number (percent)
Abbreviations: PDE5i, phosphodiesterase 5 inhibitor; BMI, body mass index; PSA, prostate specific antigen; BCR, biochemical recurrence; RP, radical prostatectomy.

Table 2. Multivariable Cox regression analyses (MVA) predicting biochemical recurrence in patients.

	MVA including use of No PDE5i use versus PDE5i use		MVA including use of On demand versus Rehabilitation	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	0.99 (0.93–1.06)	.836	0.96 (0.88–1.04)	.301
Preoperative PSA	1.01 (0.98–1.05)	.482	1.02 (0.98–1.07)	.342
Surgical technique				
Robotic	1.00 (Ref)	1.00 (Ref)		
Open	0.95 (0.37–2.43)	.921	0.97 (0.32–2.97)	.954
Pathologic Gleason score				
≤ 6	1.00 (Ref)	1.00 (Ref)		
7	1.18 (0.26–5.44)	.832	0.71 (0.14–3.50)	.673
8	7.07 (1.55–32.36)	.012	3.66 (0.74–18.06)	.112
9	11.77 (1.93–71.91)	.008	6.11 (0.83–45.18)	.076
Surgical margin status				
Negative	1.00 (Ref)	1.00 (Ref)		
Positive	3.29 (1.44–7.50)	.005	2.89 (1.12–7.50)	.029
Type of PDE5i				
Udenafil			1.00 (Ref)	
Non-udenafil			0.54 (0.17–1.69)	.291
Treatment type				
No PDE5i use	1.00 (Ref)			
PDE5i use	1.34 (0.49–3.70)	.573		
PDE5i use, on demand			1.00 (Ref)	
PDE5i use, rehabilitation			1.37 (0.35–5.37)	.646
Number of pills taken			1.00 (0.99–1.01)	.482
Period of PDE5i use			1.02 (0.96–1.08)	.504
Time to first intake of PDE5i			0.75 (0.53–1.05)	.100

Abbreviations: PDE5i, phosphodiesterase type 5 inhibitor; MVA, multivariable Cox regression analyses; HR, hazard ratio; CI, confidence interval; PSA, prostate specific antigen.

RESULTS

Among the 351 patients enrolled in this study, the no PDE5i use group included 72 patients (20.5%) and the PDE5i use group included 279 (79.5%). The PDE5i use group was divided into two groups: on demand (n = 84, 23.9%) and rehabilitation use (n = 195, 55.6%). Descriptive characteristics of 351 patients according to use of phosphodiesterase 5 inhibitor are shown in **Table 1**. The mean patient age was 65.4 ± 6.6 years. The PDE5i use group was significantly younger than the no PDE5i use group, and the rehabilitation group was significantly younger than the on demand group ($P < .001$). There was no significant differnce in BMI of each groups. The mean preoperative PSA level was 9.1 ± 9.1 ng/mL, and there was no significant difference among the groups ($P = 0.094$). Robot-assisted laparoscopic RP was performed in 247 (70.4%) patients. There were no significant differnces in surgical technique of each groups. Pathologic Gleason score and surgical margin status were not significantly different among the three groups. Positive surgical margin was shown in 141 (40.2%) patients. Among the PDE5i use group, 136 patients (48.7%) took udenafil (Zydena®, Dong-A Pharmaceutical Co., Ltd., Seoul, Korea). The rehabilitation group took a significantly greater amount of PDE5i than the on demand group and also used PDE5i significantly longer than the on demand group ($P < .001$). Time to first intake of PDE5i after RP was significantly shorter in the rehabilitation group ($P < .001$). The mean follow-up period was 34.4 ± 17.7 months and mean follow-up period of rehabilitation group was significantly shorter than the other groups ($P < .001$). Twenty-five patients (7.1%) showed BCR, and univariate analysis revealed no significant differences among the three groups ($P = 0.317$).

Multivariable Cox regression analyses (MVA) are shown in **Table 2**. Pathologic Gleason score and surgical margin status were significant factors for BCR between no PDE5i use and PDE5i use group ($P < .05$, respectively). Only surgical margin status was a significant factor for BCR between PDE5i use on demand and PDE5i use for rehabilitation group ($P < .05$). MVA showed that treatment type was not a significant factor for BCR (no PDE5i use versus PDE5i use, hazard ratio [HR] = 1.34 [0.49–3.70], $P = .573$; on demand versus rehabilitation, HR = 1.37 [0.35–5.37], $P = .646$, respectively). Type of PDE5i, number of pills taken, period of PDE5i use, and time to first intake of PDE5i were also not associated with an increased rate of BCR between the on demand and rehabilitation groups (HR = 0.54 [0.17–1.69], $P = .291$, HR = 1.00 [0.99– 1.01] $P = .482$, HR = 1.02 [0.96–1.08], $P = .504$, HR = 0.75 [0.53–1.05], $P = .100$, respectively).

Kaplan-Meier survival curves showed that there were no significant differences in PSA recurrence-free survival in the groups with no PDE5i use versus PDE5i use ($P = .339$) (Figure 1) or in the groups with on demand versus rehabilitation use ($P = .933$) (**Figure 1**).

DISCUSSION

All forms of PCa treatment, especially RP, are associated with a significant risk of ED as a result of trauma sustained by the cavernosal nerves.[15] It is a well-known fact that PDE5i significantly improves erectile function following RP in patients with PCa.[16-19] A relatively large volume of literature has shown that PDE5is represent a significant advance in the treatment of ED in patients with PCa.

Currently, sildenafil, tadalafil, and vardenafil are approved for the treatment of ED in the United States. Sildenafil is the most widely used oral agent for penile rehabilitation in post-RP patients.[20-23] However, unlike the other centers, our center studied the effect of PDE5i on penile rehabilitation after RP using udenafil 50 mg. [24] Udenafil is a selective PDE5i made available

in recent years for the treatment of ED.[24] The results of our 2016 study analyzing udenafil could provide urologists with useful information for counseling patients undergoing RP and for selecting optimal candidates for penile rehabilitation. Following the identification of patients with PCa treated with udenafil or other PDE5is, this study was designed to assess whether PDE5i is associated with BCR after RP in patients with PCa.

A review of the history of PDE5is since their introduction, from the late 1990s to early 2000, revealed that numerous studies reported that these agents showed potential as anticancer drugs. In 1999, Goluboff et al. demonstrated that the PDE5i exisulind, a sulfone metabolite of the nonsteroidal anti-inflammatory drug sulindac, suppresses the growth of human PCa in a nude mouse xenograft model by increasing apoptosis. [25] In 2001, these authors also analyzed the safety and efficacy of exisulind for the treatment of recurrent PCa after RP.[26] Moreover, Narayanan et al. showed that a combination of celecoxib with exisulind prevented prostate carcinogenesis, enhancing apoptosis.[27] With regard to commercially available PDE5is, Qian et al. showed that sildenafil citrate was not associated with any significant alteration in primary PCa tumor growth or in the development of regional or distant metastases in animal models.[28] In animal and in vitro studies on the effects of PDE5is on anti-cancer immune responses, sildenafil treatment resulted in increased T-cell infiltration into tumor cells, enhancing tumoricidal activity.[29]

According to more recent studies of the effect of PDE-5is on PCa, Gallina et al. showed in 2015 that among patients treated with RP, PDE5i use was not associated with an increased risk of BCR, regardless of the therapeutic regimen used.[11] In 2016, Jo et al. analyzed records of 1082 patients who underwent bilateral nerve-sparing RP for clinically localized PCa between 2005 and 2014.[12] They concluded that PDE5i treatment following RP was not found to have any significant impact on biochemical outcome regardless of therapeutic strategy, timing, duration, or drug type, findings that suggest that PDE5i treatment following RP is oncologically safe. This study differs from ours in that Jo et al. designed their study with sildenafil but our center used udenafil, and our study showed that surgical margin status was also a predictive factor for BCR after RP.

On the other hand, in 2015, Michl et al. demonstrated that the use of PDE5i after RP may adversely impact BCR.[14] This study (median follow-up: 60.3 months) included 4,752 consecutive patients with localized PCa treated with bilateral nerve-sparing RP between January 2000 and December 2010. Of these patients, 1110 (23.4%) received PDE5i postoperatively while 3642 (76.6%) did not. Five-year BCR-free survival estimates in the PDE5i versus non PDE5i groups were 84.7% (95% confidence interval [CI]: 82.1–87.0) and 89.2% (95% CI: 88.1–90.3), respectively (P = .0006). The authors' multivariate regression analysis showed that PDE5i use was an independent risk factor for BCR (HR: 1.38, 95% CI: 1.11–1.70, P = .0035), and this was also true after propensity score matching.

Similarly, in 2016, Kim et al. raised a question about the safety of PDE5i use after RP.[13] They reviewed the results of preclinical studies showing that the nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) signaling pathway play a role in both suppression and development of PCa. These conflicting results regarding the influence of the NO and cGMP signaling pathway might be the findings that highlighted the necessity of assessing the safety of PDE5i in PCa. Moreover, a longitudinal cohort study reported that PDE5i increased the risk of the development of melanoma, a result also suggesting the adverse effect of PDE5i on some kinds of cancers.

With regard to our study, some limitations include the retrospective and single-center study design. The follow-up periods were relatively short compared to those in other studies. Furthermore, in this retrospective study, high grade prostate cancer was included a lot when comparing with general study cohort and high proportion of high grade prostate cancer may be part of limitations. High ratio of positive surgical margin is as a result of these points. Still, there are some controversies about adjuvant therapy in patients with positive surgical margin. According to policy of our urologic center, we do not perform adjuvant therapy routinely in patients with positive surgical margin who were confirmed as having pT2N0M0 disease. When BCR is developed, we perform hormonal therapy or radiation therapy. Post-operative PSA of most patients was observed at an undetectable level. And finally, the rehabilitation therapies were not uniform for all patients.

CONCLUSIONS

In summary, our study demonstrated that PDE5i use, either on demand or as a rehabilitation therapy, is not associated with an increased risk of BCR in patients treated with nerve-sparing RP for localized PCa. We think that PDE5i use for penile rehabilitation following bilateral nerve-sparing RP is oncologically safe. However, conflicting data have recently emerged regarding adverse effects of PDE5is on BCR. Therefore, prospective, randomized, multicenter trials should be performed in the future.

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This study was approved by the Ethics Committee of the Kyungpook National University School of Medicine (IRB Number KNUH 2016-08-017).

CONFLICT OF INTEREST

The authors report no conflict of interest.

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