

EFFICACY AND SAFETY OF COMBINED PHOSPHODIESTERASE TYPE 5 INHIBITORS AS A SALVAGE MEDICAL TREATMENT IN PATIENTS WITH ERECTILE DYSFUNCTION AFTER NERVE-SPARING RADICAL PROSTATECTOMY

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ABSTRACT

Purpose

Penile rehabilitation therapy using phosphodiesterase type 5 inhibitors (PDE5i) is used widely as a first-line therapy in patients with erectile dysfunction (ED) after radical prostatectomy (RP). However, many patients undergoing such therapy still complain of inappropriate erectile function (EF). Therefore, we evaluated the efficacy and safety of combined PDE5i therapy as a salvage medical treatment in patients nonresponsive to initial penile rehabilitation using daily PDE5i after nerve-sparing RP.

Methods

We retrospectively reviewed 58 nonresponders (Erection Hardness Score [EHS] of 2 or less) to penile rehabilitation using tadalafil (5 mg) daily for more than 12 weeks and who subsequently received combined PDE5i therapy (tadalafil [5 mg] once daily with sildenafil [50 mg] or udenafil [100 mg] on demand). Success after combined therapy is defined by EHS scores of 3 or 4. Safety was assessed by observing drug tolerability and adverse events.

Results

Of the 58 patients, combined therapy was successful in 39.7% of cases. The mean preoperative International Index of Erectile Function (IIEF-5) score was significantly higher in the success group after combined

PDE5i therapy compared with the failure group (success group, 15.9 ± 5.1 versus failure group, 12.3 ± 5.6 ; $p = 0.018$). According to ED classification based on preoperative IIEF-5 scores, the success rates of no/mild/mild-to-moderate ED group and moderate/severe ED group were 50.0% (18/36) and 22.7% (5/22), respectively ($p = 0.039$). The success and failure groups did not differ significantly in any other characteristic. The drugs were tolerated well by all patients and no serious adverse events were observed.

Conclusion

Combined PDE5i therapy improves EF in patients nonresponsive to standard penile rehabilitation using daily PDE5i after nerve-sparing RP, especially for patients without preoperative moderate or severe ED. In such patients, combined PDE5i therapy could be considered before invasive therapies.

Keywords: *erectile dysfunction; phosphodiesterase 5 inhibitors; prostate cancer; prostatectomy; treatment outcome*

INTRODUCTION

Cancer therapy in prostate cancer (PCa) patients who have undergone radical prostatectomy (RP) are guaranteed excellent long-term oncologic outcomes; however, erectile dysfunction (ED) is a complication that is very difficult to be restored to the preoperative state and this adversely affects patients' quality of life.¹ Although great advances in anatomic understanding, surgical techniques, and devices have been made in the field of RP, ED is still highly prevalent.²⁻⁵ Several strategies for the prevention and therapy of ED after RP are available, including phosphodiesterase type 5 inhibitors (PDE5i), vacuum erection devices, intracavernous injection, and penile implants.² Penile rehabilitation, defined as the use of any drug or device at or after RP, has been proposed to accelerate recovery of erectile function (EF) after RP. PDE5i has revolutionized ED treatment with its demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on quality of life. Several pieces of evidence support the use of PDE5i as a first-line therapy in patients who have undergone nerve-sparing radical prostatectomy (NSRP) regardless of the surgical technique used.^{6,7}

Based on favorable outcomes of PDE5i therapy in patients with ED after NSRP, various penile rehabilitation programs using a diversity of PDE5i

agents have been suggested in clinical practice.⁸ A recent study shows low dose tadalafil once daily is the most effective drug for penile rehabilitation of patients with ED following NSRP. In addition, low-dose tadalafil once daily showed benefits for preserving the structure of corporeal cavernosum and the size of the penis.⁹ However, despite an active treatment strategy in clinical practice that includes daily PDE5i, many post-RP patients still complain lack of EF. Patients who are not adequately treated or satisfied after PDE5i therapy are considered candidates for intracavernous injection and penile implants.¹⁰ However, these invasive treatments require a high degree of patient motivation and adherence because of the inconvenience, irreversibility, and complications related with these procedures.^{11,12}

More clinical studies are needed for a novel penile rehabilitation protocol using PDE5i. The current approach requires maximization of EF because there is no consensus yet regarding the appropriate PDE5i type, dose, and regimen. Notably, combining PDE5i therapy using tadalafil (5 mg once daily) with sildenafil (50 mg as needed) can improve EF.¹³ Therefore, we evaluated the efficacy and safety of combined PDE5i agents as a salvage medical treatment for patients who fail to respond to initial penile rehabilitation using daily PDE5i after NSRP.

MATERIALS AND METHODS

From November 2017 to March 2019, we enrolled nonresponders who had received penile rehabilitation using tadalafil (5 mg once daily) for more than 12 weeks after NSRP and subsequently received combined PDE5i therapy. All patients had undergone NSRP using either the open retroperitoneal approach or robot-assisted transperitoneal approach by a single surgeon. “Nonresponder” is defined as a patient scoring 0 to 2 points in the Erection Hardness Score (EHS, a scoring system to evaluate EF)¹⁴ after initial penile rehabilitation using daily PDE5i for more than 12 weeks. We excluded patients with any of the following: congenital genital disorder; hypogonadism; uncontrolled blood pressure; current cardiovascular instability, or nitrite use; serious liver, kidney, or blood disease; disorder of the nervous system; or undergoing neo-adjuvant or salvage therapy for PCa.

In our institution, the protocol for combined PDE5i therapy consists of tadalafil (5 mg once daily) combined with sildenafil (50 mg) or udenafil (100 mg) on demand. The type of PDE5i used on demand was chosen by the physician. All patients were recommended to use the on-demand PDE5i at least twice a week. This regimen was continued for 12 weeks without any adverse events. All patients did not receive any other treatment for ED during the 12 weeks of combined PDE5i therapy.

Efficacy was evaluated by EHS and the 5-item version of the International Index of Erectile Function (IIEF-5). EHS and IIEF-5 were assessed before the combined PDE5i therapy and after the 12-week treatment, respectively. IIEF-5 was also evaluated at different times from pre-operation to endpoint. Success is defined as an EHS score of 3 or 4 at 12 weeks after combined PDE5i therapy. IIEF-5 was analyzed as a both continuous and categorized variable. IIEF-5 scores were classified into five categories: severe (5–7), moderate (8–11), mild-to-moderate (12–16), mild (17–21), and no ED (22–25).¹⁵ Safety was assessed by observing drug tolerability

during administration and adverse events, including dyspepsia, muscle pain, flushing, headache, and nasal congestion. We evaluated the clinical outcomes after combined PDE5i therapy to determine treatment success using the Student’s t-test and Chi-square test. Statistical analyses were performed using SPSS for Windows, version 23 (IBM Corp., Armonk, NY, USA), and statistical significance was established with $p < 0.05$.

The present study protocol was reviewed and approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (Reg. No. KNUCH 2020-02-022).

RESULTS

A total of 58 nonresponders to initial penile rehabilitation were analyzed in this study who were using only tadalafil (5 mg once daily) for more than 12 weeks and who subsequently received tadalafil (5 mg once daily) with sildenafil (50 mg) or udenafil (100 mg) on demand as a combined PDE5i therapy. Mean patient age was 65.5 ± 5.0 years and mean body mass index (BMI) was 25.0 ± 2.0 kg/m². Hypertension (HTN) history, diabetes mellitus (DM) history, dyslipidemia, and smoking status were observed in 44.8, 29.3, 17.2, and 29.3% of all patients, respectively. Preoperative IIEF-5 score of all patients was 13.8 ± 5.7 ; and subgroups based on preoperative IIEF-5 scores have the following levels of severity: 6.9% in no ED, 27.6% in mild ED, 27.6% in mild-to-moderate ED, 17.2% in moderate ED, and 20.7% in severe ED.

Of all 58 patients, success (defined as $EHS \geq 3$) after combined PDE5i therapy was observed in 23 patients (39.7%). Patient demographics and clinical characteristics of the groups that improved or failed to improve in response to combined PDE5i therapy are shown in Table 1.

The mean preoperative IIEF-5 score is significantly higher in the success group after combined PDE5i therapy compared to the failure group (success group, 15.9 ± 5.1 ; failure group, 12.3 ± 5.6 ;

TABLE 1 Baseline Demographic and Clinical Characteristics between Success Group and Failure Group after Combined Phosphodiesterase Type 5 Inhibitors Therapy.

	Total (N = 58)	Success group (n = 23)	Failure group (n = 35)	p-value
Age, years	65.5 ± 5.0	65.3 ± 5.4	65.6 ± 4.8	0.802
BMI kg/m²	25.0 ± 2.0	25.1 ± 1.0	25.0 ± 2.2	0.880
HTN, n (%)	26 (44.8%)	12 (52.2%)	14 (40.0%)	0.260
DM, n (%)	17 (29.3%)	7 (30.4%)	10 (28.6%)	0.553
Dyslipidemia, n (%)	10 (17.2%)	6 (26.1%)	4 (11.4%)	0.138
Smoking, n (%)	17 (29.3%)	7 (30.4%)	10 (28.6%)	0.553
Preoperative IIEF-5 (continuous)	13.8 ± 5.7	15.9 ± 5.1	12.3 ± 5.6	0.018
Preoperative IIEF-5 (categorized), n (%)				0.018
No	4 (6.9%)	3 (75.0%)	1 (25.0%)	
Mild	16 (27.6%)	8 (50.0%)	8 (50.0%)	
Mild-to-moderate	16 (27.6%)	7 (43.8%)	9 (56.2%)	
Moderate	10 (17.2%)	3 (30.0%)	7 (70.0%)	
Severe	12 (20.7%)	2 (16.7%)	10 (83.3%)	
Initial PSA, ng/mL	11.8 ± 18.1	13.4 ± 21.0	10.9 ± 16.2	0.613
Surgical technique, n (%)				0.420
Robot	51 (87.9%)	21 (91.3%)	30 (85.7%)	
Open	7 (12.1%)	2 (8.7%)	5 (14.3%)	
pT stage (2/3), n	39/19	17/6	22/13	0.380
Gleason grade (1/2/3/4), n	9/27/19/3	3/12/7/1	6/15/12/2	0.907
Type of PDE5i used as on-demand, n (%)				0.584
Sildenafil 50 mg	28 (48.3%)	11 (47.8%)	17 (48.6%)	
Udenafil 100 mg	30 (51.7%)	12 (52.2%)	18 (51.4%)	

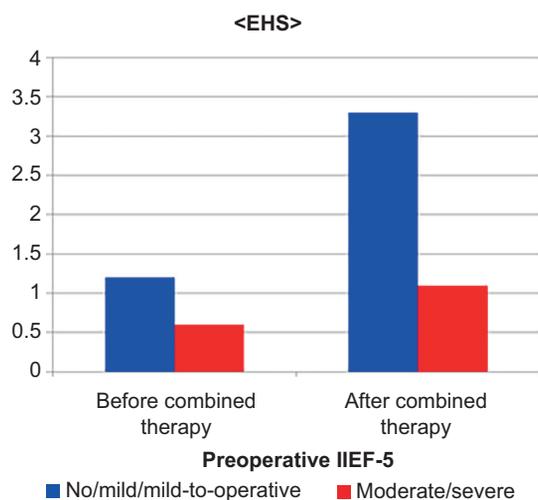
BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; pT, Pathological T; PSA, prostate-specific antigen; PDE5i, phosphodiesterase type 5 inhibitors.

p = 0.018). In addition, the classification of IIEF-5 severity is significantly correlated with success rates after combined PDE5i therapy (p = 0.018), that is, the success rates of the no/mild/mild-to-moderate ED group and moderate/severe ED group were 50.0% (18/36) and 22.7% (5/22), respectively (p = 0.039). Age, BMI, HTN, DM, dyslipidemia, and smoking status did not differ significantly between these two groups. In addition, prostate-specific antigen, surgical technique, and pathological results (including pathological stage and Gleason grade)

did not differ significantly between the success and failure groups. Regarding the PDE5i agents used on demand, sildenafil (50 mg) and udenafil (100 mg) were used in 48.3 and 51.7% of all patients, respectively; the success rate of on-demand PDE5i did not differ significantly.

All patients tolerated the drugs well during administration. Among all patients, dyspepsia was observed in two patients (3.4%), muscle pain in two patients (3.4%), flushing in one patient (1.7%), and headache in one patient (1.7%). All adverse events

were mild or moderate. Adverse events did not differ significantly between success and failure groups (Table 2).



The change in Erection Hardness Score (EHS) before and after combined PDE5i therapy according to severity of preoperative 5-item version of the International Index of Erectile Function (IIEF-5).

DISCUSSION

There are several applicable therapeutic strategies for post-RP ED. Penile rehabilitation with low dose of tadalafil once daily is currently accepted as the most effective drug-assisted therapy to restore EF following RP,^{8,9} although such treatment has met with limited success in clinical practice. Using PDE5i in a novel protocol could be used to improve

EF before invasive therapeutics, such as intracavernous injection and penile implants, are implemented. We aimed to estimate the therapeutic efficacy and safety of combined PDE5i therapy after nonresponsiveness to tadalafil alone for post-RP ED. We retrospectively assessed nonresponders after the initial penile rehabilitation using tadalafil once daily following NSRP and who subsequently received the combined PDE5i therapy using tadalafil and either sildenafil or udenafil on demand. The combined PDE5i therapy was effective and safe as a salvage therapeutic option for nonresponders to initial penile rehabilitation following RP. In addition, the severity of preoperative EF correlates with the outcome of combined PDE5i therapy.

Although advances in surgery guarantee excellent long-term oncologic outcomes as well as improved postoperative functional outcomes in PCa patients who have undergone RP, such patients still face significant physical, cognitive, sexual, and socioeconomic problems associated with the treatment of the disease.¹⁶ Post-RP ED, an inevitable postoperative complication,^{2-4,17} is caused by the neurapraxia of the cavernous nerve during NSRP, hypoxia, oxidative stress, and structural changes related EF, and is prevalent in several (30–87%) NSRP series.^{18,19} Therefore, relatively poor outcome for postoperative EF has led to the development of various therapeutic strategies and several penile rehabilitation programs.

TABLE 2 Comparison of Adverse Events between Success and Failure Groups during Combined PDE5i Therapy.

Adverse event % (n)	Total (n = 58)	Success group (n = 23)	Failure group (n = 35)	p-value
Dyspepsia	3.4% (2)	4.3% (1)	2.9% (1)	
Muscle pain	3.4% (2)	0% (0)	5.7% (2)	
Flushing	1.7% (1)	0% (0)	2.9% (1)	
Headache	1.7% (1)	4.3% (1)	0% (0)	
Nasal congestion	0% (0)	0% (0)	0% (0)	
Total, % (n)	10.3% (6)	8.7% (2)	11.4% (4)	0.464

The therapeutic strategies include different medicines, procedures, and surgical implants. Moreover, the emergence of PDE5i has revolutionized ED treatment, as several studies have proven its benefits for post-RP ED.^{2,6,7} Although various penile rehabilitation programs using different types of PDE5i therapies have been practiced clinically worldwide, penile rehabilitation with once daily dose of tadalafil is currently considered as the most effective drug-assisted therapy to restore EF in patients with ED following NSRP.^{2,8,9} Montorsi et al. reported that tadalafil once daily is the most effective drug for enhancing EF, and it also protects against structural changes in patients with ED after NSRP.⁹ However, the use of various PDE5i-based agents and methods for penile rehabilitation in clinical practice still results in a significant number of patients suffering from unsatisfactory EF and side effects such as headache, flushing, and palpitations.^{3,17} Second- or third-line of treatment strategies, such as intracavernous injection, vacuum erection device, or penile implants, may be used in nonresponders after initial penile rehabilitation using oral PDE5i therapy.¹⁷ However, such treatments are inconvenient, time-consuming, and expensive; and they may result in unnatural penile features, mechanical failure, and infection issues.^{3,17} Considering that such second- or third-line of treatment strategies requires a high degree of patient motivation and adherence,^{11,12} it is important to maximize the usage of first-line of treatment options such as PDE5i, ensuring that they are quick and easy to administer, discreet, and appropriate for the patient. In addition, quick and highly efficacious penile rehabilitation at an early stage is beneficial for patients' emotions, instilling confidence and compliance; it also maintains the structure of erectile tissue, thus protecting against the development of penile fibrosis.^{7,17} However, penile rehabilitation using PDE5i requires a novel approach to overcome known limitations. In this study, we estimated the efficacy of a combination of PDE5i agents as a novel salvage therapeutic approach to maximize the

recovery of EF in patients nonresponsive to a single PDE5i after RP. Our results show significantly improved EF in 39.7% of patients nonresponsive to low dose of tadalafil once daily. Moreover, preoperative degree of EF is a predictor of enhanced EF after combined PDE5i therapy. Similarly, Cui et al. reported the results of prospective and open-label trials of low-dose tadalafil once daily combined with sildenafil as needed at the early stage of ED treatment.¹³ The combined medication improved EF in participants who received no ED treatments during a 4-week run-in period. In addition, the authors suggested that combined medication benefitted patients with severe ED.¹³

Although novel attempts have been made for penile rehabilitation using PDE5i, it is still necessary to establish the optimum traits that describe the best candidates for a new treatment strategy. The key task is to identify the characteristics of the most suitable patient subgroup among nonresponders to initial PDE5i therapy. Generally, several factors influence the incidence and severity of postoperative ED in patients with PCa. These include age, preoperative EF, degree of neurovascular preservation, changes to erectile hemodynamics during RP, and the experience of surgeon.^{20,21} A recent meta-analysis on the use of oral PDE5i for treating ED subsequent to NSRP shows the following are associated with a greater efficacy of PDE5i therapy: higher dose, longer duration of treatment, on-demand dosing, and mild ED.²¹ Similarly, in this study, combined PDE5i therapy was more effective at escalating the dose and responding to on-demand dosing than single PDE5i therapy. In addition, the severity of preoperative EF was a predictor of the clinical success of combined PDE5i therapy after nonresponsiveness to tadalafil once daily. The mean preoperative IIEF-5 score of the success group is higher than that of the failure group (success group, 15.9 ± 5.1 ; failure group, 12.3 ± 5.6 ; $p = 0.018$). In addition, the no/mild/mild-to-moderate ED group shows a relatively higher success rate compared to the moderate/severe ED group (50.0% versus 22.7%,

$p = 0.039$). Therefore, we recommend prioritizing combined PDE5i therapy as a salvage medical treatment for patients with relatively good preoperative EF, but who have failed to respond to daily PDE5i therapy. On the other hand, nonresponders with poor preoperative EF should be informed about the relatively low success rate of combined PDE5i therapy and other available options such as second- or third-line of treatment-strategies. This approach combined with counseling will help in the recovery of EF in post-RP patients by minimizing discomfort and time spent on therapy.

The mechanism underlying the combined PDE5i therapy is not yet clearly understood. The types of PDE5i therapies used in this study, including tadalafil, sildenafil, and udenafil, are the most widely administered ED drugs, and they are metabolized differently. Low-dose tadalafil once daily maintains a steady state blood concentration that repairs damaged endothelium and improves EF, while sildenafil and udenafil are more rapidly absorbed; their high bioavailability enables the achieving of proper penile hardness.^{22–24} Therefore, we assumed that combining a rapid-acting PDE5i with low-dose tadalafil once daily may allow patients to achieve adequate erectile hardness and improve EF quickly. In addition, previous studies report that not only does combined therapy recover EF by repairing the damaged endothelium, it is also able to achieve better compliance and efficacy by improving erectile hardness and psychological factors such as couples' confidence.^{13,25,26} Safety is another noteworthy concern for PCa patients undergoing PDE5i therapy after RP. A previous systematic review reports no severe cardiovascular adverse events related to such therapy.²¹ Although some adverse events linked to PDE5i usage is higher than that of placebo, PDE5i-related adverse events such as headache, flushing, and dyspepsia are mostly mild to moderate, and the overall safety profile remains good. Therefore, recent studies, including ours, find no obviously increased adverse events associated with combined PDE5i therapy.¹³ We assume that

patients are better able to tolerate low doses of two PDE5i drugs compared to the maximum prescribed levels. In addition, another important concern is the effect of PDE5i use on the oncological outcome of patients who have undergone RP. Previous studies have questioned the safety of PDE5i, raising the possibility of an adverse impact on biochemical recurrence after RP.^{27,28} However, several studies, including a recent meta-analysis, conclude that the use of PDE5i for EF after RP is oncologically safe.²⁹ In addition, Korean population studies, including our institutional experience, support the safety of various PDE5i therapies in terms of their oncological outcomes after RP.³⁰

Several limitations of our study should be considered. First, this retrospective study was conducted on a small number of patients at a single institution. Most patients wanted additional medical therapy after undergoing the initial single PDE5i therapy and selecting the subjects to enroll for the study involved unavoidable bias. In addition, the optimum dosage and duration of PDE5i used in combined therapy was not evaluated in this study. Finally, the long-term efficacy and safety of combined therapy, including oncological outcome, should be viewed with caution. These limitations highlight the need for more standardized study designs and outcome reporting methods in the future. Although this retrospective study has several limitations, it demonstrates that combined PDE5i therapy is safe and improves EF during salvage medical treatment in patients nonresponsive to initial penile rehabilitation using daily PDE5i after NSRP; it is especially recommended for patients without preoperative moderate or severe ED. The results of this study will be useful for physicians creating appropriate treatment plans for nonresponders after initial PDE5i therapy following RP.

CONCLUSIONS

Combined PDE5i therapy using tadalafil (5 mg) once daily with sildenafil (50 mg) or udenafil

(100 mg) on demand improves EF in patients non-responsive to standard penile rehabilitation after NSRP, especially for patients without preoperative moderate or severe ED. Physicians should consider this novel therapeutic strategy before invasive therapy for ED after RP.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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