ONCOLOGY

Efficacy of Tadalafil in Penile Rehabilitation Started Before Nerve-Sparing Robot-Assisted Radical Prostatectomy: A Double-Blind Pilot Study

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ABSTRACT

Background: Despite the widespread practice of nerve-sparing robot-assisted radical prostatectomy (nsRARP) for the treatment of localized prostate cancer (PCa), erectile dysfunction remains a significant sequela of radical prostatectomy.

Aim: This study aimed to compare the efficacy of tadalafil 5 mg once daily for erectile function recovery in patients who underwent nsRARP according to the timing of rehabilitation initiation.

Methods: In this double-blind, prospective pilot study, a total of 41 patients who underwent nsRARP were randomly assigned into 2 groups according to the timing of rehabilitation initiation. In the preRARP group (n = 20), tadalafil was started 2 weeks before nsRARP, and in the postRARP group (n = 21), it was started 4 weeks after nsRARP. Erectile function recovery after nsRARP was defined as an International Index of Erectile Function (IIEF-5) score of ≥17.

Outcomes: The measures of EF recovery were the changes in IIEF-5 score.

Results: The rate of erectile function recovery at 12-month follow-up was 80.0% and 71.4% in the preRARP and postRARP groups, respectively. The mean differences between baseline and postoperative IIEF-5 scores at 1-, 3-, 6-, and 12-month follow-up were -11.7 ± 3.2, -7.4 ± 3.2, -5.6 ± 1.5, and -4.1 ± 1.1 in the preRARP group and -14.7 ± 4.7, -12.0 ± 5.0, -9.7 ± 3.9, and -6.0 ± 3.1 in the postRARP group, respectively (1-month, $P = .259$; 3-months, $P = .077$; 6-months, $P = .014$; 12-months, $P = .007$).

Clinical implications: Preoperative tadalafil 5 mg once a day could be used effectively and safely as a strategy for penile rehabilitation after nsRARP.

Strengths and Limitations: This study is the first prospective trial of penile rehabilitation with tadalafil 5 mg once a day prior to nsRARP. This is a pilot study with the limitations of a small sample; further and large-scale studies with multiple cohorts, such as an untreated control group and an early immediate rehabilitation group for EF recovery, are needed.

Conclusion: This study suggests that preoperative penile rehabilitation using tadalafil may lead to better erectile function recovery than postoperative penile rehabilitation using tadalafil. **Noh T, Shim JS, Kang SG, et al. Efficacy of Tadalafil in Penile Rehabilitation Started Before Nerve-Sparing Robot-Assisted Radical Prostatectomy: A Double-Blind Pilot Study. Sex Med 2022;10:100508**.

Key Words: Erectile Dysfunction; Penile Rehabilitation; Radical Prostatectomy

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INTRODUCTION

Advances in robotics have led to a paradigm shift in the surgical management of clinically localized prostate cancer (PCa).[1] Erectile dysfunction (ED) is an inevitable sequela of radical prostatectomy (RP).[2] To reduce some adverse effects associated with

urinary and erectile function (EF) after RP, a nerve-sparing approach to RP was introduced in the 1980s.[3] Nerve-sparing RP is based on accumulated experience and the understanding of periprostatic anatomy, and it has been widely applied for the treatment of PCa.[4,5] Despite the widespread practice of nerve-sparing robot-assisted radical prostatectomy (nsRARP), ED remains a significant sequela of RP that affects patients' quality of life, even after a successful nerve-sparing surgery.[6] The recovery rate of EF was estimated to be <50% at 3 months after nsRARP, and the recovery of EF in patients reporting neuropraxia requires a period of >24 months.[7−9] Various protocols of penile rehabilitation using phosphodiesterase type 5 inhibitors (PDE5-Is) have been shown to be effective in promoting early recovery of EF.[10−12] In particular, tadalafil, a long-acting PDE5-I, has been shown to be well tolerated and effective for rehabilitation in patients with ED after nsRARP.[13,14]

Penile rehabilitation using PDE5-Is has been recommended for decades; however, the consensus on its efficacy and optimal timing of its application for the best outcomes has not been reached yet.[15,16]

Is preoperative use of long-acting PDE5-I more effective than postoperative use in improving EF recovery after nsRARP? Herein, we investigate the efficacy of tadalafil 5 mg once a day (OaD) for the recovery of EF and spontaneous functional erection in patients who underwent nsRARP according to the timing of rehabilitation initiation (preoperative vs postoperative).

PATIENTS AND METHODS

Study Population and Design

This was a double-blind, prospective pilot study. Patients with PCa who underwent bilateral nsRARP performed by a single surgeon between June 2017 and May 2019 were prospectively enrolled. The surgeon had a 15-year experience in performing more than 700 RARPs and 250 total intracorporeal robot-assisted radical cystectoprostatectomy with urinary diversion.

Based on the recommended number of 12 patients per group, 41 patients were enrolled in a predetermined timeframe; the preoperative group (preRARP), in which tadalafil treatment was initiated 2 weeks before nsRARP (n = 20) and the postoperative group (postRARP), in which tadalafil treatment was initiated 4 weeks after nsRARP (n = 21).

All patients were randomly assigned to either the preoperative group (preRARP), or the postoperative group (postRARP). To match the dosing periods, 5 mg tadalafil or placebo was administered for a total period of 30 weeks in both groups. In the preRARP group, tadalafil treatment (tadalafil 5 mg OaD) was initiated 2 weeks before nsRARP and continued for 24 weeks, and placebo (OaD) was administered for the last 6 weeks. In the postRARP group, placebo (OaD) was started 2 weeks before nsRARP and continued for 4 weeks after nsRARP, and tadalafil treatment (tadalafil 5 mg OaD) was initiated 4 weeks after nsRARP and continued for 24 weeks. Figure 1 shows the stepwise participant recruitment procedure and duration of tadalafil treatment.

Patient Eligibility

Preoperative EF. For preoperative eligibility assessment, patients aged ≥40 years completed the previously validated Korean abridged 5-item version of the International Index of erectile function (IIEF-5) questionnaire[17,18] and underwent physical examination 1 month before nsRARP. A total of 84 patients were enrolled; among them, 63 were determined to be potent preoperatively based on an IIEF-5 score of ≥17 and the findings of physical examination.

The IIEF-5 questionnaire defined the degree of erectile function: IIEF-5 score 22−25, no erectile dysfunction; IIEF-5 score 17−21, mild erectile dysfunction; IIEF-5 score 12−16, mild-to-moderate erectile dysfunction; IIEF-5 score, 8−11; moderate erectile dysfunction, IIEF-5 score 5−7, severe erectile dysfunction. Three patients had difficulty completing the questionnaire even after reporting EF recovery based on an IIEF-5 score of ≥17 at previous visits. In these patients, EF recovery was defined as a self-reported successful intercourse. This substituted definition was applied to assess the recovery in 3 patients (one at the 6-month follow-up and 2 at the 12-month follow-up). Randomization was performed using a computer-generated method.

nsRARP. nsRARP was planned for all patients with localized PCa according to risk stratification based on a clinical parameter (prostate-specific antigen: <20 ng/mL), magnetic resonance imaging (MRI) findings, and prostate biopsy results. We perform magnetic resonance imaging-ultrasound fusion transperineal targeted and template systematic prostate biopsy to diagnose PCa. Previously, we have reported a protocol for this procedure as well as a risk stratification model for clinically significant PCa.[19,20] Briefly, we performed biparametric MRI using a 3.0-T scanner (Siemens Medical System, Erlangen, Germany), and prostate imaging reporting and data systems (PI-RADS) scores were assigned by uroradiologists according to PI-RADS version 2.0. Patients who were diagnosed with clinically significant PCa (Gleason score ≥7 [3 + 4]) by targeted biopsy or patients in whom suspected extracapsular extension was identified on MRI did not undergo planned nsRARP.

The area of residual nerve tissue was measured on the posterolateral aspect at the level of the mid-prostate by an uropathologist who graded the nerve-sparing quality in each patient. Full nsRARP was performed medial to the branch of lateral prostatic artery which was used as the landmark artery with interfascial nerve sparing technique, scored with the nerve-sparing grade 5 (Figure 2). For grade assessment of neurovascular bundle preservation, a uropathologist scored the grade of the nerve-sparing status based on the residual tissue as follows: 5, full nerve sparing medial to the landmark artery; 4, near-to-complete nerve sparing medial to the landmark artery and >75% of the NVB; 3, nerve

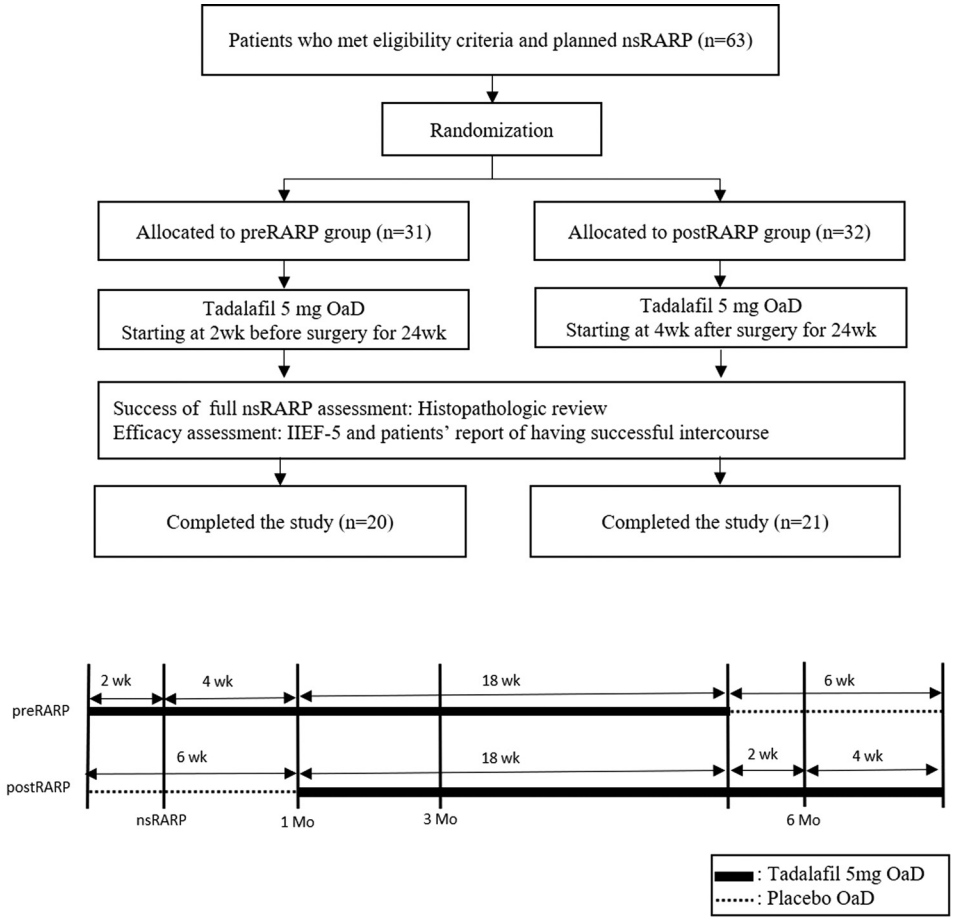


Figure 1. Flow chart of participant recruitment. IIEF-5, Korean abridged 5-item version of the International Index of Erectile Function; mo, months; nsRARP, nerve-sparing robot-assisted radical prostatectomy; OaD, once a day; wk, weeks.

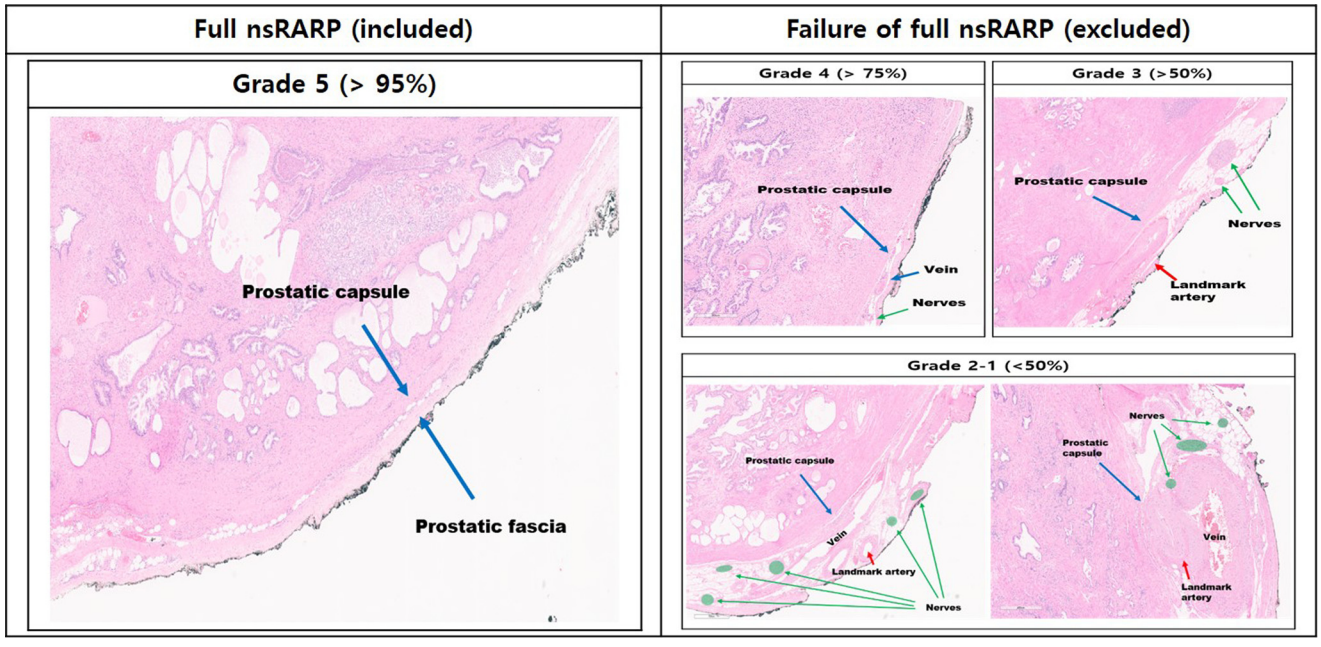


Figure 2. Histopathologic examination after bilateral nerve-sparing robot-assisted radical prostatectomy. nsRARP, nerve-sparing robot-assisted radical prostatectomy.

sparing lateral to the landmark artery with >50% of the NVB; 2, nerve sparing lateral to the landmark artery with <50% of the NVB; and 1, no NVB preservation with wide excision.[21] Sixty-three patients underwent nsRARP; among them, 17 were excluded due to the failure of full nerve sparing based on histopathological findings showing <95% neurovascular bundle preservation; grade 4 to 1. The residual tissues are indicated in Figure 2: the lateral prostatic artery (landmark) is indicated with a red arrow and nerve fibers of the pelvic plexus with green arrows.

Compliance. During the administration of tadalafil 5 mg OaD, patients who had low compliance (<70% adherence to the prescription),[22,23] and those with <12 months of follow-up were excluded.

The days on which the drug was taken were checked and calculated through patient interviews with a checklist, and a recording device. By touching the device before taking the drug, the patients recorded the timing of each dose, allowing us to assess compliance.

Endpoint

The endpoint was the efficacy of tadalafil 5 mg OaD for the recovery of EF according to the timing of initiating penile rehabilitation. After nsRARP, the recovery of EF and spontaneous functional erection were compared between the preRARP and postRARP groups.

The rate of EF recovery with an IIEF-5 score of ≥17 was compared. The difference in EF recovery at 1, 3, 6, and 12 months after nsRARP was evaluated as the difference between the preoperative and postoperative IIEF-5 scores measured at 1-, 3-, 6-, and 12-month follow-up and compared between the groups.

Data Analysis

Descriptive statistics were used to report the demographic variables and proportion of patients with recovered EF in the preRARP and postRARP groups. All statistical analyses were performed using IBM SPSS Statistics software for Windows (version 24.0; IBM Corp., Armonk, NY). The Student's t-test, Fisher's exact test, and chi-square test were used to compare categorical variables between the 2 groups. The independent-samples t-test was performed to compare the mean differences between the baseline and postoperative IIEF-5 scores. Statistical significance was set at $P < .05$.

Ethics Statement

This study was conducted according to the guidelines of the Declaration of Helsinki and current ethical guidelines. The study was reviewed and approved by the Ethics Committee and Institutional Review Board of Korea University Anam Hospital (IRB No. 2016AN0167). Written informed consent was obtained from all participants prior to their enrolment in the trial.

Table 1. Baseline demographics and clinical data of patients who were followed up for ≥1 year

Parameters	preRARP group (n = 20)	postRARP group (n = 21)	*P* Value
Age, year	59.2 ± 6.7	61.8 ± 4.0	0.095*
BMI, kg/m^2	24.3 ± 1.3	25.2 ± 3.3	0.309*
PSA level, ng/mL	8.3 ± 7.7	6.3±3.3	0.265*
Prostate volume, mL	29.9 ± 12.0	33.6±12.5	0.340*
Pathologic stage, n (%)			0.294†
pT2	17 (85)	15 (71)	
≥pT3	3 (15)	6 (29)	
Gleason score, n (%)			0.192†
6	12 (60)	9 (43)	
7	5 (25)	10 (48)	
8	3 (15)	2 (9)	
Positive surgical margin, n (%)			
Overall, n (%)	2 (10)	3 (14.3)	0.675†
In pT2 cancers, n (%)	1 (5.9)	1 (6.7)	
In pT3 cancers, n (%)	1 (33.3)	2 (33.3)	
Preoperative IIEF-5 score	19.7 ± 1.8	18.8 ± 2.0	0.124*
22–25, n (%)	4 (20)	3 (14)	0.627†
17–21, n (%)	16 (80)	18 (76)	

*Student's t-test.
†Chi-square test.BMI = body mass index; IIEF-5 = International Index of Erectile Function (IIEF-5 score 22–25, no erectile dysfunction; IIEF-5 score 17–21, mild erectile dysfunction; IIEF-5 score 12–16, mild-to-moderate erectile dysfunction; IIEF-5 score 8–11, moderate erectile dysfunction; IIEF-5 score 5–7, severe erectile dysfunction); PSA = prostate-specific antigen.

RESULTS

Patient Demographics

A total of 41 patients were included this study. Among them, 20 and 21 patients were randomly assigned to the preRARP and postRARP groups, respectively. Patient demographics in the preRARP and postRARP groups are summarized in Table 1. No differences in baseline variables were found between the groups.

Recovery of EF

At 1, 3, 6, and 12 months after nsRARP, the recovery of EF was achieved in 5 (25.0%), 9 (45.0%), 12 (60.0%), and 16 (80.0%) patients in the preRARP group and in 5 (23.8%), 8 (38.1%), 11 (52.4%), and 15 (71.4%) patients in the postRARP group, respectively. There was no significant difference in the rate of recovery of EF (IIEF-5 score of ≥17) between the preRARP and postRARP groups (1 month: 25.0% vs 23.8%, $P = .859$; 3 months: 45.0% vs 38.1%, $P = .756$; 6 months: 60.0% vs 52.4%; $P = .627$; 12 months: 80.0% vs 71.4%, $P = .365$; Figure 3).

The baseline mean IIEF-5 score in the preRARP and postRARP groups was 19.7 ± 1.8 and 18.8 ± 2.0, respectively. The mean differences between the baseline and postoperative IIEF-5 scores measured at 1-, 3-, 6-, and 12-month follow-up were

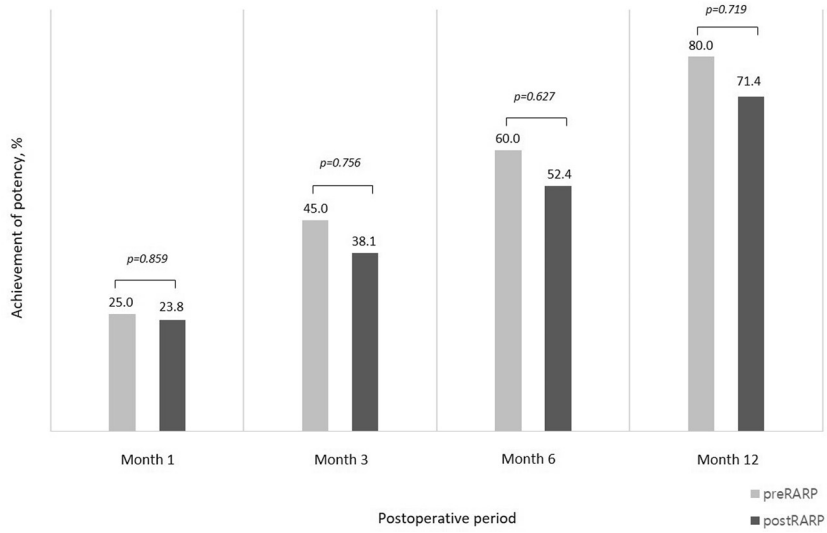


Figure 3. Bar graph showing the proportion of patients in the preRARP and postRARP groups in whom recovery of erectile function was achieved. The recovery of erectile function was defined as a postoperative IIEF-5 score of ≥17. In the preRARP group, penile rehabilitation was started 2 weeks before nsRARP and continued for 24 weeks. In the postRARP group, penile rehabilitation was initiated 4 weeks after nsRARP and continued for 24 weeks. Data were compared between the 2 groups using Student's t-test. nsRARP, nerve-sparing robot-assisted radical prostatectomy; IIEF-5, Korean abridged 5-item version of the International Index of Erectile Function.

-11.7 ± 3.2, −7.4 ± 3.2, −5.6 ± 1.5, and −4.1 ± 1.1 in the preRARP group and −14.7 ± 4.7, −12.0 ± 5.0, −9.7 ± 3.9, and −6.0 ± 3.1 in the postRARP group, respectively (1-month, P = .259; 3-month, P = .077; 6-month, P = .014; 12-month, P = .007). At 12 months after nsRARP, the IIEF-5 score in the preRARP group was significantly greater than that in the postRARP group (15.6 ± 2.1 vs 12.8 ± 3.5, P < .001; Figure 4).

Adverse Events

A total of 41 patients were included in the analysis of the safety profile of tadalafil treatment. Treatment with tadalafil 5 mg OaD was well tolerated by all patients during the study period. Of 41 patients, we observed facial flushing in 2 patients and headache in 1 patient. However, these symptoms were mild and transient. Serious adverse events and myalgias by inhibition of PDE isozymes (PDE11) due to the use of tadalafil 5 mg OaD were not observed.

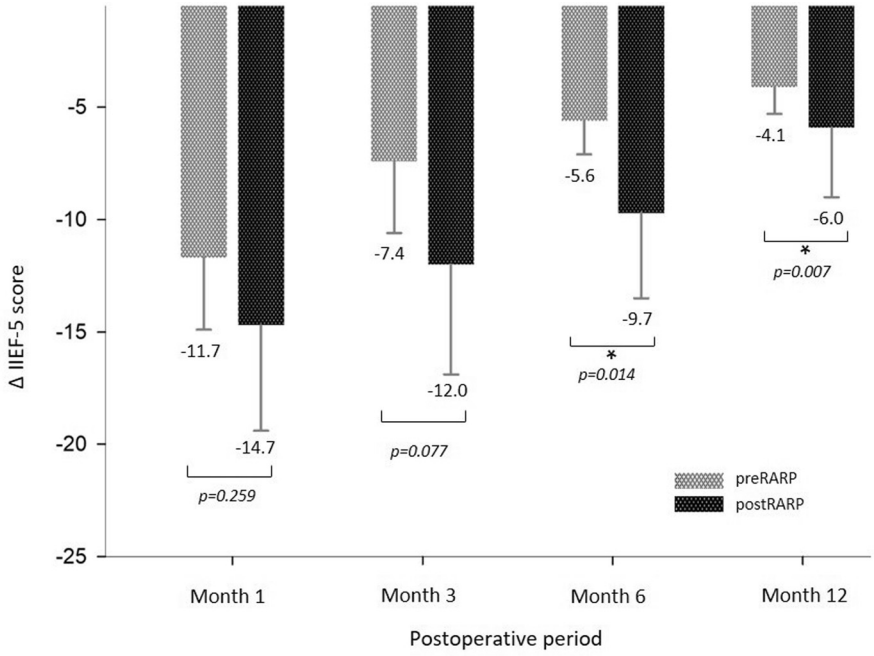
DISCUSSION

Robot-assisted radical prostatectomy (RARP) is a primary treatment modality for localized PCa,[24] and its application has been expanded.[25] However, ED, an inevitable sequela of RP, is still observed in 70.4% of patients after RARP.[26] Several factors cause ED after RARP; the most relevant one is neurapraxia caused by direct and indirect damage in the neurovascular bundles that control the complex mechanism of the cavernous erectile tissue due to stretching, heating, and ischemia.[27] To reduce neurapraxia based on enhanced vision and anatomical comprehension,[4] nsRARP has been applied with variable techniques and demonstrated to improve functional outcomes.[28]

In males, the inferior hypogastric plexus or pelvic plexus contains parasympathetic fibers and is responsible for the mechanisms of erection and ejaculation.[29] Fibers and the dense neural network of the pelvic plexus lie within the neurovascular bundle on the posterolateral aspect of the prostate; these nerves are mainly responsible for vasodilatation and the increase in arterial blood flow during erection in the corpora cavernosa.[27,30]

The method of grading nerve-sparing quality has been described by several groups; however, the scales were limited by the subjectivity and variations among observers.[21,31] Despite improvements in the quality of near-to-complete nerve sparing with nsRARP, it is difficult to completely avoid neurapraxia caused by direct and indirect damage to the neurovascular bundles during surgery. To reduce this damage to the NVB, several techniques including retrograde early release of NBV have been introduced. However, ED remains a significant sequela of RP that affects patients' quality of life, even after a successful nerve-sparing surgery.[32]

Therefore, different methods of penile rehabilitation, including intracavernosal injection, use of vacuum erection devices, and administration of PDE5-Is, have been recommended for decades for the recovery of EF after nsRARP.[33] Additionally, multi-modal penile prehabilitation regimen using the combination of oral pharmacotherapy and a vacuum erectile device may lead to expedite the recovery of EF; 78% of men who underwent penile prehabilitation using multi-modal regimen reported recovery of EF within 12 months.[10] However, consensus on the optimal penile rehabilitation protocol in terms of utility and optimal timing of application for the best outcomes has not been reached yet.[15,16]



	preRARP		postRARP		p-value	
	IIEF-5	△IIEF-5	IIEF-5	△IIEF-5	IIEF-5	△IIEF-5
Baseline	19.7 (1.8)		18.8 (2.0)		0.124	
Month 1	8.0 (3.8)	-11.7 (3.2)	4.1 (4.2)	-14.7 (4.7)	0.003	0.259
Month 3	12.3 (3.7)	-7.4 (3.2)	6.8 (3.9)	-12.0 (5.0)	0.001	0.077
Month 6	14.2 (9.1)	-5.6 (1.5)	9.1 (3.0)	-9.7 (3.9)	0.001	0.014
Month 12	15.6 (2.1)	-4.1 (1.1)	12.8 (3.5)	-6.0 (3.1)	0.004	0.007

Figure 4. Bar graph showing the change in the IIEF-5 score (ΔIIEF-5) during the follow-up period of 1 year in the preRARP and postRARP groups. In the preRARP group, penile rehabilitation was started 2 weeks before nsRARP and continued for 24 weeks. In the postRARP group, penile rehabilitation was initiated 4 weeks after nsRARP and continued for 24 weeks. Data were compared between the two groups using Student's t-test. Error bars indicate standard deviation of the mean. IIEF-5, Korean abridged 5-item version of the International Index of Erectile Function; ΔIIEF-5, difference between baseline IIEF-5 score and postoperative IIEF-5 scores; nsRARP, nerve-sparing robot-assisted radical prostatectomy.

The efficacy of several penile rehabilitation strategies and schedules have been reviewed compared to the efficacy of placebo.[12,34] In a systematic review of the literature concerning oral medication, vacuum erection devices, and counseling, the prehabilitation group showed higher rate of EF recovery than the control group (56% vs 24%; $P = .007$).[11] Starting penile rehabilitation prior to surgery may result in better postoperative recovery of EF than postoperative rehabilitation. Furthermore, currently, the administration of PDE5-Is is the most effective treatment in penile rehabilitation after nsRARP, and regular doses of PDE5-Is have significant efficacy and good tolerability without serious adverse events.[12]

Neurapraxia results in a low oxygen status in penile tissue, which, in turn, may lead to apoptosis and fibrosis in smooth muscles.[35] Moreover, neurapraxia results in progressive fibrosis in the corpora cavernosa and smooth muscle degeneration after RP. Improved oxygenation in the corpora cavernosa with continuous stimulation of long-acting PDE5-I, which activates the nitric oxide/cyclic guanosine monophosphate pathway, could reduce oxidative stress, hypoxia, and fibrosis in smooth muscles.[36] Thus, early rehabilitation using PDE5-Is may improve the recovery of EF after nsRARP.[37] The administration of tadalafil, a long-acting PDE5-I, is an efficacious and well-tolerated treatment for ED after nerve-sparing RP.[13,38] Moncada et al. reported that tadalafil 5 mg OaD shortened the time to recovery of EF.[36] In addition, tadalafil 5 mg OaD has been shown to significantly improve IIEF scores and penile length, suggesting that this treatment could contribute to the recovery of EF after nerve-sparing RP.[14]

The hypothesis of this study is that preoperative and continuous usage of long-acting PDE5-I to improve oxygenation in the corpora cavernosa would make the tissue more tolerant to direct and indirect damages during surgery. Therefore, preoperative rehabilitation with tadalafil would be more efficacious than postoperative rehabilitation.

Various factors may affect the recovery of EF. The rate of recovery after nerve-sparing RP and treatment with any PDE5-I ranges from 41.4% to 74.0%.[14,37,39] In the present study, the efficacy of preoperatively and postoperatively initiated tadalafil 5 mg OaD was compared to investigate the optimal timing of applying penile rehabilitation to maximize its effect while minimizing the interference of other causal factors. Strict exclusion criteria for undergoing nsRARP were established based on histopathologic examination and treatment compliance (≥70%). The method of grading nerve-sparing quality has been described by several groups; however, the scales were limited by the subjectivity and variations among observers.[22,31] To minimize interference from the incomplete and variable assessments of nerve-sparing quality, patients in whom full nsRARP failed by an experienced surgeon owing to extracapsular extension with neural invasion or histopathologic examination revealed inflammatory changes associated with previous infections were excluded. According to a recently published systematic review of surgeon experience and erectile function after radical prostatectomy (RP), high- and low-volume surgeons were classified when they performed >25 RP cases/year, and an annual surgeon caseload of >25 RP cases per year or total cumulative experience of >1000 RP cases resulted in better EF outcomes after RP.[40] In addition, patients were excluded due to the compliance with tadalafil of <70% or insufficient follow-up.

The reasonable exclusion criteria allowed us to compare the effect of penile rehabilitation using tadalafil 5 mg OaD initiated at different time points. Preoperative administration of tadalafil 5 mg OaD was effective for penile rehabilitation, resulting in significant improvements in the IIEF-5 scores. However, the achievement rate of EF recovery greater than the IIEF-5 score of >17 was not significantly different between the 2 groups. This may be influenced by a decrease in sexual activity and motivation, and fewer attempts at early sexual intercourse due to concerns about the recovery of general conditions and cancer control during the early period after surgery. As a result, the achievement rate of EF recovery (IIEF-5 >17) was not significantly different between the 2 groups, the gap in IIEF scores between the 2 groups may catch up over time.

To the best of our knowledge, no trial has yet investigated the differences in efficacy between preoperative and postoperative administration; therefore, we investigated the effectiveness of preoperative rehabilitation with tadalafil 5 mg once a day. However, the current study has limitations owing to the small number of enrolled patients as a pilot study and the risk of bias, including selection and detection biases from the process of randomization and attrition bias from the exclusion criteria. Furthermore, there was no untreated control group, nor was there a comparison with the early immediate start of rehabilitation after nsRARP, which has shown a better result than the later start of rehabilitation.[41] In addition, the follow-up period was limited to 12 months, which is relatively short because the recovery of EF after nsRARP usually occurs over a period of 24 months.[7,8] Thus, a larger comparative study with multiple arms, such as the untreated control and early-immediate rehabilitation groups, is needed to clarify the superior effectiveness of preoperative tadalafil.

CONCLUSION

This study suggests that preoperative penile rehabilitation using tadalafil 5 mg OaD may offer benefits leading to better recovery of EF after nsRARP than does postoperative penile rehabilitation.

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REFERENCES

1. Cao L, Yang Z, Qi L, et al. Robot-assisted and laparoscopic vs open radical prostatectomy in clinically localized prostate cancer: perioperative, functional, and oncological outcomes: A systematic review and meta-analysis. **Medicine (Baltimore) 2019;98:e15770.**
2. Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. **Lancet Oncol 2018;19:1051–1060.**
3. Walsh PC, Donker PJ. Impotence following radical prostatectomy: Insight into etiology and prevention. **J Urol 1982;128:492–497.**
4. Walz J, Epstein JI, Ganzer R, et al. A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: An update. **Eur Urol 2016;70:301–311.**
5. Nguyen LN, Head L, Witiuk K, et al. The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: A systematic review and meta-analysis. **J Urol 2017;198:760–769.**
6. Lima TFN, Bitran J, Frech FS, et al. Prevalence of post-prostatectomy erectile dysfunction and a review of the

recommended therapeutic modalities. **Int J Impot Res 2021;33:401–409.**

7. Mandel P, Preisser F, Graefen M, et al. High chance of late recovery of urinary and erectile function beyond 12 months after radical prostatectomy. **Eur Urol 2017;71:848–850.**
8. Lee JK, Assel M, Thong AE, et al. Unexpected long-term improvements in urinary and erectile function in a large cohort of men with self-reported outcomes following radical prostatectomy. **Eur Urol 2015;68:899–905.**
9. Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. **Eur Urol 2008;54:924–931.**
10. Osadchiy V, Eleswarapu SV, Mills SA. Efficacy of a preprostatectomy multi-modal penile rehabilitation regimen on recovery of postoperative erectile function. **Int J Impot Res 2020;32:323–328.**
11. Schoentgen N, Califano G, Manfredi C, et al. Is it worth starting sexual rehabilitation before radical prostatectomy? Results from a systematic review of the literature. **Front Surg 2021;8:648345.**
12. Sari Motlagh R, Abufaraj M, Yang L, et al. Penile rehabilitation strategy after nerve sparing radical prostatectomy: A systematic review and network meta-analysis of randomized trials. **J Urol 2021;205:1018–1030.**
13. Kim S, Sung GT. Efficacy and safety of tadalafil 5 mg once daily for the treatment of erectile dysfunction after robot-assisted laparoscopic radical prostatectomy: A 2-year follow-up. **Sex Med 2018;6:108–114.**
14. Montorsi F, Brock G, Stolzenburg JU, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: A randomised placebo-controlled study (REACTT). **Eur Urol 2014;65:587–596.**
15. Salonia A, Adaikan G, Buvat J, et al. Sexual rehabilitation after treatment for prostate cancer-part 1: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). **J Sex Med 2017;14:285–296.**
16. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA Guideline. **J Urol 2018;200:633–641.**
17. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. **Int J Impot Res 1999;11:319–326.**
18. Ahn TY, Lee DS, Kang WC, et al. Validation of an abridged Korean version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. **Korean J Urol 2001;42:535–539.**
19. Noh TI, Tae JH, Kim HK, et al. Diagnostic accuracy and value of magnetic resonance imaging-ultrasound fusion transperineal targeted and template systematic prostate biopsy based on bi-parametric magnetic resonance imaging. **Cancer Res Treat 2020;52:714–721.**
20. Noh TI, Hyun CW, Kang HE, et al. A predictive model based on bi-parametric magnetic resonance imaging and clinical parameters for clinically significant prostate cancer in the Korean population. **Cancer Res Treat 2020;53:1148–1155.**
21. Schatloff O, Chauhan S, Sivaraman A, et al. Anatomic grading of nerve sparing during robot-assisted radical prostatectomy. **Eur Urol 2012;61:796–802.**
22. Koesmahargyo V, Abbas A, Zhang L, et al. Accuracy of machine learning-based prediction of medication adherence in clinical research. **Psychiatry Res 2020;294:113558.**
23. Haynes RB, Taylor DW, Sackett DL, et al. Can simple clinical measurements detect patient noncompliance? **Hypertension 1980;2:757–764.**
24. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. **Eur Urol. 2017;71:618–629.**
25. Mazzone E, Dell'Oglio P, Rosiello G, et al. Technical refinements in superextended robot-assisted radical prostatectomy for locally advanced prostate cancer patients at multiparametric magnetic resonance imaging. **Eur Urol 2021;80:104–112.**
26. Haglind E, Carlsson S, Stranne J, et al. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: A prospective, controlled, nonrandomised trial. **Eur Urol 2015;68:216–225.**
27. Walz J, Burnett AL, Costello AJ, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. **Eur Urol 2010;57:179–192.**
28. Kumar A, Tandon S, Samavedi S, et al. Current status of various neurovascular bundle-sparing techniques in robot-assisted radical prostatectomy. **J Robot Surg 2016;10:187–200.**
29. Mauroy B, Demondion X, Drizenko A, et al. The inferior hypogastric plexus (pelvic plexus): Its importance in neural preservation techniques. **Surg Radiol Anat 2003;25:6–15.**
30. Baader B, Herrmann M. Topography of the pelvic autonomic nervous system and its potential impact on surgical intervention in the pelvis. **Clin Anat 2003;16:119–130.**
31. Kang SG, Schatloff O, Haidar AM, et al. Does surgeon subjective nerve sparing score predict recovery time of erectile function following robot-assisted radical prostatectomy? **J Sex Med 2015;12:1490–1496.**
32. Albers LF, Tillier CN, van Muilekom E, et al. Sexual satisfaction in men suffering from erectile dysfunction after robot-assisted radical prostatectomy for prostate cancer: An observational study. **J Sex Med 2021;18:339–346.**
33. Fode M, Ohl DA, Ralph D, et al. Penile rehabilitation after radical prostatectomy: What the evidence really says. **BJU Int 2013;112:998–1008.**
34. Tian D, Wang XY, Zong HT, et al. Efficacy and safety of short- and long-term, regular and on-demand regimens of phosphodiesterase type 5 inhibitors in treating erectile dysfunction after nerve-sparing radical prostatectomy: A systematic review and meta-analysis. **Clin Interv Aging 2017;12:405–412.**

35. Iacono F, Giannella R, Somma P, et al. Histological alterations in cavernous tissue after radical prostatectomy. **J Urol 2005;173:1673–1676.**
36. Moncada I, de Bethencourt FR, Lledó-García E, et al. Effects of tadalafil once daily or on demand versus placebo on time to recovery of erectile function in patients after bilateral nerve-sparing radical prostatectomy. **World J Urol 2015;33:1031–1038.**
37. Jo JK, Jeong SJ, Oh JJ, et al. Effect of starting penile rehabilitation with sildenafil immediately after robot-assisted laparoscopic radical prostatectomy on erectile function recovery: A prospective randomized trial. **J Urol 2018;199:1600–1606.**
38. Montorsi F, Nathan HP, McCullough A, et al. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: A randomized, double-blind, placebo controlled trial. **J Urol 2004;172: 1036–1041.**
39. Briganti A, Di Trapani E, Abdollah F, et al. Choosing the best candidates for penile rehabilitation after bilateral nerve-sparing radical prostatectomy. **J Sex Med 2012;9:608–617.**
40. Ju IE, Trieu D, Chang SB, et al. Surgeon experience and erectile function after radical prostatectomy: A systematic review. **Sex Med Rev 2021;9:650–658.**
41. Nathan A, Shukla S, Sinha A, et al. Immediate post-operative PDE5i therapy improves early erectile function outcomes after robot assisted. 2022.