Review Article

Penile rehabilitation after radical prostatectomy: does it work?

Giorgio Gandaglia[1], Nazareno Suardi[1], Vito Cucchiara[1], Marco Bianchi[1], Shahrokh F. Shariat[2], Morgan Roupret[3], Andrea Salonia[1], Francesco Montorsi[1], Alberto Briganti[1]

[1]Unit of Urology/Department of Oncology, URI, IRCCS San Raffaele Hospital, Milan, Italy; [2]Department of Urology, Medical University of Vienna, Vienna, Austria; [3]Academic Department of Urology of La-Pitié-Salpétrière, Assistance-Publique Hôpitaux de Paris (AP-HP), University Paris 6, Paris, France

Correspondence to: Alberto Briganti, MD. Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132, Milan, Italy. Email: briganti.alberto@hsr.it.

Context: Erectile dysfunction (ED) represents one of the most common long-term side effects in patients with clinically localized prostate cancer (PCa) undergoing nerve-sparing radical prostatectomy (RP).

Objective: To analyze the role of penile rehabilitation in the recovery of erectile function (EF) after nerve-sparing RP.

Evidence synthesis: Penile rehabilitation is defined as the use of any intervention or combination with the goal not only to achieve erections sufficient for satisfactory sexual intercourses, but also to return EF to preoperative levels. The concept of rehabilitation is based on the implementation of protocols aimed at improving oxygenation, preserving endothelial structure, and preventing smooth muscle structural alterations. Nowadays, the most commonly adopted approaches for penile rehabilitation after nerve-sparing RP are represented by the administration of phosphodiesterase type-5 inhibitors (PDE5-Is), intracorporeal injection therapy, vacuum erection devices (VED), and the combination of these therapies. Several basic science studies support the rational for the adoption of penile rehabilitation protocols. Particularly, rehabilitation, set as early as possible, seems to be better than leaving the erectile tissues unassisted. On the other hand, results from solid prospective randomized trials finally assessing the long-term beneficial effects of PDE5-Is, intracavernosal injections, or VED on EF recovery after surgery are still lacking.

Conclusions: Although preclinical evidences support the rationale for penile rehabilitation after nerve-sparing RP, clinical studies reported conflicting results regarding its efficacy on long-term EF recovery. Nowadays, which is the optimal rehabilitation program still represents a matter of debate.

Keywords: Prostate cancer (PCa); radical prostatectomy (RP); penile rehabilitation; phosphodiesterase type-5 inhibitors (PDE5-Is); sexual function

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Introduction

Prostate cancer (PCa) represents one of the most frequently diagnosed malignancies in the United States and Europe (1). Radical prostatectomy (RP) is one of the most commonly adopted therapeutic options in patients with clinically localized PCa (2). Although this surgical approach is associated with excellent long-term oncologic results (3-5), the risk of short- and long-term adverse events is not negligible (5). Particularly, urinary incontinence (UI) and erectile dysfunction (ED) represent long-term sequelae observed in a non-negligible proportion of patients treated with RP. Of note, these side effects are associated with a profound detrimental impact on patient health-related quality of life.

A number of studies reported satisfactory urinary continence recovery rates after surgery (5-13). However, the postoperative recovery of erectile function (EF) still represents a major challenge for patients and physicians. When considering the risk of ED after surgery, several factors should be considered. First, preoperative patient

characteristics play a major role on the subsequent probability of recovering EF after surgery, where younger and healthier individuals have substantially higher recovery rates as compared to their older and sicker counterparts (9,13-18). Second, preoperative EF represents a significant predictor of the subsequent risk of ED after surgery (14-16,19). Indeed, the probability of achieving satisfactory erections after surgery is extremely low in patients with severe ED as measured by the International Index of Erectile Function (IIEF) (14-16,19,20). Moreover, patients with higher preoperative IIEF might represent individuals more motivated to achieve satisfactory erectile and sexual function after surgery (21). Finally, the surgical technique and surgeon experience have a substantial impact on the probability of ED after surgery (20,22-28). In this context, the knowledge of the surgical anatomy, together with continuous refinements in the surgical approaches and the introduction of minimally invasive surgery might have resulted in improved potency outcomes after surgery (23-31). For example, surgical approaches aimed at preserving the neurovascular bundles deputed to erections have been developed over the last decades (23,24,26). Moreover, the better visualization of the surgical field, as well as lower intraoperative bleeding and more precise excision associated with robot-assisted RP might result into improved functional outcomes at long-term follow-up (25).

Although accurate patient selection and improvements in the surgical technique might minimize the risk of ED after surgery, the removal of the prostate leads to the temporary loss of erections. This would, in turn, result into reduced oxygenation, pro-apoptotic, and pro-fibrotic changes in the corpora cavernosa that would finally result in postoperative ED (31-34). In this context, penile rehabilitation after RP has been proposed as a therapeutic option in order to break this vicious circle, promoting erectile tissue preservation and preventing pro-apoptotic and pro-fibrotic alterations in the corpora cavernosa (31,32).

This review aims at analyzing the rationale of penile rehabilitation after RP in patients with clinically localized PCa. Moreover, we sought to comprehensively evaluate basic science and clinical evidences supporting the adoption of penile rehabilitation after RP.

Evidence acquisition

A literature review was performed in September 2014 using the Medline, Embase, and Web of Science databases. The search strategy included the terms *prostate cancer*, *penile rehabilitation*, *sexual function*, *radical prostatectomy*, *erectile dysfunction*, *phosphodiesterase type-5 inhibitors*, alone or in combination. We limited our search to large population-based retrospective studies and prospective investigations published between January 2005 and September 2014. Cited references from selected articles and from review articles retrieved in our search were also used to identify manuscripts that were not included in the initial search.

Records were considered relevant to this review if they included patients diagnosed with clinically localized PCa. Only studies including patients treated with RP were evaluated. Only studies assessing EF after RP according to validated tools were evaluated. Results coming from prospective multi-institutional trials were preferred over retrospective single-center studies. Case reports, editorials, and letters were excluded during the review process. Additionally, unpublished data or meeting abstracts were excluded because information that is needed to correctly assess the study quality is usually not available in abstracts.

The primary outcome was the recovery of EF after surgery. The definition of EF recovery was the one used by individual studies.

The articles that provided the highest level of evidence were evaluated and selected with the consensus of all the author of this manuscript. A total of 81 articles were reviewed (*Figure 1*).

Evidence synthesis

The definition of penile rehabilitation and its rationale

The pioneering work of Montorsi *et al.* (35) firstly introduced the concept of penile rehabilitation after RP in the year 1997. Nowadays, penile rehabilitation is defined as the use of any intervention or combination with the goal not only to achieve erections sufficient for satisfactory sexual intercourses, but also to return EF to preoperative levels (31). The rationale of penile rehabilitation is strongly linked to the pathophysiology of ED after RP. In healthy men, during erections the penis oxygenation rises from 35-40 to 75-100 mmHg and there is a balance between the flaccid status and erect status (36). Thus, erectile tissues oxygenation is preserved as long as men obtain erections regularly. In patients undergoing RP, neuropraxia occurs due to direct trauma, inflammation, heating, and ischemia affecting the cavernous nerves, even in men treated with nerve-sparing procedures (32,37,38). The chronic absence of erections related to cavernous nerves neuropraxia after

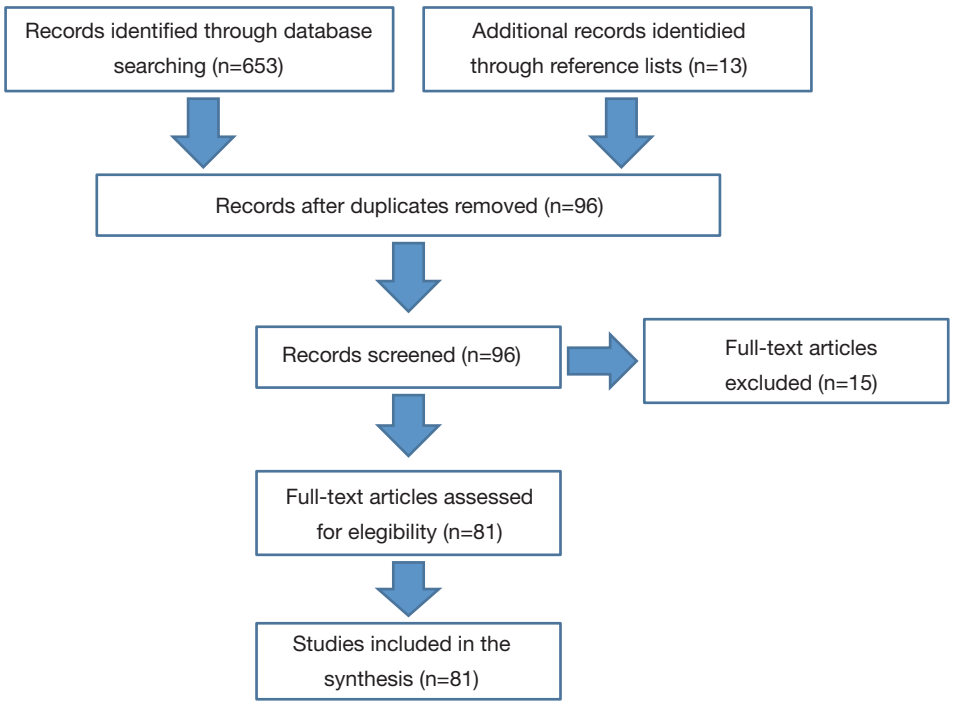

Figure 1 Flow diagram for the identification of the studies included in the literature review.

surgery would result in a state of persisting flaccidity. This, in turn, would lead to fibrogenic cytokine production (e.g., increased expression of TGF-β1, ET-1, NGF, and HIF-1α) and to structural changes in erectile tissues (36,39-41), which might finally result into smooth muscle apoptosis and fibrosis (42). The overexpression of fibrotic tissue would eventually impair the corpora cavernosa elasticity compressive action on subtunical venules, ultimately resulting in postoperative ED (32).

The concept of penile rehabilitation is based on the implementation of therapeutic protocols aimed at improving cavernosal oxygenation, preserving endothelial structure, and finally preventing smooth muscle structural changes (31,36). Nowadays, the most commonly adopted approaches for penile rehabilitation after RP in PCa patients are represented by the administration of PDE5-Is, intracorporeal injection therapy, vacuum erection devices (VED), and the combination of these treatments (31,32).

Phosphodiesterase type-5 inhibitors (PDE5-Is)

The administration of PDE5-Is represents the most commonly performed type of penile rehabilitation after RP, where up to 87% of the participants adopted this treatment strategy (43,44).

Although clinical studies reported conflicting results with regards to the efficacy of rehabilitation protocols based on the administration of PDE5-Is (45-51), preclinical data support the beneficial effects of these molecules (52-64). Indeed, several investigations demonstrated that the chronic administration of PDE5-Is to rats undergoing cavernous nerve injury might decrease erectile tissue fibrosis and apoptosis of smooth muscle (52,53,61-64). In this context, Sildenafil administration has been found to affect the expression of several genes involved in smooth muscle preservation and to reduce oxidative stress (32,56,58). Additionally, the administration of PDE5-Is has been proposed to prevent the degeneration of nervous tissue and stimulate neuroregeneration (61,65). Indeed, an increased amount of nerves has been observed after cavernous nerve injury in rats treated with sildenafil compared to their counterparts left untreated (61). Finally, PDE5-Is might also have a role in endothelial cell preservation, conserving platelet endothelial cell adhesion molecule-1 (CD31) and endothelial Nitric Oxid Synthase (eNOS) expression (54,66). On the other hand, human studies evaluating the morphologic changes to cavernous tissue after the administration of Sildenafil in patients treated with RP reported conflicting results, where neither elastic fibers nor connective tissue content substantially changed compared

to preoperative levels (67,68). However, these investigations are limited by the small number of patients evaluated, by heterogeneity in the surgical technique, and by the lack of a control group.

Taken together, the results of these preclinical studies raised the hypothesis that early administration of PDE5-Is might improve EF recovery after RP and inspired the design of several prospective trials. *Table 1* depicts the characteristics and results of studies evaluating the effectiveness of penile rehabilitation protocols based on the administration of four different PDE5-Is (*Figure 2*).

In their pioneering trial, Padma-Nathan *et al.* (51) randomized 76 patients treated with nerve-sparing RP to sildenafil or placebo nightly for 36 weeks followed by a 8-week drug-free period. Interestingly the authors demonstrated that the return to baseline EF was more marked for men treated with PDE5-Is compared to their counterparts receiving placebo. Moreover, the mean Erectile Function domain of the IIEF (IIEF-EF) was substantially higher in the sildenafil group. Finally, nightly administration of PDE5-Is markedly improved nocturnal penile tumescence and rigidity in patients treated with sildenafil (69). Although this study reported encouraging results and introduced for the first time the concept of penile rehabilitation using PDE5-Is, enrolment ceased early owing to interim analyses showing a lower response rate than expected. Moreover, the lack of a group receiving on-demand dosing limits the applicability of these findings. Under this light, it is worth reporting that a recent randomized trial evaluating patients treated with bilateral nerve-sparing robot-assisted RP failed to show statistically significant differences between patients receiving sildenafil on-demand or nightly at 13-month follow-up (45). However, these results are limited by the small number of patients evaluated (n=100), as well as by the lack of a placebo group and the relatively short follow-up period.

A well-performed randomized controlled trial evaluated the efficacy of penile rehabilitation using vardenafil (50). During a 9-month double-blind period, patients were randomized to placebo, nightly 10 mg vardenafil, and on-demand 10 mg vardenafil. Interestingly, on-demand vardenafil treatment resulted in significantly greater IIEF-EF scores and higher response rates to the Sexual Encounter Profile question 3 [(SEP3); "Did your erection last long enough for you to have successful intercourse?"] than placebo over the entire double-blind treatment period. Patients were then evaluated after an additional 2-month washout period. At this time-point EF recovery was not improved by nightly or on-demand vardenafil compared to placebo (*Figure 3*). Similarly, after a 2-month open-label period no statistically significant differences were observed among treatment groups with respect to IIEF-EF score or SEP3 success rates. Of note, the superiority of the on-demand dosing during the double-blind treatment period might be related to the pharmacokinetic of vardenafil, its onset of action, and the half-life of this drug (70,71). Indeed, patients receiving the drug on-demand might have had the full effect of the treatment when needed, while those in the nightly group had an effect so far as their sexual activity coincided with the administration of vardenafil (32). On the other hand, difficulties to reach a steady state with a single daily administration might limit the efficacy of chronic vardenafil dosing in terms of preservation of erectile tissue after surgery.

When evaluating the efficacy of tadalafil in the penile rehabilitation setting, a randomized controlled study failed to show an improvement in penile length and EF recovery after the administration of 20 mg tadalafil 3 times a week for 6 months (72). However, the small number of patients, short follow-up, and excellent postoperative EF-recovery rates in the placebo group raise some concerns regarding the generalizability of these findings. More recently, a larger study by Montorsi *et al.* (48) evaluated the efficacy tadalafil compared to placebo in the recovery of EF after nerve-sparing RP. Patients were randomized to receive 5 mg tadalafil once daily, 20 mg tadalafil on-demand, or placebo. At the end of the double-blind period (9 months), the IIEF-EF score improvement exceeded the minimally clinically important difference in both tadalafil groups. However, only patients treated with tadalafil once daily had a statistically significant difference in the change in IIEF-EF compared to placebo at this time point. Although the IIEF-EF and SEP-3 improved also during the open-label phase of the study exceeding the minimal clinically important difference for all the groups, no differences were observed between patients treated with tadalafil and placebo after open-label treatment (*Figure 4*). When considering the SEP-3 question, only patients receiving tadalafil once daily had a significant improvement compared to their counterparts receiving placebo at the end of the double-blind period and after open-label treatment. However, no significant differences were observed after 6 weeks drug-free washout. Finally, significantly less shrinkage of penile length was observed in the tadalafil once daily group as compared to placebo at the end of the double-blind period. Concluding, the administration of Tadalafil once daily seems

Table 1 Characteristics of studies evaluating phosphodiesterase type-5 inhibitors (PDE5-Is) in penile rehabilitation protocols

First author and year	Design	Population	Drug	Follow-up	Results
Mulhall *et al.* 2005	Single center non-randomized trial	Patients with functional preoperative erections treated early postoperatively (within 6 months) with oral sildenafil (n=58) Non responders were switched to intracavernosal injection therapy (n=74)	Sildenafil	18 months	• 64% patients in the rehabilitation group were responding to sildenafil with erections sufficient for sexual intercourse *vs.* 24% in the no rehabilitation group (P<0.001) • 52% *vs.* 19% patients in the rehabilitation *vs.* no rehabilitation group experienced natural erections • 95% *vs.* 76% patients in the rehabilitation *vs.* no rehabilitation group responded to intracavernous injection therapy
Padma-Nathan *et al.* 2008	Multicenter double blind placebo controlled randomized controlled trial	Four weeks after bilateral nerve-sparing radical retropubic prostatectomy, men with normal erectile function before surgery were randomized to double-blind sildenafil [50 (n=23) or 100 mg (n=28)] or placebo (n=25) nightly for 36 weeks, followed by an 8-week drug-free period before assessment of erectile function	Sildenafil	11 months	• Return to baseline erectile function: 27% *vs.* 4% for patients receiving sildenafil *vs.* placebo, respectively • RigiScan "responders"—100 mg: 33%, 50 mg: 24%, placebo: 5%
Bannowsky *et al.* 2008	Single center non randomized study	41 sexually active patients treated with nerve-sparing radical prostatectomy 23 patients with preserved nocturnal erections received sildenafil 25 mg/day at night. A control group of 18 patients was then followed	Sildenafil	12 months	• Sexual Health Inventory for Men (SHIM) score: 14.1 *vs.* 9.3 in patients treated with sildenafil *vs.* controls • Erections sufficient for vaginal penetration: 86% *vs.* 66% for patients treated with sildenafil *vs.* controls

Table 1 (*continued*)

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First author and year	Design	Population	Drug	Follow-up	Results
Montorsi *et al.* 2008	Multicenter double-blind double-dummy randomized controlled trial	A total of 628 men, aged 18-64 yrs, were randomized to treatment. Study design consisted of a 9-mo double-blind treatment period, a 2-mo single-blind washout period, and an optional 2-mo open-label period Patients received placebo, nightly vardenafil 10 mg, or on-demand vardenafil	Vardenafil	11 months	• On-demand vardenafil treatment resulted in significantly greater IIEF-EF scores and better SEP3 response rates than placebo over the entire double-blind treatment period • No statistically significant differences were observed among treatment groups in the proportion of patients with an IIEF-EF score of ≥22 or in SEP3 success rates after the washout period
Aydogdu *et al.* 2011	Randomized controlled trial	A total of 65 patients underwent bilateral nerve sparing radical prostatectomy Patients were randomized to control without rehabilitation (group 1) or tadalafil 20 mg 3 times a week for 6 months rehabilitation group (group 2)	Tadalafil	12 months	• In group 1 there was significant decrease in penile measurements at month 3 compared to preoperative measurements • At the 12-month follow-up, there were no differences between stretched penile length in the two groups and no significant differences in erectile function between the two groups
Mulhall *et al.* 2013	Double blind, placebo-controlled randomized study	298 patients aged 18 to 70 years with a history of erectile dysfunction of 6 months or more after bilateral nerve-sparing radical prostatectomy Patients were randomized to 100 or 200 mg of avanafil or placebo on demand for 12 weeks	Avanafil	12 weeks	• After 12 weeks there were significantly greater increases in SEP2 and SEP3 and change in mean IIEF-EF domain score with 100 and 200 mg avanafil *vs.* placebo ($P<0.01$) • Following dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful *vs.* 4.5% (2 of 44) for placebo ($P<0.01$)

Table 1 (*continued*)

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First author and year	Design	Population	Drug	Follow-up	Results
Pavlovich *et al.* 2013	Single-institution, double-blind, randomized controlled study	100 preoperatively potent patients with clinically localized prostate cancer treated with nerve-sparing robot-assisted radical prostatectomy Patients were randomized to either nightly sildenafil and on-demand placebo (nightly sildenafil group), or on-demand sildenafil and nightly placebo (on-demand sildenafil group; maximum on-demand dose six tablets/month) for 12 months. Patients then underwent a 1-month washout period	Sildenafil	13 months	• No significant differences were observed between treatments (nightly *vs.* on-demand sildenafil) in terms of postoperative IIEF-EF and return to baseline IIEF
Montorsi *et al.* 2014	Randomized double-blind double-dummy placebo controlled trial	Men ≤68 year of age with prostate cancer (Gleason ≤7) and normal preoperative EF who underwent nerve-sparing RP at 50 centers from nine European countries and Canada (n=423) A 1:1:1 randomization to 9 months of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-week drug-free washout and 3-month open-label tadalafil once daily (all patients)	Tadalafil	13.5 months	• 20.9%, 16.9%, and 19.1% of patients in the tadalafil once daily, on demand, and placebo groups, respectively, achieved IIEF EF scores ≥22 after drug-free washout • At the end of double-blind treatment, mean IIEF-EF score improvement significantly exceeded the minimally clinically important difference (MCID: ΔIIEF-EF ≥4) in both tadalafil groups • For SEP-3 (MCID ≥23%), this was the case for tadalafil once daily only • At the end of double-blind treatment, penile length loss was significantly reduced versus placebo in the tadalafil once daily group only (P=0.03)

MCID, minimal clinically important difference; SEP, Sexual Encounter Profile; IIEF-EF, International Index of Erectile Function-Erectile Function domain.

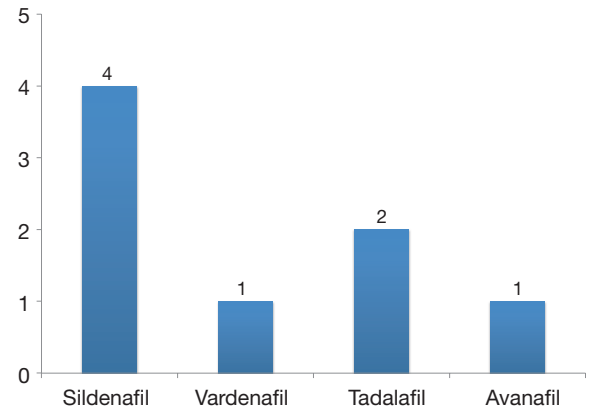

Figure 2 Number of studies assessing the efficacy of PDE5-Is stratified according to the type of drug administered. PDE5-Is, phosphodiesterase type-5 inhibitors.

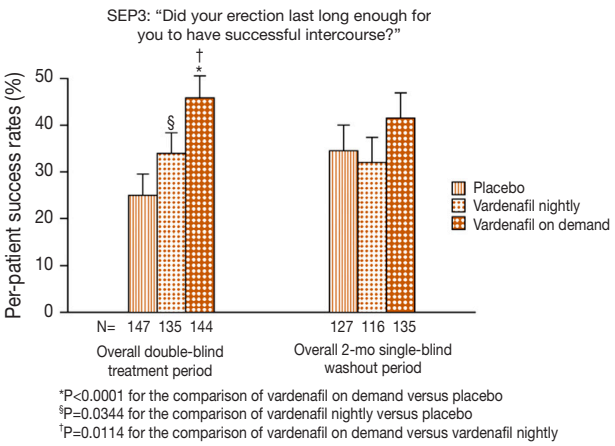

Figure 3 SEP question 3 patient success rates for the overall double-blind treatment and single-blind washout study periods. SEP, Sexual Encounter Profile. Reproduced with permission from Elsevier (50).

to be to be more effective than placebo and on-demand dosing in patients with ED following nerve-sparing RP. Although these results were not maintained at the end of the washout period, the administration of tadalafil once daily might have contributed to the preservation of erectile tissue, preventing alterations to the cavernosal integrity as a sequel of neuropraxia typical of patients undergoing RP (36,39-41). A subanalysis performed in the same cohort by Moncada *et al.* (73) recently demonstrated that the administration of tadalafil once daily significantly shortened the time to EF recovery during the 9-month double-blind treatment period. Additionally, at Cox regression analyses

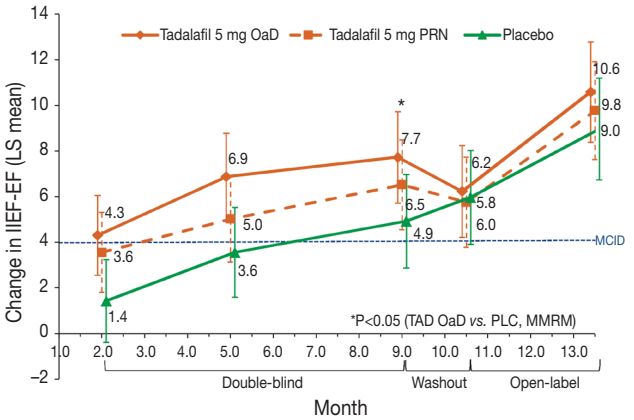

Figure 4 LS mean change in IIEF-EF score over time (error bars present the 95% confidence interval). IIEF-EF, International Index of Erectile Function-Erectile Function domain; LS, least squares; MCID, minimal clinically important difference; MMRM, mixed-effect model for repeated measures; OaD, once a day; PLC, placebo; PRN, on demand; TAD, tadalafil. Reproduced with permission from Elsevier (48).

patients treated with tadalafil once daily had substantially 1.9-fold higher probability of recovering EF after surgery as compared to their counterparts treated with placebo. However, this did not hold true for patients receiving tadalafil on-demand. Of note, the pharmacokinetic profile of tadalafil and his half-life might confer to this molecule the best profile for its use in the rehabilitation setting compared to other PDE5-Is such as sildenafil and vardenafil (70,71,74).

More recently, the efficacy of avanafil in the recovery of EF after RP has also been tested. A randomized trial by Mulhall *et al.* (75) demonstrated that patients receiving 100 or 200 mg avanafil on-demand had substantially higher IIEF-EF and SEP-3 response rates compared to placebo at 12-week follow-up after bilateral nerve-sparing RP. However, the lack of a group of patients receiving avanafil daily precludes a proper generalization of these findings in the penile rehabilitation context.

Taken together, these observations demonstrate that penile rehabilitation might improve postoperative EF in patients treated with nerve-sparing RP for clinically localized PCa (45,48,50,51,69,75). Nonetheless, while basic science studies support the efficacy of PDE5-Is in the preservation of erectile tissues after RP, clinical investigations report contrasting findings. Although chronic administration of tadalafil might represent the best choice in order to prevent alterations to cavernous tissues typical

of patients undergoing RP (48,74), the superiority of this treatment over on-demand administration of PDE5-Is is still debated. Nowadays, none of the available randomized controlled trials definitively demonstrated the superiority of daily administration of PDE5-Is compared to the on-demand dosing. Moreover, the beneficial effects of penile rehabilitation protocols using PDE5-Is compared to placebo do not seem to be maintained after the washout period. Nonetheless, basic science and clinical data support the idea that rehabilitation treatments with PDE5-Is are undoubtedly better than leaving the cavernous tissues untreated after nerve-sparing surgery (49,76,77). Further well-designed and well-performed studies with proper patient selection are needed to finally address this issue (74). Indeed, the main limitations of currently available prospective randomized-controlled trials assessing the efficacy of PDE5-Is in the penile rehabilitation setting reside in the relatively short follow-up period, treatment duration and timing of drug administration, type of PDE5-Is chosen, and stringent selection criteria. Patients receiving PDE5-Is in a penile rehabilitation setting should begin treatment as soon as possible and as close to surgery as possible (31,32,49,78,79). Therefore, future randomized trials should include patients treated as early as the removal of the catheter or during the very first months after surgery (80). Moreover, a recent study demonstrated that a 9-month double-blind treatment period was too short to achieve satisfactory EF recovery in the majority of the patients enrolled (73). Therefore, longer treatments could be considered in future studies. Additionally, tadalafil might have the best profile for its use in the penile rehabilitation setting due to his long half-life (70,71,74). Therefore, future studies might focus on this molecule. Finally, patient selection might play a crucial role in the context of prospective randomized-controlled trials assessing the role of PDE5-Is on EF recovery after surgery. Indeed, the inclusion of best candidates for EF recovery (i.e., younger and healthier patients with lower probability of ED after surgery) might limit the effects of PDE5-Is administration (14-16,74). On the other hand, the maximal effect of chronic use of PDE5-Is might be achieved in patients with less favorable preoperative characteristics (14-16,74). Therefore, future studies should adopt less stringent criteria to evaluate the efficacy of PDE5-Is on EF recovery in these patients.

It should also be noted that a recent study demonstrated that patients receiving PDE5-Is after surgery might be more likely to experience biochemical recurrence compared to their counterparts left untreated (81). However, these data come from one single study and are not fully supported by preclinical evidences (81-85). Moreover, the lack of details on the type of PDE5-Is used, as well as dosing and duration of treatment strongly limits the applicability of these findings. Further well-designed studies are needed to better address this issue.

Intracavernosal injections

Montorsi *et al.* (35) in the year 1997 performed a pioneering study aimed at assessing the efficacy of intracavernosal injections of alprostadil for the recovery of spontaneous erections after nerve-sparing RP. Although the study was partially limited by the relatively small number of patients evaluated, early administration of alprostadil significantly increased the recovery rates of EF after surgery. From a biological standpoint, the administration of alprostadil might result into erections, which improve cavernosal oxygenation and penile stretch, finally resulting into a protective effect on erectile tissues (31). Of note, other non-randomized studies supported the efficacy of intracavernosal injections in the recovery of EF after surgery, even after initial administration of sildenafil (86-88). However, when considering this approach, high patient motivation and adherence to protocol are required to increase the compliance to this treatment modality and minimize the dropout rates (21,86). Concluding, intracavernosal injections might be effective in men who have tried oral agents and their condition has failed to respond. Despite this, evidences supporting the efficacy of intracavernosal injections in a rehabilitation setting are still scarce. Additionally, patient compliance is still sub-optimal. Taken together, these aspects prevent clinicians to routinely recommend the adoption of this treatment modality in penile rehabilitation after RP (49).

Vacuum devices

Vacuum devices create a vacuum around the penis. This results into a transient increase in arterial flow and oxygen supply to the erectile tissues (31,32,36,89). Preclinical studies in rats undergoing cavernous nerve injury demonstrated that VED therapy might facilitate EF recovery after surgery acting both on the preservation of smooth muscle and endothelial integrity via anti-hypoxia, anti-apoptosis, and antifibrotic mechanisms (90). These observations were only in part confirmed by randomized studies comparing EF recovery in patients receiving VED or placebo after nerve-sparing RP (91-93). In their pioneering study, Raina *et al.* (92)

evaluated 109 patients who developed ED after nerve-sparing surgery. The authors demonstrated that early use of VED facilitated early sexual intercourses, sexual satisfaction, and early return of natural erections sufficient for vaginal penetration. More recently, Basal *et al.* (93) randomized more than 200 patients treated with robotic-assisted RP to VED, PDE5-Is alone, VED and PDE5-Is, or placebo. Of note, the authors demonstrated that only PDE5-Is or the combination of PDE5-Is and VED had a beneficial effect on the recovery of EF after surgery. On the other hand, VED alone failed to show a beneficial effect with regards to postoperative EF recovery. These results were limited by the low number of patients and by the heterogeneity in preoperative characteristics, where a non-negligible proportion of these individuals had ED before surgery.

Concluding, VED alone or in association with PDE5-Is might represent a treatment option for penile rehabilitation in patients treated with nerve-sparing RP. However, evidences supporting the efficacy of this approach are scarce. Moreover, large well-designed and performed prospective randomized studies assessing the superiority of this approach compared to PDE5-Is and/or intracavernous injections are still lacking. Lastly, available studies do not support a long-term effect of this approach on postoperative EF recovery. As a consequence, VED is not recommended by clinical guidelines for the recovery of EF after surgery. Despite this, VED might represent a treatment option in selected patients.

Although we comprehensively reviewed the currently available literature regarding the role of penile rehabilitation after RP, our manuscript does not represent a systematic review and/or a meta-analysis. Therefore, it cannot provide the same level of evidence of these types of articles. Meta-analyses of currently available prospective randomized trials evaluating the role of PDE5-Is, intracavernosal injections, and vacuum devices are needed to definitively assess the role these therapies in the penile rehabilitation setting.

Conclusions

Currently available penile rehabilitation protocols are based on the administration of PDE5-Is, intracavernosal injections, and VED. Basic science evidences support the rationale of penile rehabilitation after nerve-sparing RP in patients with clinically localized PCa. However, clinical trials report conflicting results regarding the potential benefit of penile rehabilitation in terms of EF recovery and erectile tissue preservation after nerve-sparing RP. Although rehabilitation, set as early as possible, seems to be better than leaving the erectile tissues unassisted, which is the optimal rehabilitation program still represents a matter of debate.

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Footnote

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