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REVIEW

Current penile-rehabilitation strategies: Clinical evidence

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Abstract We review the current strategies used for penile rehabilitation (PR) after a radical prostatectomy, where PR is defined as the attempt to restore spontaneous erectile function so that the patient can generate erections with no need for erectile aids. We searched PubMed for relevant reports, using the keywords 'radical prostatectomy', 'penile rehabilitation', 'phosphodiesterase inhibitors', 'vacuum erection device', 'injection therapy', 'urethral suppository', and 'erectile dysfunction'. In all, 155 articles were identified and reviewed, and had a level of evidence ranging from 1b-4. The use of PR strategies should be based on the patient's goals after a thorough explanation of realistic expectations, and the risks and consequences of the various treatment options. While a multitude of studies suggest a benefit with PR

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ABBREVIATIONS

PR, penile rehabilitation;
RP, radical prostatectomy;
ED, erectile dysfunction;
PDE-5, phosphodiesterase-5;
IIEF-EF, international index of erectile function-erectile function domain;
CCI, Charlson comorbidity index;
ICI, intracavernous injection;
VED, vacuum erection device;
IUA, intraurethral alprostadil;
SHIM, sexual health in men (questionnaire)

strategies, there are no established, proven regimens. Further research is needed to establish the optimal approaches to PR.

Introduction

The two most common long-term complications after radical prostatectomy (RP) are erectile dysfunction (ED) and urinary incontinence. However, the complication that is perhaps most feared might be ED [1], and the effect of ED on quality of life can be more severe [2]. While in most series the risk of persistent incontinence is low, the risk of ED is much higher, even in the ideal surgical candidate (most urological oncologists choose young, healthy men with no risk factors for ED, who have the greatest ability to recover erections after bilateral nerve-sparing RP). Furthermore, even if erectile function is recovered, it very often is a long, protracted course which can take years. Penile rehabilitation (PR), defined as medical treatment at the time of or after RP to improve the restoration of natural penile mechanics, and which results in spontaneous erectile function [3], is gaining attention, with a variety of strategies using all currently available therapeutic options for ED. The purpose of this review is to describe the available evidence supporting the use of PR, and to describe regimens that might be used.

The rationale for PR

PR is subtly different from the treatment for ED after RP, which is characterised by the administration of medication to achieve a more rigid erection that permits penetrative intercourse. In PR, the goal is to bring about recovery of the erectile mechanism so that, at least ideally, the patient is not dependent on any erectile aid, and hopefully can generate erections as he did before surgery. The goal of the latter treatment, however, is the attainment of a rigid erection. The importance of this distinction cannot be understated, and many patients and clinicians might not fully appreciate the difference.

The rationale for PR is that the ultimate erectile capacity of the penis is compromised as a result of the chronic absence of erections that the patient experiences postoperatively. Due to this inability to achieve erections, the normal cycling of arterial blood flow to the penis is disrupted and results in penile hypoxia, which leads to intracorporal fibrosis [4–6]. In preclinical models of ED after RP, improved oxygenation of cavernosal tissue, either via hyperbaric oxygen administration or phosphodiesterase-5 (PDE-5) inhibitors, yields improved erectile haemodynamics and prevents smooth muscle loss and fibrosis [7–11]. This fibrosis not only directly contributes to the penis being unable to achieve an erect state due to direct penile tissue disruption, but also contributes to veno-occlusive penile dysfunction, characterised by the tunica albuginea of the corporal bodies being unable to expand sufficiently to allow for compression of subtunical venules and blood retention within the penis. Clinically, even in the presence of good arterial penile inflow, this can manifest as the patient being able to achieve, but not maintain, an erection satisfactory for penetrative intercourse. Furthermore, a statistically significantly smaller proportion of patients with veno-occlusive ED subsequently recover functional erections than do patients with arteriogenic ED [12]. As such, even in flawless surgery with perfect nerve-sparing

and preservation of any accessory penile arteries [13,14], the recovery of erections is not guaranteed, as ED after RP is typically multifactorial.

As a result, it is recommended that some form of PR be used after RP, as this '...is undoubtedly better than leaving the erectile tissue to its unassisted, unfavourable fate' [15]. Furthermore, initiating therapy/rehabilitation soon after RP might be better than starting after a delay, although there is currently insufficient evidence to support specific recommendations about timing. Indeed, surveys of clinicians show that >80% recommend some sort of PR to their patients [16,17]. Although all treatment options were used, the most common initial therapy was PDE-5 inhibitors, and treatment was most commonly initiated at catheter removal, and lasted for 12–18 months. Interestingly, 97% of responders in these surveys did not expect full rigidity with PR. For those who do not use PR, the cost, absence of evidence-based therapy, and lack of familiarity with PR were cited as reasons.

Defining the ideal candidate for PR

Who is most likely to benefit from a rehabilitative protocol? Briganti et al. [18] attempted to shed some light on this issue by retrospectively analysing 435 patients who had undergone bilateral nerve-sparing RP, and who were stratified into three groups according to their risk of ED after RP. Low-risk patients were those aged <65 years, had a preoperative International Index of Erectile Function-Erectile Function domain (IIEF-EF) score of >26 and a Charlson Comorbidity Index (CCI) of <1. Those at intermediate-risk were aged 66–69 years, had a preoperative IIEF-EF score 11–25 and a CCI of <1. At high-risk were patients aged >70 years, with an IIEF-EF score of <10 and a CCI of >2. In all groups, treatment with either daily or on-demand PDE-5 inhibitors resulted in a significant improvement in postoperative erectile function as measured by the IIEF-EF. In the intermediate group, daily PDE-5 inhibitor use was associated with a significantly greater erectile recovery at 3 years, whereas for the low- and high-risk groups, there was no difference in erectile recovery between daily and on-demand PDE-5 inhibitor use. These authors showed that any patient might benefit from treatment with PDE-5 inhibitors.

In a similar study [19] trying to address this issue, on multivariate analysis, factors which predicted a lack of success for a PR protocol (in this study consisting of thrice weekly sildenafil to achieve a penetration-rigidity erection for ⩾18 months after RP, with intracavernous injection, ICI, to be used if oral therapy failed) included those aged >60 years, non-bilateral nerve-sparing surgery, the presence of two or more vascular comorbidities (hypertension, dyslipidaemia, coronary artery disease, diabetes mellitus), initiating the PR program >6 months after surgery, lack of response to sildenafil by 12 months after RP, and the need for an ICI Trimix dose of >50 units. Based on these two studies, it appears that several factors, including patient demographics (age), preoperative erectile functional status, comorbid status, type of surgery (nerve-sparing), timing of the initiation of PR, and response to ED therapy, should assist in determining the capacity to respond to a PR protocol.

Options for PR

All currently available non-surgical options for managing ED have been studied for the purpose of PR after RP. These include PDE-5 inhibitors, penile ICI therapy, vacuum erection devices (VED) and intraurethral alprostadil (IUA) suppositories.

PDE-5 inhibitors

Most of the data available on PR address the use of PDE-5 inhibitors [20]. For many practitioners they are considered the first-line therapy for rehabilitative purposes as well as ED, relating to their ease of use and safety [16,17]. Bannowsky et al. [21] showed a benefit for nightly low-dose sildenafil (25 mg) in the recovery of erectile function in patients after nerve-sparing RP in a small study; 43 patients, after catheter removal at 7–14 days from RP, were studied, with 23 patients randomised to sildenafil 25 mg nightly starting the day after catheter removal, and a control group of 18 were followed with no sildenafil administration. The IIEF scores were then recorded at various times after surgery. Over the course of the first year there was a gradual increase in the IIEF scores for patients in both groups. However, in the group on nightly sildenafil there was a significantly higher IIEF score at 36 and 52 weeks after RP than in the controls (9.6 vs. 6.4, 14.1 vs. 9.3, respectively). At 52 weeks, 47% of men taking nightly sildenafil were able to achieve and maintain erections sufficient for intercourse, compared to 28% in the control group ($P < 0.001$). Furthermore, when on-demand sildenafil 50–100 mg was used for patients in both groups, the overall potency of the nightly sildenafil group increased to 86%, compared to 66% in the control group. The conclusion of the authors, that '...daily low-dose sildenafil leads to significant improvement in the recovery of erectile function', is limited by the few patients and the absence of a true control group (i.e. patients administered a placebo).

A higher dose of nightly sildenafil, 50 or 100 mg, and its effect on the recovery of erectile function was assessed by Padma-Nathan et al. [22]. In a randomised, double-blind, placebo-controlled study of men having undergone nerve-sparing RP, patients were assigned to placebo, sildenafil 50 mg or sildenafil 100 mg nightly, commencing 4 weeks after RP for 36 weeks. At 48 weeks, 4% of the placebo group was deemed to have

responded, whereas 26% of those in the sildenafil 50 mg nightly group were responders, and 29% of those in the sildenafil 100 mg group were responders (both $P < 0.05$). Based on these results, the authors concluded that the nightly use of sildenafil markedly increased the return of normal spontaneous erections. However, these conclusions are tempered by the substantial limitations of the study, i.e. the few patients enrolled, the withdrawal rate, the significantly lower placebo response rate than that published in other studies, and the non-validated primary outcome of the study (responders were defined based on individual questions from the IIEF-EF, not the overall score).

Vardenafil had been studied for its efficacy in improving the recovery of erectile function [23]. Of particular importance in this study was that patients had a unilateral nerve-sparing RP, and that there was no significant difference between doses of 5 mg and 10 mg vardenafil on erectile recovery according to the IIEF-5 (equivalent to the Sexual Health in Men, SHIM, questionnaire). The utility of nightly vs. on-demand therapy with vardenafil on the recovery of erectile function after bilateral nerve-sparing RP was assessed [24]. The design consisted of a 9-month double-blind treatment period, a 2-month single-blind washout period and an optional 2 month open-label period, to start within 2 weeks of surgery. The primary outcome measure was the percentage of men with an IIEF-EF score of >22 after the washout period. The intention-to-treat population consisted of 628 men randomised to treatment. Whereas at the end of the treatment period there was a significantly higher proportion of patients with an IIEF-EF score of >22 in the on-demand group, there were no significant differences between on-demand and nightly dosing at the end of the washout period. The authors concluded that these results support a change towards on-demand dosing in a rehabilitative context in men with ED after RP. While certainly interesting, the trial is limited by the potentially inexact definition of potency according to the IIEF-EF, as well as the failure to report the number of tablets consumed in the on-demand group. As such, it is unclear (although unlikely) whether patients in the on-demand group used similar doses to those in the nightly dosing group.

There are no clinical studies specifically addressing the role of tadalafil for PR for the recovery of erectile function after RP.

ICI

Montorsi et al. [25] were the first to conceive of PR, using ICI with alprostadil. In that study, after a bilateral nerve-sparing retropubic RP, 30 men were randomised into two groups, 15 having an injection with alprostadil three times per week for 12 weeks, and 15 being observed only, with no erectogenic treatment. After 6 months, in the control group, only three of the 15 patients had normal erectile function, compared to eight of 12 in the experimental group ($P < 0.01$). Despite there being several notable limitations to this study, including the few patients, no discussion of the preoperative variables of erectile function and patient comorbidities, and despite the claim of 'spontaneous recovery of erections', as erectogenic aids were still required, this served as the basis for further studies assessing PR, using different treatments and protocols for ED. Another study of PR involving ICI assessed the combination of intracavernous alprostadil or triple therapy with sildenafil started at the time of hospital discharge after bilateral nerve-sparing RP [26]. Injections were started within 3 weeks of catheter removal. This early combined therapy was shown to facilitate early sexual intercourse, improve patient satisfaction and possibly promote an earlier return of spontaneous erections in 22 men. Sildenafil was taken daily and the ICI was done two or three times per week until natural erections occurred. The combination also allowed for a lower dose of ICI, which minimised penile discomfort. This study was also limited by the few patients, as well as the absence of a control group.

The VED

The data supporting the use of the VED in the context of PR exceed those available for primary ED treatment. In a pilot study of early use of the VED (starting 1 month after RP, 10 min/day using the device), Köhler et al. [27] showed better erectile function only at 3 and 6 months after RP, according to the IIEF in the treated group (compared to a control group), but they also maintained stretched penile length, which was significantly shorter in the control group. In another prospective study [28], daily VED use (no constriction ring was used, unless attempting intercourse) was compared to no erectogenic treatment in 109 men, starting 1 month after surgery for a total of 9 months. There was a modest benefit in the VED group for vaginal penetration with no erectile aid. While these studies suggest a role for the VED in PR, opponents would argue that because no more than 60% of blood drawn to the penis using a VED is arterial [29], the potential benefit of VED in this context might be limited compared to treatments which target and are meant to enhance penile arterial blood flow, and hence the direct recovery of penile tissue, such as PDE5 inhibitors, ICI or IUA.

IUA

IUA has been shown to be of benefit for PR. In a prospective study of 91 men after bilateral nerve-sparing RP, with a median follow-up of 6 months, 56 men treated with 125 or 250 μg of intraurethral prostaglandin-E1 three times per week, starting 12–15 days after catheter removal, reported higher SHIM scores, and had a higher

proportion recovering spontaneous erections than in the control group who had no PR treatment [30]. Notable was the 32% withdrawal rate for patients in the IUA group. The drawbacks of this study included a lack of intent-to-treat analysis and randomisation, and self-selection of intervention, as well as the absence of a statistical analysis between groups. Another study [31] was a prospective randomised trial comparing nightly IUA vs. sildenafil for PR after RP in 212 patients randomised to receive nightly IUA (initially 125 μg, with titration up to 250 μg at 1 month after RP) or sildenafil. Patients were followed regularly over the first 12 months after RP. By the end of the study period, there were no differences in the IIEF-EF scores or intercourse success rates between the groups. The withdrawal rate for patients in the IUA group was higher than in the sildenafil group (30% vs. 19%), and the drug compliance rate (measured by the dispensed-to-returned medication ratio) was lower (79% vs. 98%). The rationale for the use of a subtherapeutic dose (125 μg) of IUA initially was that higher doses might have led to an unacceptably high withdrawal rate due to local adverse effects. Practically speaking, given the absence of a clear benefit with IUA vs. sildenafil, it seems unlikely that clinicians and patients would elect to pursue nightly IUA for PR when a seemingly more convenient oral therapy gives similar outcomes. Nevertheless, for patients interested in some form of PR, should PDE5 inhibitors be contraindicated due to risk, adverse effect or cost, IUA might be considered.

The various methods of PR after RP are summarised in Table 1.

Issues related to PR protocols

The success of a PR program is not solely defined by the ability of the participants to generate their own erections. Compliance is an important issue to consider; no matter what the potential is for achieving success, should the regimen be too intensive, costly or fraught with too many adverse effects, patients will not adhere to the protocol, with incomplete erectile recovery. In a study of 430 consecutive patients after RP, Polito et al. [32] showed that 36.5% ultimately declined to participate in a PR protocol involving ICI with alprostadil, and of those who participated, 18.6% eventually withdrew from the program, giving a total of 55.1% of the overall patient cohort not participating in their programme. Reasons for declining to participate included the patient's lack of sexual interest (51.6%), lack of interest by the partner (30.2%), and presence of urinary incontinence (26.7%), and reasons for withdrawal after starting the programme included disappointment with treatment efficacy (64.7%), injection pain (45%), and difficulties with or fear of administering the injection by themselves or by the partner (35.2%). Men who declined or withdrew from participation were significantly older, had inferior preoperative erectile function and sustained more adjuvant therapy (androgen deprivation and/or radiotherapy) than those who carried out the program. Although the exact PR regimen with regard to the frequency of injections was not specified, and notwithstanding that these results might not be generally applicable to other PR regimens (especially with other ED treatments), the important point of this study is that compliance with PR is an important issue to consider.

Another issue that must be considered is whether PR is cost-effective. Although the cost of the use of these therapies has not been studied specifically in the context of PR, their cost in treating ED has been examined, with undecided results, with up to 10-fold differences, depending on the analysis [33,34]. The reasons why an exact cost estimate cannot be ascribed to ED therapy are many, and include dated cost estimates from older studies, the upsurge in ED treatment use over time, the inability to capture the opportunity cost of how ED affects other aspects of life (such as other health problems, i.e. depression, relationship discord, and time missed from work) and the limitations of the various methods of answering the question (retrospective claims analyses, decision-analytical models). Furthermore, most patients must cover most, or at times, all of the costs associated with ED treatment themselves. For example, in the USA, ≈60% of sildenafil prescriptions are paid by the patient [35]. As such, many of the expenses associated with ED therapies are not even accounted for in these studies. Therefore, while an exact monetary figure cannot be estimated for the different therapies, either for primary ED treatment or PR, the socio-economic impact on the patient, as well as on society, is not negligible, and should at least be considered when prescribing these therapies. Indeed, while the cost of therapy was not cited as a reason for refusal or withdrawal from PR in the study discussed above [32], in our anecdotal experience, for some patients, the continued cost of both oral and injectable therapies, and even the one-time cost of a VED, have been cited as reasons for not pursuing PR after RP.

While the myriad of studies previously discussed allude to the beneficial effect of some sort of PR regimen, more research in the field is still needed. There has been no randomised trial comparing different PR protocols. It is not known which ED treatment (if any) is best, and for each method what the optimal timing, dose, frequency and duration of therapy is, respectively, to achieve maximum erectile recovery. Furthermore, as implied by the study of Montorsi et al. [24], perhaps on-demand therapy, if the patient is motivated and engages in attempted sexual intercourse frequently enough (ample frequency itself not being adequately defined as of yet), is sufficient to rehabilitate erectile function after RP. If so, this might be of interest to patients, as it enables them to not have to rely on a daily dose of

Table 1 A summary of PR strategies.

Treatment	Dose	Regimen	Duration	Success	Level of Evidence	Ref.
Sildenafil	25 mg	Nightly, starting the day of catheterremoval	52 weeks	Improvement in IIEF-5	2b	[21]
Sildenafil	50–100 mg	Nightly, starting 4 weeks after RP	36 weeks	Improvement in spontaneous EF and satisfaction	2b	[22]
Vardenafil	10 mg nightly 5/20 mg on-demand	Nightly vs. on-demand	9 months	No difference in IIEF-EF between nightly vs. on-demand	1b	[24]
Alprostadil ICI	Optimised per patient (2.5–14 μg, mean 8 μg)	3 Times weekly, starting 1 month after RP	12 weeks	Recovery of spontaneous erections	2b	[25]
Alprostadil/ trimix ICI + sildenafil	1–4 μg 20 U 50 mg	Injections 2–3 times weekly; sildenafil daily at hospital discharge	6 months	50% patients recovered partial spontaneous erections	4	[26]
VED	Not specified	Daily starting 2 weeks after surgery	9 months	Improvement in IIEF-5 in the early daily VED use	2b	[28]
MUSE	125 μg with Possible titration to 250 μg	3 times weekly starting 3 weeks after RP	9 months	Improvement in SHIM	4	[30]
MUSE (vs. sildenafil)	125 μg (vs. 50 mg)	Nightly starting within 1 month of RP	9 months	No difference in recovery MUSE vs sildenafil groups	4	[31]

medication, and limits the cost and possible adverse effects of the therapy. Indeed, patient (as well as partner) motivation has been noted to be a key factor in determining the type of PR protocol in which to enlist the couple [36].

In all likelihood, there is no single PR protocol that will be definitely shown to be superior to all others; more likely, therapy will have to be tailored to patients, based on their goals, expectations, motivation, socio-economic and relationship status, medical comorbidities and need for any adjuvant cancer treatment, which in turn can also affect erectile and sexual function. The optimal strategy, customised to the individual patient, will probably involve not just one drug, but several treatments, which might include a cocktail of medications, the application of devices, and lifestyle modifications in both the peri- and postoperative periods to maximally enhance erectile recovery. The physiology of human erection is complex, and integrates neural, vascular, endocrine and psychological components to achieve the end result. All of these might be exploited using available and yet-to-be-defined therapies to achieve erectile recovery after RP.

Overall, when counselling patients and their partners about the prospect of PR after RP, many factors should be considered, i.e. patient-related (pre-existing comorbidities, motivation, recovery from surgery), partner-related (presence or absence of a regular sexual partner, motivation, partner comorbidities which may preclude regular sexual attempts, motivation) and disease-related (pathological stage and need for adjuvant therapy). As in other aspects of managing ED after RP, managing the expectations of the patient and partner is critical, and the provision of reliable and honest data is important for patients to make their best informed decision about participating in a PR protocol.

Conclusion

ED is a common adverse effect of RP, the effects of which can be severe for both patient and partner. With the concept of PR, erectile function independent of the need for erectile aids might be re-established. When counselling patients about treatment options, realistic expectations should be provided, and treatment for patients should be selected based on the best chance for their success in realising patients' goals. More research is needed to better define the concepts of erectile functional recovery and PR.

Conflict of interest

None.

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