Erectile preservation following radical prostatectomy

Ther Adv Urol
(2011) 3(1) 35–46
DOI: 10.1177/1756287211400492

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***Abstract*:** Prostate cancer is the most common cancer among men, representing approximately 25% of all new cancer diagnoses in the USA. For clinically localized prostate cancer, the gold standard for therapy remains radical prostatectomy. One of the main adverse effects of this procedure is erectile dysfunction, which can have a significant impact on the patient's quality of life. There are several mechanisms of erectile dysfunction postprostatectomy, including arteriogenic, venogenic and neurogenic types, as well as the potentially heightened risk of postprostatectomy patients to develop Peyronie's disease. The purpose of this review is to explain the various treatment options available, including phosphodiesterase type 5 inhibitors, intracavernosal injections, intraurethral alprostadil suppositories, vacuum erection devices, and penile prostheses. The role of these therapies in an erectile-dysfunction-treatment function, as well as in penile rehabilitation, will be discussed. Finally, a review of research on novel therapies will also be presented. A comprehensive literature review was performed using the PubMed database. Articles were chosen based on topical relevance and assessed for methodology and major findings. There are data to support the use of each of the therapeutic options in both treatment and rehabilitative roles. More study is needed, however, specifically in regard to penile rehabilitation, to confirm its benefits, as well as to determine optimal rehabilitation protocols.

***Keywords*:** erectile dysfunction, penile rehabilitation, prostate cancer, radical prostatectomy

Introduction

Prostate cancer is the most common cancer among men, representing approximately 25% of all new cancer diagnoses in the USA [Jemal *et al.* 2009]. For clinically localized prostate cancer, the gold standard for therapy remains radical prostatectomy (RP), with proven improvement in overall survival in properly selected patients when compared with watchful waiting [Bill-Axelson *et al.* 2008; Holmberg *et al.* 2002]. More recently, the trend has been an increasing use of minimally invasive techniques for prostate extirpation [Hu *et al.* 2008a, 2008b], with similar outcomes to open RP with respect to postoperative general medical and surgical morbidity [Lowrance *et al.* 2010].

The major urological complications of this procedure are incontinence and erectile dysfunction (ED). With respect to open *versus* minimally invasive techniques, despite a demonstrated decrease in postoperative hospital stay, it was shown that the risk of incontinence and ED with minimally invasive techniques may not be improved over open surgery [Hu *et al.* 2009]. Furthermore, it has been shown that the impact of sexual dysfunction is greater than that of incontinence [Arai *et al.* 1999], and can have a significant negative impact on quality of life [Litwin *et al.* 1999]. This is despite an improved understanding of penile autonomic innervation as well as prostatic anatomy [Walz *et al.* 2010], which has led to refinements in surgical technique [Walsh and Donker, 1982].

The reported incidence of ED following RP is as high as 90% in contemporary series [Mulhall and Morgentaler, 2007]. Delayed recovery of erectile function (EF) is a frequent occurrence; it can take up to 3 years for the return of partial erections, if at all [Burnett, 2005]. The purpose of this review is to describe the etiology of post-RP ED and to explain the various treatment options, including the possible roles of novel therapies

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currently under study, for this common and feared problem.

Etiology

There are several underlying mechanisms of ED post-RP, which have been explored in both animal and human studies. Arteriogenic ED appears to result from transection of accessory or aberrant pudendal arteries, which can be the sole arterial supply to the corpora cavernosa unilaterally or bilaterally. They are present in up to 75% of men, and can occupy a lateral or apical position [Walz *et al.* 2010]. Preservation of these vessels may lead to improved outcomes [Rogers *et al.* 2004].

Venogenic ED is based on corporal smooth muscle fibrosis, with evidence of increased expression of profibrotic cytokines, such as transforming growth factor beta, which lead to heightened collagen expression [Leungwattanakij *et al.* 2003]. If as a result of this collagenation the corporal smooth muscle cannot expand sufficiently to allow for compression of subtunical venules, then venous leakage will occur. As demonstrated with Doppler penile ultrasound or dynamic infusion cavernosometry and cavernosography (DICC), the risk of venous leakage following RP, which increases over time with a peak at 12 months postoperative, is up to 50% [Mulhall *et al.* 2002]. Furthermore, a statistically significantly smaller proportion of patients with venogenic ED subsequently recover functional erections compared with arteriogenic ED.

Peyronie's disease has been noted to be more common in men post-RP than in the general population, with an incidence of almost 16% [Tal *et al.* 2010]. Risk factors for Peyronie's development in post-RP patients include younger age and Caucasian race. In patients with Peyronie's disease, the risk of ED is up to 50% [Bella *et al.* 2007]. While a direct link between the surgery itself and the subsequent development of Peyronie's has not been found, it has been speculated that penile curvature results from attempts at intercourse with a relatively flaccid penis, with ensuing tunical injury and scarring.

A hypogonadal-state postbilateral cavernous nerve injury has been demonstrated in a rat model [Vignozzi *et al.* 2009]. Following administration of testosterone in hypogonadal rats, some aspects of ED, including collagenization of penile smooth muscle and endothelial dysfunction, were improved.

Finally, neural injury may result following cavernous nerve traction or dissection, in addition to transection. Any neural trauma can lead to reduction in nitric oxide synthase-producing nerves [Carrier *et al.* 1995], as well as corporal smooth muscle atrophy and fibrosis [User *et al.* 2003]. The delay in return of EF post-RP may reflect a healing neuropraxia. The result of all of these combined issues is failure to achieve regular cavernosal cycling between the flaccid and erect states, which may lead to further cavernosal smooth muscle structural damage [Mooreland, 1998].

Clinical options

Once the diagnosis of ED post-RP is reached via patient history, use of sexual-function questionnaires, such as the International Index of Erectile Function (IIEF) and/or more elaborate testing, such as penile Doppler ultrasonography or DICC, there are several treatment options available to the patient that must be discussed. They range from medical, to more invasive self-administered therapies, to surgical means of therapy. Each of the options should be presented to the patient, with realistic goals and expectations enumerated. The pros and cons of each therapy should be explained, with a thorough understanding of the risks associated with each therapy.

There is strong support for some program of post-RP penile rehabilitation, defined as medical treatment at the time of, or after, RP to improve the restoration of natural penile mechanics, which results in spontaneous EF. This is in contrast to therapy for the treatment of ED post-RP, characterized by the administration of medication that enables penetrative intercourse with a sufficiently hard erection. As will be demonstrated in subsequent sections of this review, examples of penile rehabilitation regimens have been proposed for each of the ED therapies post-RP.

The rationale is that as with other muscles, there is a 'use it or lose it' component of the erectile capacity of the penis. This may be due to either a chronic absence of erections postoperatively (due to sexual inactivity as the patient recovers from his surgery or the inability to achieve erections), or penile hypoxia (secondary to interruption of the penile arterial inflow), which may lead to

intracorporal fibrosis [Iacono *et al.* 2005]. Animal studies have shown that improved oxygenation (via administration of hyperbaric oxygen) of corporal tissues yields improved EF recovery after cavernous nerve injury [Muller *et al.* 2008]. Furthermore, administration of phosphodiesterase (PDE) inhibitors to rats following cavernous nerve injury improves erectile hemodynamics and cavernous smooth muscle-to-collagen corporal ratios [Kovanecz *et al.* 2008a, 2008b; Ferrini *et al.* 2006].

As is evident from the landmark clinical study of Montorsi and colleagues, who were the first to conceptualize penile rehabilitation by revealing the benefit of intracorporal alprostadil injections to ameliorate erectile recovery post-RP, in the control group, only 3 out of 15 (20%) patients had normal EF 6 months postoperative, compared with the experimental group (8/12, 67%, $p < 0.01$) [Montorsi *et al.* 1997]. Although the sample size was not large and preoperative parameters of EF were not mentioned, this underscores that the likelihood of spontaneous recovery of erections is not high (at least immediately postoperatively), and as such means to enhance EF should be pursued and encouraged.

Phosphodiesterase type 5 inhibitors

PDE type 5 (PDE5) inhibitors are considered first-line therapy for post-RP ED. The dosing is oral, and the instructions for patients to take them are fairly straightforward, which makes them ideal as a therapy. There are different strategies of employing them, with goals ranging from erection facilitation (ED treatment) to erection priming/conditioning (penile rehabilitation). The use of PDE5 inhibitors, however, supposes that there is an intact cavernous nerve supply to the penis, as they function to increase cyclic guanosine monophosphate levels, promoting cavernous smooth muscle relaxation, via the production of nitric oxide by neuronal nitric oxide synthase (required for the initiation of erection) [Hatzimouratidis *et al.* 2009]. Interestingly, the benefits have even been noted in patients who had undergone non-nerve-sparing surgery, suggesting nonneuronal stimulation of nitric oxide production via endothelial nitric oxide synthase [Garcia-Cardoso *et al.* 2010].

Several studies have been carried out exploring the potential role of penile rehabilitation using PDE5 inhibitors. Bannowsky and colleagues showed a benefit of nightly low-dose sildenafil in recovery of EF in patients following nerve-sparing RP [Bannowsky *et al.* 2008]. Twenty-three patients were administered sildenafil 25 mg nightly and a control group of 18 patients was followed without sildenafil administration. IIEF scores were then measured at 6, 12, 24, 36, and 52 weeks after surgery. Over the course of the first postoperative year, there was a gradual increase in the IIEF scores for patients in both groups. In the nightly sildenafil group, however, there was a significantly higher IIEF score at 36 and 52 weeks postoperative. At 52 weeks, 47% of men taking nightly sildenafil were able to achieve and maintain erections sufficient for intercourse, compared with 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 with 66% in the control group. The authors concluded that daily low-dose sildenafil in the presence of nocturnal erections led to an improvement in the recovery of EF, and they insinuated that nocturnal tumescence should be a criterion for initiation of penile rehabilitation with PDE5 inhibitors.

A higher dose of nightly sildenafil, 50 or 100 mg, and its impact on recovery of EF was assessed by Padma-Nathan and colleagues. In a randomized 1 : 1 : 1 fashion, double-blind, placebo-controlled study of men undergoing nerve-sparing RP, patients were assigned to placebo, sildenafil 50 mg or sildenafil 100 mg nightly commencing 4 weeks postoperatively for 36 weeks. Normal EF was defined as a score of ≥ 8 on IIEF questions 3 and 4, as well as an affirmative answer to the question: 'over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?'. 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 nightly use of sildenafil markedly increased the return of normal spontaneous erections [Padma-Nathan *et al.* 2008]. The limitations of the study, namely the low number of patients enrolled, the dropout rate and the significantly lower placebo response rate than that published in the literature, curb the potential generalizability of these results.

The efficacy of vardenafil in treating erectile dysfunction post-RP has been assessed [Nehra *et al.*

2005]. In this study, 440 patients who previously had undergone nerve-sparing RP between 0.5 and 5 years before (mean 1.7 years) enrollment were randomized to placebo, vardenafil 10 mg or vardenafil 20 mg to take in an on-demand fashion for 12 weeks after a 4-week treatment-free screening period. At the end of the study period and a 7-day follow-up and assessment period, the patients in the vardenafil groups had significantly higher scores in IIEF intercourse satisfaction, orgasmic function, and overall sexual satisfaction domains, as well as erection hardness scores, compared with placebo. Additionally, vardenafil 20 mg was also noted to lessen depressive symptoms as measured by the Duke Health Profile. While these results demonstrate the benefit of vardenafil for ED treatment post-RP, they do not shed light on the rehabilitative benefits, if any, of the medication.

A landmark paper by Montorsi and colleagues comparing the utility of nightly *versus* on-demand therapy with vardenafil on EF recovery following nerve-sparing RP was published in 2008 [Montorsi *et al.* 2008]. The study 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 subjects with an IIEF-EF score of $\geq$22 after the washout period. The intention-to-treat population consisted of 628 men randomized to treatment. Whereas at the end of the treatment period there was noted to be a significantly higher proportion of patients with IIEF-EF $\geq$22 in the on-demand group, there were no significant differences between on-demand and nightly dosing at the end of the 2-month washout period. The authors concluded that these results support a paradigm shift toward on-demand dosing in a rehabilitative context in men post-RP. This could be of interest to patients who wish to maintain sexual activity following surgery. It enables them to not have to rely on a daily dose of medication, and limits the cost of the therapy. While definitely interesting, the trial was limited by the failure to report the number of tablets consumed in the on-demand group. As such, it is unclear whether patients in the on-demand group used similar doses to those in the nightly dosing group.

The effect of tadalafil, the longer-acting PDE5 inhibitor, on ED therapy post-RP was studied by Montorsi and colleagues. In this placebo-controlled, double-blind, randomized study, 303 men were studied for 12–48 months following bilateral nerve-sparing RP [Montorsi *et al.* 2004]. They were randomized in a 2 : 1 fashion to receive either tadalafil 20 mg on demand ($n = 201$) or placebo ($n = 102$) for 12 weeks after a 4-week, treatment-free run-in period during which baseline erectile function and eligibility for the study (at least four sexual intercourse attempts in 4 weeks) were established. At the conclusion of the study period, the patients in the tadalafil group had a statistically significantly higher IIEF-EF score and reported a higher proportion of successful penetration and intercourse attempts ('yes' answers to Sexual Encounter Profile questions 2 and 3). The authors thus concluded that tadalafil 20 mg is an efficacious and well-tolerated treatment for ED post-RP. While these results seem valid, it must be emphasized that they were viewed in a treatment, and not a rehabilitative, framework, and the role of tadalafil in terms of penile rehabilitation clinically is still to be determined.

In summary, PDE5 inhibitors have proven to be effective in the treatment of post-RP ED. With respect to penile rehabilitation, the contrasting results of the trials of Padma-Nathan and colleagues and Montorsi colleagues have brought into question the success of this intervention in general and its role with PDE5 inhibitors in particular [Montorsi *et al.* 2008; Padma-Nathan *et al.* 2008]. Until further prospective, randomized, double-blind, placebo-controlled studies further assessing penile rehabilitation are performed, evaluating efficacy, long-term benefit, agent, dose, timing, schedule, and inclusion criteria conclusions remain limited.

Intracorporeal injection therapy

Intracorporeal injections (ICIs) with alprostadil, a synthetic prostaglandin E1 (PGE1) derivative, either alone or in combination with papaverine and/or phentolamine, are effective treatments for ED.

In terms of ED therapy, Ciaro and colleagues retrospectively showed that men post-RP with normal erectile function preoperatively, among whom over 40% had failed prior ED treatments, had good success with ICIs (alprostadil, papaverine, and phentolamine-triple therapy) [Ciaro *et al.* 2001]. Success, defined by ability to engage in sexual intercourse with a hard erection, was achieved in 94.6% of patients. In a study

assessing long-term efficacy and compliance with ICIs, Raina and colleagues showed that one third of men post-RP who presented with ED (102/306) chose ICIs (either alprostadil alone, or low-dose or high-dose triple therapy) as first-line therapy [Raina *et al.* 2003]. Of these, 48% (49/102) continued long-term therapy (mean 3.7 years), with significant increases in Sexual Health Inventory in Men (SHIM) (analogous to IIEF-5) scores compared with preoperative scores. Furthermore, the total SHIM scores during ICI therapy were similar to preoperative scores. Reasons for discontinuation included insufficient erections in 33%, preference for oral therapy in 32%, fear of injections in 11%, troublesome procedure in 8%, priapism in 1%, and return of natural erections in 1%. When the combination of ICI alprostadil (15 or 20 μg) and PDE5 inhibitors (sildenafil or vardenafil) was employed in patients who were not completely satisfied with PDE5 inhibitors alone (eight doses of oral therapy maximum), 68% (22/32) reported an improved erection based on SHIM scores [Mydlo *et al.* 2005]. They also reported that the use of ICIs was helpful in the maintenance of PDE5 inhibitor effectiveness, and 36% of patients were able to decrease to intermittent from regular ICI use after 7 months of therapy as their erections were adequate with intermittent ICI and regular PDE5 inhibitor use. Conclusions based on these studies are limited because of their retrospective natures, small patient numbers, absences of control or placebo groups for comparison, and unspecified lengths of follow up.

With respect to the role of ICIs in penile rehabilitation, beyond Montorsi and colleagues' initial experience in 1997, early combination of ICI alprostadil or triple therapy with sildenafil started at the time of hospital discharge following RP was assessed [Nandipati *et al.* 2006; Montorsi *et al.* 1997]. It was shown to facilitate early sexual intercourse, improve patient satisfaction and possibly promote earlier return of spontaneous erections in 22 men. Sildenafil was taken daily and the ICIs were carried out 2–3 times per week until natural erections occurred. The combination also allowed for a lower dose of ICIs, which minimized penile discomfort. This study was limited by the small patient number as well as the absence of a control group.

ICIs with PGE1, papaverine, phentolamine, or combinations thereof at doses based on patient response in a monitored setting are quite successful at achieving erections for men with post-RP ED, especially in men for whom cavernosal nerve-sparing surgery could not be achieved. This strategy is effective for men who have tried and failed oral agents. Some evidence exists of the benefit of ICIs in a rehabilitative setting; however, the studies were small and uncontrolled, which prevents definitive conclusions from being reached.

Intraurethral alprostadil suppositories

Intraurethral alprostadil suppositories (IUAs) have been shown to be an effective treatment for organic ED [Padma-Nathan *et al.* 1997]. As such, studies have been performed to evaluate its effectiveness for treatment of post-RP ED. Costabile and colleagues demonstrated a significantly higher rate of erections resulting in sexual intercourse at least once in 126 men who took IUAs (57.1%; 125–1000 μg) compared with 137 who were given placebo (6.6%) [Costabile *et al.* 1998]. There was an overall success rate (likelihood of treatment resulting in intercourse) of 40% in men taking IUAs, and the proportion of administrations of the medication that resulted in intercourse increased over time, from 63% in the first month of therapy to 73% by the third month. Although the success of the treatment was statistically significantly lower in post-RP ED patients compared with other etiologies of ED (57.1% *versus* 67.8%, $p < 0.001$), the authors felt that IUAs were able to circumvent the neurovascular deficit induced by the surgical trauma effectively, allowing them to conclude that this was an effective means of post-RP ED therapy. The main adverse effects included penile and urethral pain.

Raina and colleagues assessed prospectively whether early initiation of IUAs can be of benefit in a penile rehabilitation capacity and studied its impact on time to erectile recovery [Raina *et al.* 2007]. Fifty-six patients were started on a regimen of on-demand use of IUAs three times per week starting at a mean of 12–15 days after catheter removal. They were compared with 35 control patients who sought no early treatment to facilitate erectile recovery. At 9 months, the compliance in the IUA group was 68%, with reasons for discontinuation being lack of efficacy/insufficient erections in half of those who stopped early, and adverse effects of the medication (urethral pain or burning) in 22%. However, for those who completed the study, 28 out of 38 (74%) were able to achieve erections satisfactory for

vaginal intercourse, with the SHIM score post-IUA use being significantly higher than that prior to treatment. Of these patients, 75% reported spontaneous recovery of erections sufficient for satisfactory intercourse 'almost always'. In addition, the SHIM score was higher in IUA users *versus* controls, allowing the authors to conclude that use of IUAs may lead to earlier recovery of erections if started immediately postoperatively. Finally, they found that there were no differences between the 125 and 250 μg groups. It was recognized that patients were not randomized to treatments and self-selection of intervention with lack of intent-to-treat analysis bias results.

McCullough and colleagues were the first to perform a prospective randomized trial comparing nightly IUAs *versus* sildenafil for post-RP penile rehabilitation [McCullough *et al.* 2010]. In a 2 : 1 fashion, 212 patients were randomized to receive nightly IUAs (initially 125 μg, with titration up to 250 μg at 1 month postoperative) or sildenafil, and were followed up regularly over the first 12 postoperative months. By the end of the study period, there were no differences noted in the IIEF-EF scores or intercourse success rates between the two groups. Notably, the dropout 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 may have led to an unacceptably high dropout rate due to local adverse effects, but there was no explanation as to why the titration was performed.

In a nonrandomized, open-label study examining the benefit of combination sildenafil and IUAs in patients who were unhappy with EF responses to 100 mg of sildenafil alone following nerve-sparing RP, Raina and colleagues found that the combination was indeed superior to sildenafil alone [Raina *et al.* 2005b]. With a regimen of 100 mg sildenafil 1 h prior to intercourse and 500 μg IUA immediately prior to intercourse, 83% (19/23) patients reported higher IIEF-5 scores and erection rigidity scores after taking the combination.

In summary, it is unclear that there is a benefit in administration of IUAs in a penile rehabilitation capacity. The success in a salvage context for ED therapy when PDE5 inhibitors have failed is suggested but not proved. These studies were limited, however, by their small subject enrollments, as well as the fact that there is not one proven rehabilitation regimen that is proven superior. As such, while IUAs seemingly can be used to treat ED post-RP, further studies are required to clarify its place as rehabilitation therapy.

Vacuum erection devices

Vacuum erection devices (VEDs) are an attractive option for certain men with ED. They function through the creation of a vacuum around the penis, which leads to an erection by engorgement of penile tissue, thereby not relying on the neurogenic and vasculogenic mechanisms of erectogenesis. The devices are easy to use, have few contraindications to their use (such as intermittent priapism and bleeding disorders), require no testing prior to use, and can be used when other modalities have failed. Although the erections achieved with VED use are different from 'natural' erections (i.e. softer, cooler with penile numbness and bruising), the reported satisfaction rates are up to 92% [Lehrfeld and Lee, 2009].

There are few studies examining VED use specifically after RP. A pilot study of 28 men randomized to either early daily VED use for 10 min/day starting 1 month postoperatively for 5 months or on-demand VED use after 6 months was performed [Kohler *et al.* 2007]. IIEF-5 scores were significantly higher ($p < 0.05$) at both 3 and 6 months in the daily VED use. Furthermore, stretched penile length was maintained after daily VED use, whereas it was significantly decreased, by approximately 2 cm, in the control group at 3 and 6 months. The authors concluded that early initiation of daily VED use improves early sexual function and aids to preserve penile length.

Another open-label study by Raina and colleagues prospectively compared daily VED use (no constriction ring unless attempting intercourse) *versus* no erectogenic treatment in 109 men starting at 1 month following surgery for a total of 9 months [Raina *et al.* 2006]. A modest benefit of men capable of vaginal penetration without erectile aid compared with the placebo group (17% *vs.* 11%) was noted. Perhaps most importantly, the results were not affected by whether or not the surgery was nerve sparing. The dropout rate (18% in the VED group at

3 months) was not insignificant, which may have impacted on the final success rates given the absence of an intent-to-treat analysis.

Assessing a subset of patients from the aforementioned study, Raina and colleagues showed that in patients in whom VED alone was insufficient for sexual function, the addition of 100 mg sildenafil 1–2 h prior to VED use significantly improved the erectile function (as measured by the IIEF-5 questionnaire) [Raina *et al.* 2005a]. In addition, the penile rigidity score improved significantly with the combination compared with VED alone, as perceived by both the patient as well as the partner. The study was limited by the small number of patients included (31), with a dropout rate of 22%.

Although the number of studies is limited in this patient population, it seems that VEDs may offer some benefit in terms of penile rehabilitation post-RP, although any conclusions must be tempered given the small numbers of patients in the studies, and the lack of agreement on a standard rehabilitation program. It appears that patients who have undergone non-nerve-sparing surgery in particular can be aided with VEDs, and the combination of a VED and sildenafil may be better than a VED alone in those who do not respond to a VED alone.

Penile prostheses

Penile prostheses are typically reserved for those patients who have no interest in, or more commonly, fail medical therapy after a reasonable trial period. Most practitioners will attempt previously discussed therapies as initial therapies for postprostatectomy ED given their efficacies and less invasive natures.

A recent study [Salonia *et al.* 2008] revealed that of those men who opted to start a regimen of ED therapy post-RP (either on-demand or daily PDE5 inhibitor use), the overall treatment discontinuation rate at 18 months postsurgery was 73%. Reasons for discontinuation included treatment effect below expectation (with or without dose titration) in 84% and loss of interest in sex (either patient or partner) in 16%. Interestingly, the high cost and side effects of medication were not cited as reasons by any patient. This underscores that in patients in whom interest in maintaining sexual activity is a consideration, use of penile prostheses can significantly contribute to an improved quality of life [Hassan *et al.* 2008].

In an analysis of SEER-COST data, it was found that 50% of men post-RP elected to try ED therapy, with 1.9% undergoing insertion of penile prosthesis, the least commonly used therapy. It was, however, reported to be the most helpful ED treatment [Stephenson *et al.* 2005].

The different penile prostheses available for implantation include noninflatable and inflatable devices. Noninflatable devices are less costly and less prone to malfunction. They are, however, at greater risk for erosion and may lead to higher patient discomfort due to the constant erect state [Lane *et al.* 2007]. Inflatable devices can come in two-piece or three-piece configurations, with the latter having a fluid reservoir that can be implanted in an epigastric, subcutaneous, subrectus, or retroperitoneal location.

A study conducted by Ramsawh and colleagues examined the benefits of simultaneous placement of penile prosthesis at the time of RP [Ramsawh *et al.* 2005]. The patients who opted for this procedure reported greater overall quality of life, EF, and more frequent sexual contact than those who underwent RP alone. The authors conclude that this may be a good option for patients in whom nerve-sparing surgery would not be feasible.

Investigational prospects

Gene therapy

Gene therapy has been proposed as a novel treatment for ED, especially in those men who are refractory to PDE5 inhibitors. Multiple preclinical studies have confirmed its feasibility, and there are numerous candidate genes that can be targeted, depending on the underlying etiology of the ED, from nitric oxide-mediated genes, to ion channels to a variety of growth factors [Kendirci *et al.* 2006; Yoshimura *et al.* 2010]. Better understanding of the physiology of erection, the pathophysiology of ED, and the principles of gene therapy and the technology required to transfer has enabled progress in this field. A clinical trial targeting a potassium channel in the cavernous smooth muscle for treatment of diabetes-related ED has been performed [Melman *et al.* 2005].

With respect to ED secondary to cavernous nerve injury, the presumed primary mechanism for post-RP ED, gene therapy seemingly would have to target the expression of neurotrophic factors to promote neuron survival or stimulate regeneration of affected neurons regulating EF.

Multiple options have been explored. In a study on rats after cavernous injury induced by freezing, the brain-derived neurotrophic factor gene was transfected via intracavernosal injection of adeno-associated virus vector [Bakircioglu *et al.* 2001]. At 4 and 8 weeks posttransfection, higher intracavernosal pressure (ICP) during cavernous nerve stimulation was noted, as well as greater neuronal nitric oxide synthase staining in major pelvic ganglion neurons compared with the control group. Similar studies were also conducted utilizing glial cell-derived neurotrophic factor (GDNF) and neurturin, with herpes simplex virus vector-mediated delivery around damaged cavernous nerves [Kato *et al.* 2009, 2007]. Delivery occurred in approximately 60% of major pelvic ganglia cells, and ICP during cavernous nerve stimulation in the GDNF and neurturin groups were significantly higher than in controls after 4 weeks. These measurements, however, did not reach the control levels measured prior to cavernous nerve injury.

Erythropoieitin

Erythropoietin (EPO) is a cytokine that stimulates erythropoiesis under hypoxic conditions [Koul *et al.* 2007]. EPO and its receptor have been found abundantly within both the central and peripheral nervous systems [Campana and Myers, 2001; Marti *et al.* 1996], and exogenous administration of EPO in animal models of neural degenerative disease as well as toxic insults to the brain, spinal cord, and sciatic nerve has demonstrated attenuated neuronal damage and hastened functional nerve recovery [Erbayraktar *et al.* 2003; Celik *et al.* 2002; Brines *et al.* 2000]. A recent trial demonstrated the efficacy of recombinant human EPO in recovery following acute ischemic stroke in humans [Ehrenreich *et al.* 2002].

EPO as a neuromodulatory agent for treating neurogenic ED has also been assessed in preclinical studies. First, the expression of the EPO receptor in the human urogenital tract was confirmed by Liu and colleagues. By employing an antibody for the EPO receptor, immunolocalization using light microscopic techniques demonstrated staining in the neuronal cell bodies of the periprostatic neurovascular bundles, prostatic glandular epithelium, penile dorsal nerves, sinusoidal endothelium of the corpus cavernosum and endothelium lining dorsal veins and arteries of human prostatic and penile tissues [Liu *et al.* 2007]. The authors postulated that this finding suggests a role for endogenous EPO within these tissues. In a rat model, Allaf and colleagues showed that administration of EPO promoted the recovery of erectile function following cavernous nerve injury [Allaf *et al.* 2005]. Specifically EPO promoted axonal regeneration when evaluated by electron microscopy.

The only clinical study in humans specifically addressing the role of EPO in erectile recovery following RP was conducted by Burnett and colleagues. In this retrospective study, after appropriate counseling regarding the potential yet off-label role of EPO injection as a treatment for neurogenic ED, 15 patients undergoing nerve-sparing RP elected to receive a 40,000 IU subcutaneous injection of EPO on their preoperative day [Burnett *et al.* 2008]. The control group consisted of 21 patients who did not undergo injection and who employed PDE5 inhibitors in an 'on-demand' fashion for ED treatment. The two groups did not differ with respect to age, comorbidities, prostate-specific antigen, cancer grade, preoperative IIEF-5 scores or operative factors (such as estimated blood loss, postoperative hemoglobin and hematocrit). Patients with a history of venous thromboembolism or a hypercoagulable state were excluded. IIEF questionnaire data were compiled at 3, 6, and 12 months postoperatively. Patients in the treatment group demonstrated significantly higher IIEF-5 scores than those in the control group. In addition, although the rate of patients who were sexually active was not significantly different, a significantly higher proportion of patients in the EPO group reported clinically meaningful erections allowing for completion of sexual intercourse than in the control group. The authors concluded that men who received a single dose of EPO preoperatively recovered functionally relevant erections more significantly than those who did not, and that this therapy holds promise for treatment of ED postprostatectomy. Prospective clinical trials are necessary, however, for confirmation.

Conclusion

ED is and will continue to be a significant problem for patients undergoing RP. In spite of improved and less-invasive surgical techniques for prostate removal, studies consistently reveal ED as a frequent adverse effect. Furthermore, as these patients continue to grow older and live longer with an emphasis on maintenance of good quality of life, it will be incumbent on physicians

to find therapies that suit patients with respect to improved erectile response, while minimizing adverse effects and cost. Although there are multiple novel therapies on the horizon for post-RP ED, more studies are warranted to characterize further their feasibility, clinical utility, and their place within the ED therapy armamentarium. Finally, for established therapies, more studies are needed to confirm the benefits of penile rehabilitation therapy (with larger patient populations) as well as optimal rehabilitation protocols (with respect to type of therapy, timing of therapy initiation, duration of treatment as well as dose), and to verify the potential benefits of combination therapies to treat this common and feared problem.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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