Postprostatectomy Erectile Dysfunction: The Role of Penile Rehabilitation

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Radical prostatectomy has become the gold standard for the treatment of prostate cancer in patients who have a longer than 10-year life expectancy. Surgical treatment has led to severe quality-of-life issues in these patients, especially urinary incontinence and erectile dysfunction (ED). This article reviews the etiology and pathophysiology of postprostatectomy ED, and current management strategies for these patients.
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Key words: Penile rehabilitation • Erectile dysfunction • Prostatectomy

Prostate cancer is the most common solid organ malignancy among men, as well as the second most common type of cancer and the third leading cause of cancer deaths among male patients, according to the National Cancer Institute (NCI).[1-3] In 2009, NCI estimates for new cases of diagnosed prostate cancer were at 192,280, with 27,360 deaths attributed to this malignancy.[4] As of the late 1980s, a large number of men were diagnosed with clinically localized prostate cancer with the introduction of prostate-specific antigen (PSA) screening.[1]

With the introduction of PSA screening and current recommendations by the National Comprehensive Cancer Network and American Cancer Society for an annual digital rectal exam and PSA screening beginning at age 50—based on risk and patient counseling—the detection of low-risk prostate cancer has increased from 29.8% in 1989-1992 to 45.3% in 1991-2001.[1,5] Earlier detection has significantly improved cancer cure rates and pushed physicians to concentrate their

focus on postprostatectomy quality-of-life issues.[6] Han and colleagues reported a 15-year overall actuarial cancer-specific survival rate of 90% for Gleason 6 or Gleason 7 (3+4) prostate cancer treated with radical prostatectomy.[2,7,8] This trend of increased detection and improved survival of low-grade prostate cancer necessitates discussion with patients about their treatment options.

Radical prostatectomy (RP) is the gold standard therapeutic option for patients with clinically localized prostate cancer who have a life expectancy of longer than 10 years.[9-12] Other therapeutic options include brachytherapy, external beam radiation therapy, androgen deprivation therapy, cryotherapy, and active surveillance/watchful waiting.[5,13,14] Mulhall and associates reported that, in the United States, over 50,000 RPs are performed each year; whereas other reports suggest this figure is as high as 161,000 men per year who undergo RP.[15,16] Surgical treatment of prostate cancer is associated with severe quality-of-life issues, primarily urinary incontinence (UI) and erectile dysfunction (ED).[2,13,17]

Since the introduction of anatomic nerve-sparing radical prostatectomy as described by Walsh and Donker in 1982, surgical morbidity associated with total and stress urinary incontinence (SUI) has decreased to $<$ 10%.[18,19] Numerous reports show that ED rates after RP range from 14% to 90%.[3,16,20,21] Bergman and colleagues reported that 30% to 50% of men treated for localized prostate cancer reported use of erectile aids within 5 years after therapy.[22] The potency rates after RP vary from 16% to 86% depending on whether the surgery was performed at a center of excellence or by a community urologist.[6,23] These widely varying rates for ED following RP have led urologists to seek therapy to improve post-RP ED. This sexual dysfunction is associated with both organic and psychogenic causes and encompasses loss of ejaculation, ED, decreased orgasmic pleasure, diminished libido, socioeconomic parameters, age, and comorbidities.[14,24]

Etiology of Post-RP ED

Several theories have been proposed for the cause of post-RP ED. These theories include neurapraxia, vascular injury leading to ischemia, loss of veno-occlusive mechanism, tissue cell death within the penis leading to loss of smooth muscle content, local inflammatory effects due to surgical manipulation, and penile hypoxia.[8,10,11,15,25-27]

Neuropraxia is inevitable despite technically advanced surgical techniques for RP. Neuropraxia may be due to multiple factors such as nerve stretching during prostate retraction, nerve cutting, thermal damage from electrocautery, nerve ischemia due to loss of accessory pudendal arteries by hemostatic techniques during prostate removal, and local inflammatory effects associated with surgical trauma and degree of nerve sparing undertaken.[8,10,11,15,25-27] During this period of neuropraxia, there is absence of spontaneous nocturnal erections that leads to the loss of production of nitric oxide (NO), both by the neuronal isoform of nitric oxide synthase (nNOS) via the nerves themselves and the inducible isoform of nitric oxide synthase (iNOS) via the cavernosal smooth muscle cells, due to loss of tissue oxygenation produced by tumescence.[11,14,15] These changes induce the production of proapoptotic factors and profibrotic factors within the corpora cavernosa.[11]

The loss of nocturnal erections or damage to the accessory pudendal arteries during RP contributes to prolonged periods of penile smooth muscle hypoxia/ischemia, which leads to the production of transforming growth factor-β1 (TGF-β1) and TGF-β1–dependent endothelin-1 (ET-1).[25] ET-1 has been shown to be a potent constrictor of penile smooth muscle and a profibrotic peptide, which induces collagen deposition in cavernosal tissue.[25] Daley and associates showed that the production of prostaglandin E-1 (PGE-1) suppressed TGF-β1–induced collagen accumulation in cavernosal muscle cells.[28] Moreland and colleagues also showed that the addition of PGE-1 to cavernosal cultures suppressed TGF-β1-induced collagen synthesis.[29] Thereby, loss of erections due to decreased vascular inflow or loss of NO-induced tumescence contributes to the loss of PGE-1 feedback control on TGF-β1 production and perpetuates penile fibrosis, apoptosis, and programmed cell death.[25]

Some studies have shown in rats after bilateral neurectomy and in men after RP that smooth muscle degradation is followed by increased levels of collagen type I and collagen type III deposition.[10] User and coauthors[30] demonstrated loss of penile wet weight in rats that underwent both bilateral and unilateral cavernous nerve transection. Their data show that the average penile weight reduction was 13.6%, with the greatest reduction of 17.4% seen in the bilateral cavernous neurotomy group on postoperative day 60 ($P < .005$). A statistically significant decrease in penile wet weight of 10.5% was seen at the 60-day point in the unilateral denervated penes ($P = .029$). They also demonstrated a statistically significant decrease in DNA content in the bilaterally denervated penes ($P < .05$). Klein and associates showed increased DNA fragmentation and elevation of sulfated glycoprotein-2 (SGP-2) in the erectile tissue of denervated rat penes, which are both markers of apoptosis.[27] Conversely, Müller and colleagues demonstrated the early use

of hyperbaric oxygen therapy in rat cavernous nerve injury model improved erectile function recovery, endothelial nitric oxide synthase (eNOS), and nerve growth factor expression.[31] The development of penile fibrosis leads to the long-term development of corporal veno-occlusive dysfunction/venous leakage because of the loss of cavernosal smooth muscle cell mass to adequately compress the subtunical veins during tumescence. Fibrosis also contributes to long-term ED and penile shortening.[15]

Munding and colleagues reported on 3-month post-RP flaccid stretched penile lengths and showed that 48% had shortening greater than 1 cm.[32] Fraiman and associates[33] evaluated penile length and girth after nerve-sparing radical prostatectomy (NSRP). In their cohort of 100 men, they showed that there was a 19% and 22% change by volume in the flaccid and erect states documented between 4 and 8 months postoperatively, as well as an 8% and 9% decrease in the flaccid and erect states postoperatively.[10] These data support the need for early intervention after radical prostatectomy to prevent penile length losses and fibrosis.

Theoretically, steroids have been evaluated after RP with the thought that they may decrease postoperative inflammation. Efforts have not shown any benefit in postoperative sexual function to this point, yet few studies have been done and timing and length of dosage may need to be reconsidered. In a placebo-controlled, randomized trial using methylprednisone starting 16 to 22 hours after surgery for a total of 6 days in 70 men undergoing bilateral NSRP (BLNSRP), a statistically significant difference was seen in postoperative Sexual Health Inventory for Men (SHIM) scores at 3 months over placebo that disappeared by 6 months.[14] Another study using intraoperative betamethasone administration to the neurovascular bundle area during surgery in 60 men did not show any difference in postoperative sexual function.[14] Further studies need to be conducted before steroids may be considered useful in the treatment of post-RP ED.

The pathophysiology of post-RP ED is multifactorial and a concern to the patient after surgery; therefore, the need for therapies to prevent post-RP ED are increasingly in demand. Montorsi and colleagues were the first to show that early use of intracavernosal injection therapy with alprostadil after RP improved the incidence of return to spontaneous erection by 67% in the treatment group versus 20% in patients without treatment.[34] Although the success rates from this study have not been duplicated in contemporary series, it did stimulate more interest in therapies for post-RP ED now termed *penile rehabilitation*.

Strategies for Penile Rehabilitation

Vacuum Erection Device

Gedding Osbon, Sr. invented the vacuum erection device (VED) after having undergone RP. The device was later adopted by the medical community and was approved for usage by the US Food and Drug Administration (FDA) in 1982. VED use for penile rehabilitation is questionable because theoretically it can potentiate corporal fibrosis, ischemia, acidosis, and lack of smooth muscle relaxation leading to penile fibrosis.[14] Conversely, small series suggest that early usage of this device decreases the loss of stretched penile length after RP and increases the chance of early erectile recovery sufficient for vaginal intercourse. VED usage has also been shown to be more cost effective than daily phosphodiesterase type 5 inhibitor (PDE5-I) usage.[25]

Raina and associates, in a nonrandomized study of 109 patients at the Cleveland Clinic, evaluated the use of early VED after RP. There were two groups in this study. Group 1 (74 patients) used the VED at least twice weekly with the constrictor ring starting 1 month after RP for a total of 9 months.[6] Group 2 (35 patients) was the control group and did not receive any erectogenic treatment.[6] The investigators looked at compliance, change in penile length and circumference, return to natural erections, and ability for vaginal intercourse.[6] Overall, 17% of Group 1 had erections sufficient for sexual intercourse versus 11% in the control group. Approximately 23% of Group 1 patients who were compliant with VED usage complained of decreased penile length and girth as compared with 85% who were noncompliant in Group 1.[6] There was a 63% reported decrease in penile length and girth in the control group. Köhler and associates looked at early (starting 1 month after RP) versus late (starting 6 months after RP) usage of the VED without a constriction ring. The VED was used for a total of 5 months after RP, and showed an improvement in International Index of Erectile Function (IIEF) scores and stretched penile length in the early usage group.[35] Follow-up was obtained prior to surgery and then at 1, 3, 6, 9, and 12 months postoperatively. Stretch penile length was significantly decreased at both the 3- and 6-month follow-up by approximately 2 cm ($P = .013$) in the late usage group, whereas stretched penile length was preserved in the early usage group. IIEF scores were also significantly higher in the early usage group versus the late at both the 3- and 6-month follow-up visit. These 2 studies support early usage of VED in preventing penile shortening and improving time to natural erection, but have not addressed the issue of penile ischemia.

Bosshardt and coauthors[36] evaluated corporal blood gas after VED-assisted erection with the placement of a constrictor ring. The blood gas from the corpora cavernosa was compared with arterial blood from the arteria radii and venous blood from the vena cubiti. They found the mean oxygen saturation to be 79.2% within the corpora cavernosa. Overall, 58% of the blood induced by the VED was of arterial origin. Because oxygen saturation dropped off significantly at 30 minutes with the constrictor ring in place, these authors recommended not using the constrictor band with penile rehabilitation programs. The 30-minute limit on constrictor ring placement is also supported by the manufacturers of the VED.[10]

Overall satisfaction rates with the VED ranged from 68% to 80% depending on what series was evaluated.[10] The main complications associated with VED use are minor and include pain with pump usage and constrictor ring placement, anejaculation, and ejaculatory discomfort. In addition to using the VED for penile rehabilitation, it has been shown to be the only successful nonsurgical modality for use in patients with ED after an explanted penile prosthesis.[10]

Intracorporeal Injections

Montorsi and colleagues were the first to show human data supporting penile rehabilitation in their published randomized trial comparing men using intracavernosal injections of alprostadil three times weekly for 12 weeks after radical prostatectomy with those using no treatment.[34] At the conclusion of the study, they found 67% of the patients in the injection therapy arm had natural erections sufficient for intercourse at 6 months, as compared with 20% in the control arm of the study. Doppler penile ultrasound on these patients at the conclusion of the study showed that patients who failed to recover erectile function had venous leak. Mulhall and colleagues performed a nonrandomized study in patients who were nonresponders to sildenafil.[37] These patients were switched to intracorporeal injection (ICI) therapy with alprostadil (3 times/week). These patients had to be followed for a minimum of 18 months and had to complete at least three post-RP IIEF questionnaires. They followed those patients who were committed to the rehabilitation program and those who were not. At 18 months post-RP, their data showed that patients who were capable of having medication-unassisted intercourse were 52% in the compliant group versus 19% in the nonrehabilitation group ($P < .001$).[37] Both of these studies suggest that early erections after RP are important for long-term erectile recovery.

PDE5-Is tend to be first-line therapy in the United States for penile rehabilitation because of its convenience, safety profile, and tolerability, yet, in France, ICI therapy with PGE-1 (alprostadil) represents the most commonly used first-line treatment of post-RP ED.[38,39] This school of thought may have originated from previous literature as well as the mechanism of action of PGE-1. PGE-1 induces erections by directly stimulating the production of cyclic AMP within the smooth muscle cells of the corpora; therefore, PGE-1 does not require functional nerves to induce smooth muscle relaxation.[14] This fact is important after RP when neuropraxia is resolving. During this period of recovery, PDE5-Is may not be effective.

Medicated Urethral System for Erection Therapy (Intraurethral PGE-1/Alprostadil)

Costabile and associates, in their multi-institution study, evaluated erectile response rates to intraurethral PGE-1 beginning at least 3 months after RP.[40] Approximately 70% of those men treated in their clinic developed erections sufficient for intercourse. The responders were then randomized into a 3-month home trial with either PGE-1 or placebo. Approximately 57% of the patients in the PGE-1 group had erections sufficient for intercourse versus 6.6% in the placebo group. More recently, Raina and colleagues at the Cleveland Clinic evaluated 54 patients from a single surgical series who used the medicated urethral system for erection (MUSE®; Meda AB, Stockholm, Sweden) after RP.[41] All patients were followed for at least 6 to 9 months, and their response to MUSE was assessed by the IIEF-15 and IIEF-5 questionnaires and the Cleveland Clinic Post Prostatectomy Questionnaire (CCPPQ). All patients experienced ED for at least 6 months after their RP before starting MUSE therapy. Overall, 55% of patients achieved and maintained erections sufficient for intercourse, 48% continued long-term therapy with an average usage of four times per month, and there was a 61% spousal satisfaction rate.

The most common reasons for discontinuation of MUSE are insufficient erections, switch to other ED therapies, natural return of erections, and urethral pain and burning. MUSE has been shown to be an effective therapy for post-RP ED with a compliance rate of 63% to 68%.

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erections, switch to other ED therapies, natural return of erections, and urethral pain and burning.[41] MUSE has been shown to be an effective therapy for post-RP ED with a compliance rate of 63% to 68% shown in some series.[14,41] Like ICI therapy, intraurethral PGE-1 has been shown to increase intracorporal oxygenation by 37% to 57%.[14] PGE-1 has been shown in rat models to rescue dorsal root ganglion neurons from apoptosis and improve axonal regeneration in diabetic rats. These mechanisms of action will further help prevent post-RP fibrosis and stimulate neurovascular bundle regeneration after RP.

Combination Therapy

Combination therapy can include ICI with PDE5-I, or VED and PDE5-I. Montorsi and coauthors randomized patients to receive ICI of alprostadil three times per week for 3 months with on-demand sildenafil for 3 months versus monotherapy with sildenafil on demand starting 3 months after RP.[25] Patients in the combination arm had an 82% response rate to sildenafil versus 52% in the monotherapy group.[25] Mydlo and colleagues retrospectively looked at 34 men after RP with subsequent ED.[42] The patients were then titrated on either sildenafil or vardenafil to their maximum doses. All patients had suboptimal responses after a maximum of eight doses as assessed by the SHIM score. These patients were then started on ICI therapy with alprostadil in addition to their oral therapy with 68% reporting a much better erection with combination therapy. Nandipati and associates evaluated early combination therapy with ICI therapy with alprostadil and oral sildenafil versus low-dose TriMix (papaverine, phentolomine and PGE-1) versus low-dose PGE-1 after RP.[23] Sildenafil, 50 mg, was started daily at discharge from the hospital, and ICI therapy with alprostadil or low-dose TriMix was started within 3 weeks or at catheter removal. This therapy was to be attempted two to three times weekly. Their results were compiled using the abridged version of the IIEF-5 questionnaire. The patients were followed every 3 months for a 12-month period. At a mean follow-up of 6 months, 96% were sexually active. Approximately 45% were sexually active in the injection-only group versus 50% with combination therapy. Doppler studies showed that peak systolic velocities were higher in the low-dose TriMix population compared with the low-dose PGE-1 alone group. These data support a stronger response of penile vasculature with TriMix.

Yassin and colleagues reported on combination therapy with VED and PDE5-I for early penile rehabilitation following nerve-sparing RP.[43] The patients were started on sildenafil, 25 mg, three times per week or tadalafil, 5 mg, twice weekly with VED being used twice daily. This combination therapy was started 11 days after RP and continued for 3 months. Overall, 56% of the patients on combination therapy obtained erections sufficient for intercourse. Patients on sildenafil reported higher success rates than those on tadalafil (78% vs 64%).[43] This study had short follow-up and poor study design; therefore, no significant conclusions can be made.

Combination therapy with ICI and PDE5-I should be considered in patients who have failed monotherapy or as a primary modality because it has shown synergy in recent series. This combination may further reduce penile fibrosis and penile smooth muscle degradation after RP. VED and PDE5-I combination therapy may also be synergistic, yet further randomized studies need to be completed to elicit its effectiveness.

Oral Therapy (PDE5-I)

Currently sildenafil, tadalafil, and vardenafil are approved for the treatment of ED in the United States. Sildenafil is the most widely used oral agent for post-RP ED. The response rates to sildenafil after RP depend on age, dosage, interval to start of therapy, and degree of cavernous nerve damage.[44] Response rates with sildenafil were 80% in BLNSRP, 50% in unilateral nerve-sparing RP, and 15% in non-NSRP.[44] The likelihood of response to PDE5-Is increases with time, and has been shown to be ineffective in the first 6 to 9 months after RP in some series.[44] Treatment satisfaction rates peak at 60% around 18 months to 2 years after RP. Montorsi and associates showed that sildenafil taken nightly enhances nocturnal penile tumescence (NPT) after RP.[45] Padma-Nathan and colleagues reported on a prospective trial of sildenafil, 50 mg or 100 mg, daily and nightly versus placebo after BLNSRP.[46] These patients were randomized 4 weeks after RP. Overall, 27% of the patients in the treatment group were responders with return of spontaneous erectile function compared with 4% in the placebo group. Early high-dose therapy with sildenafil has also been shown to preserve

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the smooth muscle content within the corpora cavernosa.[47] Zippe and colleagues showed that response rates to sildenafil increase with time after RP with response rates of 44% at 3 to 6 months, 55% at 6 to 12 months, and 53% at greater than 12 months.[48]

In a multicenter, placebo-controlled, randomized trial from the United States and Canada, a 12-week parallel arm study comparing placebo with vardenafil, 10 mg and 20 mg, was completed. A total of 71% receiving vardenafil, 20 mg, and 60% receiving vardenafil, 10 mg, after RP reported improved erectile function.[47]

Tadalafil was evaluated in a large multicenter, placebo-controlled trial of 303 patients in North America and Europe.[40] A total of 71% of patients treated with tadalafil, 20 mg, reported improvement in their erectile function as compared with 24% in the placebo group, where 52% of patients were able to achieve intercourse.[47]

The use of PDE5-Is will only be successful in post-RP patients who have had some type of nerve-sparing procedure. It appears that the induction of neural NO as discussed previously contributes to its mechanism of action. Preservation of smooth muscle content has been seen with these agents, which will prevent venous leak from developing. Early usage of these agents may not be as effective as long-term usage because of neuropraxia, which may resolve as late as 2 years after RP, although recent studies have suggested that early use of PDE5-Is, regardless of neuropraxia, improves long-term erectile recovery.

Gene Therapy

Advances in molecular biology have allowed transfer of genetic material to humans and other animals with the aid of vectors. This technology is now being expanded to a disease process like ED. Currently, human trials with FK506, GPI-1046, and potassium channel gene therapy have just begun.[27] George Christ, PhD, has classified gene therapy into two categories: increasing the supply of the erectile stimulus and decreasing the physiologic demand for the erectile tissue.[27]

Brain-derived neurotrophic factor (BDNF) has been shown to improve erection in rats using adeno-associated virus as a vector after cavernous nerve injury, which subsequently increases NO and NOS.[27] Vascular endothelial growth factor (VEGF) has been shown to increase vascular supply in rat models.[27] FK506 and GPI-1046 have been shown to accelerate nerve regeneration after crush injury in rat sciatic nerves by protecting neurons from chemotoxin-induced cell death.[25,27] All these therapies have been shown to increase the supply of NO or the regeneration of nerves that supply NO. Conversely, in the demand category RhoA and manipulation of potassium channels (*hSlo*) help to sensitize calcium relaxation of smooth muscle and potassium-related smooth muscle tone in the penis, which ultimately leads to improved erectile function.

These gene factors show promise in animal studies and may be the future ED therapy in post-RP patients, yet randomized, controlled human studies need to be conducted because long-term side effects are unknown.[27]

Conclusions

There are many factors that contribute to post-RP ED. Preoperatively, the patient's age at the time of surgery, partner's age, preoperative erectile function, and comorbidity profile should be assessed.[9] Intraoperative factors that contribute to recovery of erectile function after RP are surgical approach and amount of nerve preservation and surgical expertise. Postoperative factors that contribute to recovery of erectile function after RP are time to erectile function assessment after surgery and ED treatment.[9] This review concentrated on the latter.

There are many factors that contribute to post-RP ED. Preoperatively, the patient's age at the time of surgery, partner's age, preoperative erectile function, and comorbidity profile should be assessed.

It appears that early administration of PDE5-I, ICI therapy, or MUSE should be started at the time of catheter removal and continued until erectile function improves. The treatment length may be as long as 2 to 3 years after RP. Patients may discontinue therapy or switch to another therapy as side effects dictate. PDE5-Is are considered first-line therapy in the United States because they have been shown in one series to have the lowest annual cost per user.[12] European urologists use ICI therapy/MUSE as first-line therapy for post-RP ED, although they tend to have a higher discontinuation rate due to the side effect of penile pain. VED therapy, although controversial, should be started within 1 month after surgery and continued for at least 6 months to help prevent loss of penile length. Combination therapy is also effective and has shown a synergistic effect in the studies reviewed. Gene therapy is on the horizon and randomized human studies need to be completed to further elicit their usefulness. VED should be used in patients with ED who have undergone removal of a

penile prosthesis. For patients who fail to respond to all therapies within a 2-year span, penile prosthesis should be considered.[44] Patient and partner satisfaction rates are in the range of 85% with these devices.[44]

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Main Points

- Radical prostatectomy (RP) is the gold standard therapeutic option for patients with clinically localized prostate cancer who have a >10-year life expectancy. The pathophysiology of post-RP erectile dysfunction (ED) is multifactorial and a concern for patients after surgery; therefore, therapies to prevent post-RP ED are increasingly in demand.
- In the United States, phosphodiesterase type 5 inhibitors (PDE5-I) are considered first-line therapy for post-RP ED due to their convenience, safety profile, and tolerability—although their use will only be successful in patients who have had a nerve-sparing procedure. European urologists use intracorporeal injection therapy (ICI)/medicated urethral system for erection (MUSE®) as first-line therapy.
- The vacuum erection device, although controversial, carries satisfaction rates that range between 68% and 80%; minor complications include pain with pump usage and constrictor ring placement, anejaculation, and ejaculatory discomfort.
- MUSE is an effective therapy for post-RP ED with compliance rates at approximately 63% to 68%. The most common reasons for discontinuation of MUSE are insufficient erections, switch to other ED therapies, natural return of erections, and urethral pain and burning.
- Combination therapy with ICI and PDE5-Is should be considered in patients who fail with monotherapy. For patients unresponsive to all therapies within a 2-year span, a penile prosthesis should be considered—patient and partner satisfaction rates are in the range of 85% with these devices.

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