

MANAGEMENT OF ERECTILE DYSFUNCTION AFTER RADICAL PROSTATECTOMY

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Radical prostatectomy (RP) has been the reference standard treatment for organ/specimen-confined prostate cancer for several decades. Although improved surgical techniques have decreased the rate of “total” and stress-induced incontinence to less than 10%, urologists still report that most patients experience erectile dysfunction (ED) after RP.^{1,2} Although the surgical technique and experience remain the dominant variables in outcome, other factors affecting postoperative ED include patient age, preservation of the neurovascular bundles, urinary incontinence, and adjuvant treatments (radiotherapy, hormonal therapy).³

A current dilemma surrounding ED after RP is the wide variation in the potency rates reported in published studies. Erectile function after RP by experienced surgeons at centers of excellence ranges between 40% and 85%;⁴ however, for most urologists, the return of erectile function ranges from 9% to 40%.⁵⁻⁷ This variation appears to be surgeon dependent, but it may also reflect nonuniformity in data collection.

Although ED is a common surgical complication that needs to be addressed, it is amenable to treatment if patients have the interest and desire. Safe, nonsurgical treatments with reasonable efficacy include intracorporeal injection of vasoactive drugs, transurethral vasodilators (medicated urethral system for erection [MUSE Vivus, Mountain View, Calif.]), vacuum constriction devices (VCDs), and oral therapy (sildenafil citrate). All of these “erectaid” treatments can potentially work and can have excellent compliance in an individual patient.

We summarize the standard treatments used to treat ED, as well as the newer options using oral

medications and our experience in early penile rehabilitation.

NONORAL TREATMENTS

VACUUM CONSTRICTION DEVICE

Cookson and Nadig⁸ reported long-term efficacy and patient satisfaction rates of more than 80% in patients with ED treated with a VCD. They also reported a statistically significant increase in the frequency of successful intercourse attempts in 79% of the patients using the VCD for 1 year.⁸

Although VCD efficacy rates range from 60% to 80%, the compliance after 1 year of activity decreases to 50% to 70%.⁹ Noncompliant patients typically complain of tightness or pain from the constriction ring and diminished sensation of the phallus and glans.¹⁰

Nonetheless, current models are safe, and the rigidity is sufficient for vaginal penetration and intercourse in most patients. Satisfaction scores are generally high for both patients and their partners.

INTRAURETHRAL ALPROSTADIL (PROSTAGLANDIN E₁)

With intraurethral alprostadil, prostaglandin E₁ (PGE₁) is delivered to the erectile tissue by means of a medicated pellet (MUSE). Intraurethral alprostadil, when introduced by Padma-Nathan *et al.*¹¹ in 1997, was reported to have an overall efficacy rate of 44% after RP. Subsequent investigators, however, not only failed to confirm these initially favorable results, but also reported adverse effects (urethral pain and burning).¹¹ Paolone *et al.*¹² at the Cleveland Clinic reported that MUSE had long-term effectiveness in only 15% of a group of men who had undergone pelvic surgery.

The long-term efficacy of intraurethral alprostadil (PGE₁) after RP was recently reported. The efficacy and compliance of MUSE was studied in a contemporary RP series (27 patients from 1996 to 2000) at the Cleveland Clinic using the abridged version of the International Index of Erectile Function questionnaire, also known as the Sexual Health Inventory for Men (SHIM). MUSE was effective in 13 (48%) of the 27 patients after a mean

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TABLE I. Response of MUSE after radical prostatectomy (n = 27): SHIM (IIEF-5) analysis

IIEF-5 Questionnaire	Before Surgery (n = 27)	After Surgery (n = 27)	After MUSE Use (n = 27)
Q5, maintenance ability	4.36 ± 0.19	1.34 ± 0.13	3.00 ± 0.36*
Q15, erection confidence	3.43 ± 0.28	1.11 ± 0.04	3.05 ± 0.29*
Q4, maintenance frequency	4.21 ± 0.22	1.17 ± 0.06	3.33 ± 0.06*
Q2, erection firmness	3.35 ± 0.29	1.20 ± 0.08	3.21 ± 0.12*
Q7, intercourse satisfaction	3.78 ± 0.28	0.36 ± 0.12	3.67 ± 0.40*
Total mean IIEF-5 score	19.13 ± 1.26	5.18 ± 0.43	16.26 ± 0.23*

KEY: MUSE = medicated urethral system for erection; SHIM = Sexual Health Inventory for Men; IIEF = International Index of Erectile Function; Q = question.
Data presented as mean ± SD.
* P < 0.05 after surgery vs. after MUSE use was considered significant. (Wilcoxon signed-rank test was used.)

of 2.2 years. However, 14 (52%) of 27 patients had discontinued treatment after a mean of 8 ± 1.4 months, mainly because of an inadequate response or side effects¹³ (Table I).

Our study has shown that although MUSE is effective in nerve-sparing (NS) and non-NS RP patients, one of every two users discontinued therapy, mainly because of an insufficient erectile response.

INTRACAVERNOSAL INJECTION THERAPY

With intracavernosal injection (IC) therapy, patients inject drugs such as PGE₁ or alprostadil, in combination with papaverine and phentolamine (as a triple mixture), directly into the cavernosal blood vessels to obtain an erection.^{14,15} Although phentolamine is a direct adrenoceptor blocker, alprostadil and papaverine act by modulating the levels of cyclic 3',5'-adenosine monophosphatase in the cells, eventually increasing penile blood flow by relaxing the arterial and trabecular smooth muscles.¹⁶

Dennis and McDougal¹⁷ were the first to document the use of IC therapy in previously potent RP patients; they reported a success rate of 85%. A recent study by Rodriguez *et al.*¹⁸ in 1997 revealed that IC PGE₁ injection provided adequate rigidity in 95% of patients.

However, the dropout rates in many series have exceeded 40%, despite a therapeutic efficacy of more than 85%,¹⁹ owing to injection pain (14%), difficulty in reproducing a successful injection (10% to 20%), and penile fibrosis (2% to 15%).²⁰ In addition, many patients have physical and emotional difficulty using a needle for any length of time. The noncompliance rate has ranged from 40% to 60% after 1 year of use as a result of the need for regular needle use.²¹

Using an institutional questionnaire, Mulhall *et al.*²¹ found a good response to IC injection in 75% of their patients with ED. They reported an attrition rate of 31% during a 38-month period, with cost, penile discomfort, and patient-partner prob-

lems the major reasons for discontinuation. A lack of efficacy was the primary reason for discontinuation in only 14.1% patients.

Detailed instruction, guidance, and close follow-up are essential to the success of self-injection therapy.

Long-Term Efficacy and Compliance of IC Injections After RP. We conducted a study to evaluate the long-term efficacy and compliance of IC injection therapy in a post-RP population.²² We found that 69 (68%) of our 102 post-RP patients were satisfied with IC injection therapy and that 49 (48%) chose to continue with the therapy on a long-term basis (mean 3.5 years). However, the compliance rate was 70.6%, in part because the patients had either lost a partner or experienced a return of natural erections. The primary reasons for discontinuation in our study included inadequate erections. We believe periodic follow-up, combined with realistic expectations, increases patient compliance and lowers the attrition rate. Additional studies are required to determine whether other injectable agents (forskalin, vasoactive intestinal peptide, and moxislylate) alone or in combination can increase efficacy and long-term compliance.

IC Injection Versus VCD. Turner and associates²³ prospectively compared IC injections of papaverine/phentolamine and VCD. They found that both treatments were efficacious and safe, although the dropout rates were greater for the IC injection group (60% versus 20%).²³ The dropout rates associated with VCD and the risk of complications were lower than those associated with IC injection. VCD may be a reasonable alternative in patients who do not like IC injection therapy because of the need for needles.

ORAL THERAPY

The treatment algorithm for patients with ED after RP improved dramatically in 1998 when the first effective oral therapy—sildenafil citrate (Viagra, Pfizer

TABLE II. Factors associated with successful outcome of sildenafil citrate after radical prostatectomy

Variable	Percentage (Responders/Total)	P Value*
Neurovascular bundle status (NS vs. non-NS)	71 (94/132) vs. 14 (6/42)	<0.001
Preoperative erectile function (IIEF-5 >15 vs. IIEF-5 <15)	67 (92/137) vs. 22 (8/37)	<0.001
Overall age (<60 vs. 60–65 vs. >65 yr)	75 (36/48) vs. 57 (42/74) vs. 42 (22/52) [†]	0.001 [‡]
Interval from RP (3–6 vs. 6–12 vs. 12–18 vs. >18 mo)	24 (4/17) [§] vs. 57 (24/42) vs. 63 (66/104) vs. 91 (10/11)	<0.001 [‡]

KEY: NS = nerve sparing; IIEF = International Index of Erectile Function; RP = radical prostatectomy.
 * Chi-square test for overall association, unless noted.
[†] Significantly different from <60 yr.
[‡] Cochran Armitage test for trend.
[§] Significantly different from <12, 12–18, and >18 mo.

Pharmaceutical)—became available. Following the publication by Goldstein *et al.*²⁴ in 1998, sildenafil revolutionized the evaluation and treatment of ED to the extent that oral therapy is now the first treatment option for patients with ED caused by a variety of organic and psychogenic causes.

Data from various clinical trials have demonstrated improved erectile function in patients with a cross-section of etiologies of ED.²⁵ However, early reports did not stratify the various types of organic etiologies and did not include pertinent data from the subset of patients who had undergone RP, such as the impact of the presence or absence of the neurovascular bundles.²⁶

Researchers at the Cleveland Clinic were among the first to investigate the effects of this new oral medication for patients after RP and to study the impact of the presence or absence of the neurovascular bundles. Our initial publication reported that 12 of 15 patients undergoing bilateral NS procedures showed efficacy with vaginal penetration with sildenafil at 1 year after RP.²⁷ Subsequently, we updated our experience to include 91 patients treated with sildenafil after RP.²⁸ That study showed that sildenafil citrate can improve ED in about 70% of impotent, motivated patients after RP if a bilateral NS procedure has been performed and in 50% of patients if a unilateral NS procedure was done.

The impact of nerve preservation and the efficacy of sildenafil was also reported by Zagaja *et al.*,²⁵ who showed an 80% response rate in men younger than 55 years old when both nerve bundles were spared and a 40% response when one bundle was spared. However, in the 56 to 65-year-old group, the response rate dropped to 45% in the group with two nerves preserved and 0% in those with one nerve preserved.²⁵

LONG-TERM EFFECT OF SILDENAFIL CITRATE ON ED AFTER RP: THREE-YEAR FOLLOW-UP

In our 3-year long-term follow-up study, most patients who responded at 1 year (72%) continued to have effective erections with sildenafil citrate.

The SHIM scores were comparable at 1 and 3 years. The degree of neurovascular bundle preservation continued to stratify the response rates to sildenafil. The dropout rate was 27%. Long-term results showed that 76% of preoperative sexually potent men with good bilateral NS surgery can recapture that function with sildenafil treatment.²⁹

EFFICACY AND FACTORS ASSOCIATED WITH SUCCESSFUL OUTCOME OF SILDENAFIL CITRATE USE FOR ED AFTER RP

In another Cleveland Clinic study, we assessed the factors that determine the drug's clinical efficacy. The responses were stratified on the basis of patient age, number of neurovascular bundles preserved, preoperative erectile function as determined by SHIM analysis, and the interval after surgery to the initiation of drug treatment.

After treatment with sildenafil, 100 (57%) of 174 patients responded to the drug: 76% in the bilateral NS group, 53.5% in the unilateral NS group, and 14.2% in the non-NS group. Four factors were significantly associated statistically with a successful outcome: the presence of at least one neurovascular bundle, a mean preoperative SHIM score of 15 or more, age of 65 years or younger, and interval from RP to drug use of longer than 6 months ($P < 0.001$; Table II).³⁰ We also found that preoperative erectile function and the interval between surgery and initiation of the drug therapy were associated with a successful outcome.

COMBINATION THERAPY

A recent area of interest is the use of combination therapy for ED after RP when individual therapies are ineffective.

SILDENAFIL CITRATE ENHANCES SEXUAL SATISFACTION IN VCD FAILURES AFTER RP

We assessed the effectiveness of combining sildenafil citrate with VCD in 31 men who were unsatisfied with the results of VCD alone after RP

(mean follow-up 4.5 months). The patients were instructed to take 100 mg of sildenafil 1 to 2 hours before using a VCD for sexual intercourse.

Of the 31 patients, 7 (22%) had no improvement with the addition of sildenafil and discontinued the drug and 24 (77%) reported improved penile rigidity and sexual satisfaction. They reported that sildenafil enhanced their erections 100% of the time. Thus, adding sildenafil to VCD use improved sexual satisfaction and penile rigidity in patients unsatisfied with VCD alone.

MUSE ENHANCES SEXUAL SATISFACTION IN SILDENAFIL CITRATE FAILURES AFTER RP

Using both cyclic adenosine monophosphatase and cyclic guanosine monophosphate-mediated vasodilation may be more efficacious in the salvage of patients who desire noninvasive therapy but in whom a single-treatment modality fails. A study conducted by Nehra and colleagues³¹ demonstrated that a combination of sildenafil (100 mg) and intraurethral PGE₁ (1000 µg) salvaged a refractory population of men with ED. Recently, Jaffe *et al.*³² reported that 5 (50%) of 10 patients in whom sildenafil citrate alone failed successfully responded to a MUSE and sildenafil combination.

We have examined the effectiveness of MUSE-sildenafil combination therapy in patients who were unsatisfied with sildenafil citrate alone for ED after RP. Of the 23 patients, 19 (83%) reported improved penile rigidity and sexual satisfaction. The other 4 patients did not improve and discontinued taking sildenafil. We concluded that the addition of MUSE to sildenafil therapy improves sexual satisfaction and penile rigidity.

SILDENAFIL ENHANCES SEXUAL SATISFACTION WHEN COMBINED WITH IC INJECTIONS

One study showed that combining IC injections with oral therapy in patients who did not respond to sildenafil alone is effective. Thirty-six patients who wanted to switch from IC injections to sildenafil were included in the study.³³ Of the 36 patients, 7 were not satisfied with sildenafil alone. These 7 patients used IC injections with sildenafil to enhance their response. IC injections produce cyclic adenosine monophosphatase-mediated vasodilation and enhance the sildenafil response.

SWITCHING PATIENTS FROM STANDARD TO ORAL THERAPY

When sildenafil citrate was first introduced, many patients expressed a desire to try oral therapy. A study was conducted at our center to determine whether patients with ED after RP who had been successfully treated with IC injection therapy with PGE₁ alone or in combination with papaver-

ine and phentolamine could successfully switch to oral sildenafil citrate.

Of 36 patients using IC injections, 15 (41%) successfully switched to sildenafil, and 14 (38%) found sildenafil ineffective and continued using IC injections. Seven patients (19%) found sildenafil alone to be suboptimal but continued using it, enhancing their response with IC injections.³³ The results of that study suggested that patients who are successfully treated with IC injection therapy should be offered the option of using oral therapy.

PENILE IMPLANTS

The role of penile prosthesis in current practice is limited to patients who do not respond to any systemic medications and who are not interested in using conventional treatments. Gerstenberger *et al.*³⁴ reported a 75% satisfaction rate after penile prosthesis. McLaren and Barrett³⁵ reported that 83% of the men were satisfied with the results of implant surgery. A study that compared penile prosthesis (n = 65) and injection therapy (n = 115) demonstrated that 70% of the implant patients were having coitus on a regular basis but that only 41% of the injection patients were sexually active in the follow-up period.³⁶ Infection of the prosthesis is the major concern after surgery. Infection rates range from 1.7% to 1.8%.³⁷ The mode of insertion does not affect the rate of infection.³⁸

FUTURE DIRECTIONS AND STUDIES

NEW ORAL THERAPIES

A myriad of new therapeutic agents are emerging for the treatment of sexual dysfunction. Apomorphine SL has a central mechanism of action; at the approved doses of 2 mg and 3 mg, it induces a significantly greater percentage of erections than placebo. At the 2 to 3-mg dose, the main side effect of nausea was acceptable at 4.7%.³⁹

Tadalafil (Cialis, Eli Lilly and ICOS Corp.), a phosphodiesterase (PDE)-5 inhibitor, is safe and well tolerated. The drug significantly improved erectile function and was well tolerated at the 10 and 20-mg doses. Montorsi *et al.*⁴⁰ reported that patients receiving tadalafil showed greater improvement in all primary and secondary endpoints ($P < 0.001$) compared with placebo after RP; 54% reported successful penetration attempts, and 41% had successful vaginal intercourse.

Another PDE-5 inhibitor, vardenafil (Levitra, Bayer Pharmaceutical Corp., West Haron, Conn.), is a new selective PDE-5 inhibitor.⁴¹ Vardenafil has been tested in patients with ED after RP in a multicenter, placebo-controlled, randomized study. The results of the study showed that 71% of patients reported improvement in erectile function, and 47% were able to maintain an erection suffi-

cient for vaginal penetration.⁴² Additional clinical trials are required to assess the potential benefits in the treatment of ED after RP.

Our center has conducted a prospective study comparing the efficacy and side effects of all three oral PDE-5 inhibitors (sildenafil, vardenafil, and tadalafil). We found that the side effects determined the choice of PDE-5 inhibitor in 60% of patients, and efficacy determined the choice in the remaining 40%. The mean SHIM scores for all three drugs did not differ significantly among the users.⁴³

INTRAOPERATIVE CAVERNOUS NERVE STIMULATION

The CaverMap system (CaverMap surgical aid, Uromed, Boston, Mass.) identifies the location of the cavernous nerves during RP by monitoring the tumescence response to intraoperative cavernous nerve stimulation. It is still unclear whether the use of the CaverMap improves erectile potency. The main benefit of the CaverMap system may be that it forces the surgeon to pay particular attention to the NS component of the operation and to allocate the effort to perform it optimally.⁴⁴

INTERPOSITION OF SURAL NERVE GRAFTS

Sural nerve grafts may act as templates for potential nerve regeneration after surgery. Although nerve grafting is a time-consuming procedure that prolongs the operative time, it may be a reasonable option in a young patient who has undergone non-NS RP or unilateral NS RP.

Kim and associates⁴⁵ recently reported that 4 (33%) of their 12 patients who received a sural nerve graft had spontaneous unassisted erections sufficient for sexual intercourse compared with 1 patient in the control group (no treatment).

EARLY PENILE REHABILITATION

Nocturnal erections may play an important role in preserving normal erectile function by providing regular tissue oxygenation. Persistent penile hypoxia, due to prolonged periods of penile inactivity, may lead to the formation of lacunar fibrosis and, ultimately, a decline in erectile capacity.⁴⁶ The use of erectogenic agents may improve tissue oxygenation and prevent penile fibrosis.⁴⁷ Postoperative therapeutic intervention with MUSE and VCD may restore nocturnal erections (both frequency and duration), facilitate vascular perfusion of the corpus cavernosum, and subsequently inhibit corporeal hypoxia and fibrosis. The initial data with IC agents have been very encouraging and lend support to this hypothesis.^{47,48} Recently, Padma-Nathan *et al.*⁴⁹ reported that daily sildenafil preserved erectile function in 27% of patients after RP compared with 4% in the control group (no treatment). However, additional confirmatory studies

are needed to support the concept of early penile rehabilitation.

Efficacy of Early Use of IC Injections for Early Penile Rehabilitation After RP. Montorsi and associates⁴⁷ demonstrated the value of immediate postoperative (three times per week) IC injection after RP. They reported that 67% of patients experienced a return of natural erectile function after 6 months.⁴⁷

We performed a study of early IC injections (using 8 μ g PGE₁, three times per week) that included 6 patients. The discontinuation rate was 75% (4 of 6) within 2 months because of the lack of spontaneity, penile discomfort, and fear and apprehension. Although early IC injections had better physiologic benefit as early prophylaxis for penile rehabilitation, long-term results could not be obtained because of poor compliance.

Efficacy of Early Use of MUSE for Early Penile Rehabilitation After RP. We evaluated the role of early MUSE in a prospective study. We included 91 patients, 56 in the MUSE group and 35 without any treatment (control group).

In the MUSE group, 38 (68%) of 56 continued MUSE treatment. At 6 months, 28 (74%) of the 38 patients had regained partial erections and 15 (53%) of the 28 had natural erections sufficient for vaginal penetration without MUSE. In the control group, 13 (37%) of 35 had regained partial erections and 4 (30.7%) of the 13 had erections sufficient for vaginal penetration. Of the 18 patients who discontinued MUSE, 9 did so because of inadequate erections, 5 because of a loss in sexual interest, and 4 because of local pain/burning.⁵⁰ We concluded that early MUSE therapy after RP increases the incidence of natural erections sufficient for vaginal intercourse.

Efficacy of Early Use of VCD for ED After RP. The current area of interest includes the early intervention clinical protocols in the use of VCD to encourage early corporeal rehabilitation and prevention of post-RP venoocclusive dysfunction by increasing the frequency of tissue oxygenation. Early sexual rehabilitation after RP may enhance earlier recovery of nocturnal erections.⁴⁷ In our experience, daily use of a VCD after RP was associated with a high compliance rate (80%; 60 of 74) and few complications. Of this series, 80% of the patients at 6 to 9 months reported having sexual activity (vaginal intercourse) with the VCD at a frequency of twice per week. At a mean interval of 9 months, the early (daily) use of a VCD resulted in natural erectile function in 19 (32%) of 60 patients, with 10 (52%) of these 19 patients having erections sufficient for vaginal penetration.⁵¹ This potency rate (defined as vaginal penetration) of 52% at 9 months was significantly greater than the potency rate with our

contemporary series (without early VCD), which had a 24% natural potency rate at 12 months.

It appears that early VCD use encourages early sexual activity and interest in patients (and partners) who previously were inactive for 1 year or longer, waiting for the period of neurapraxia to resolve.

GROWTH FACTORS FOR CAVERNOUS NERVE REGENERATION

Recent animal studies have provided promising results concerning the use of nerve and vascular growth factors in promoting the regrowth of damaged cavernous nerves and return of erectile function. Lee *et al.*⁵² have shown that IC administration of brain-derived neurotrophic factors after bilateral cavernous nerve cryoablation in rats prevents the degeneration of neural nitric oxide synthase-containing neurons and enhances recovery of erectile function. In addition, IC injection of vascular endothelial growth factor in rats with arteriogenic ED protected what erectile function was left.⁵² The applicability of this concept to a human model remains to be determined.

CONCLUSIONS

Despite the advent of NS RP, ED is still a common surgical complication. Standard therapies—VCD, MUSE, and IC injections with PGE₁ alone or in combination with papaverine and phentolamine—continue to be important therapeutic options in the treatment of ED caused by RP, especially in patients who do not undergo an NS procedure. Most patients, however, prefer oral therapy because of its simplicity. Sildenafil citrate and the newer PDE-5 inhibitors are only effective when functional nerve tissue is present. Even so, oral therapy does not appear to be effective within the first 9 to 12 months after RP, when neurapraxia exists, and standard treatment options should be encouraged during this time to maintain good sexual health.

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