

Renewing Intimacy: Advances in Treating Erectile Dysfunction Postprostatectomy

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Erectile dysfunction following prostatectomy is almost universal. Herbert Lepor, MD, Professor and Martin Spatz Chairperson of Urology and Professor of Pharmacology at New York University School of Medicine and co-founder of *Reviews in Urology*; Andrew McCullough, MD, Director of the Sexual Health and Male Fertility and Microsurgery Programs at New York University School of Medicine; and Jason D. Engel, MD, Vice Chairman of Urology and Director of Urologic Robotic Surgery at George Washington University Hospital, discuss treatment options for erectile dysfunction postprostatectomy.

Herbert Lepor, MD: What is the mechanism of postprostatectomy erectile dysfunction (ED)?

Andrew McCullough, MD: The etiology of ED after surgery for prostate cancer is likely multifactorial. Prostate cancer strikes men in their seventh decade of life, when many are already experiencing ED. Although presurgical erectile function is a significant factor in determining erectile function after surgery, other invoked mechanisms include vascular and nerve injury.

The role of arterial injury as a cause of ED is unclear. In a large series of preoperatively potent men with postoperative ED undergoing penile Doppler imaging after radical prostatectomy (RP),¹ the incidence of arterial injury was less than 10%. In men with no arterial disease, the most common finding was veno-occlusive disease.

A neurogenic injury is the most likely initial cause of post-RP ED. Damage after cavernous nerve injury and prostate surgery reduces the amount of neuronal nitric oxide synthase (n-NOS) and nitric oxide (NO) that can be released during sexual activity, thereby reducing erectile function. A certain degree of recovery can be documented in the cavernous nerve injury rat model. Consistent with the importance of surgical technique, there appears to be an advantage to nerve-sparing over non-nerve-sparing ablation and bilateral to unilateral nerve ablation. Gralnek and colleagues² reported a study involving 129 men who responded to a questionnaire, 83 of whom had non-nerve-sparing radical retropubic prostatectomy (NNSRRP) and 46 who had a unilateral nerve-sparing radical retropubic prostatectomy (UNSRP). The sexual function score, which included questions regarding spontaneous erections and the use of erectile aids, showed a statistically significant difference in sexual function in men with a unilateral versus a non-nerve-sparing surgery.

In a series of almost 3500 men, Kundu and coworkers³ reported erections sufficient for intercourse in 76% of preoperatively potent men treated with bilateral nerve-sparing radical retropubic prostatectomy (BNSRRP) and 53% of men with UNSRRP. In men younger than 70 years of age, the response rates were 78% and 53%, respectively. This series retrospectively included men from 1983, prior

to standardized ED questionnaires, and men currently taking phosphodiesterase type 5 (PDE-5) inhibitors.

These data suggest that preservation of local nerves is important for maintenance of erectile function. Decreased or loss of enervation within the erectile tissues has a number of deleterious effects: it prevents the release of NO from nonadrenergic, noncholinergic nerves; decreases the production of cyclic nucleotides within the vascular smooth muscle of the erectile tissues; and reduces the subsequent relaxation of these tissues. As a result, the increased blood flow and tumescence that would normally occur during nocturnal penile tumescence (NPT) or sexual stimulation is abolished or diminished.

Herbert Lepor, MD: My group recently reported in the *Journal of Urology* a series of 1110 men undergoing RP whose erectile function was prospectively followed for at least 2 years using a self-administered University of California at Los Angeles Prostate Cancer Index.⁴ A multivariate analysis demonstrated that age, prior history of diabetes, and the number of cavernous nerves spared were the factors that significantly predicted return of potency. The difference in potency rates between men undergoing bilateral versus unilateral nerve-sparing surgery was 14%. This is consistent with other reports in the literature.

How common is erectile dysfunction after RP?

Jason D. Engel, MD: One of the problems in answering this question has been the moving target that the reporting of postprostatectomy ED has been in the literature. The most commonly accepted definition of potency is *an erection adequate for intercourse with or without the use of a PDE-5 inhibitor*. Using this definition, a highly experienced surgeon can show potency rates of nearly 90% at

1 year. However, most of these men will not report themselves as potent. Using validated surveys, which are a much stricter format, you almost always find that nearly 50% of men will have significant ED at 1 year. I tell all of my patients before surgery that all men will have severe ED after surgery, and that this will persist for a minimum of 6 months. Some men will start to have return of function at that point with help, but only 50% to 60% of men with good erectile function before surgery will consider themselves fully potent at 1 year. This scenario gives a much more realistic picture to the patient, and creates a setting whereby the patient realizes he and his partner will have to manage expectations.

Herbert Lepor, MD: I agree with this perspective. Some experts will report potency rates of 90%, but this is only in a highly selected group and, often, validated, self-administered questionnaires are not used to assess potency. In our reported series,⁴ a 50-year-old man with excellent baseline erections and no cardiovascular risk factors who undergoes bilateral nerve-sparing surgery will have over an 80% likelihood of recovering erectile function. However, our series also included men who are 70 years of age, who, despite being classified as potent at baseline, have only fair erections and cardiovascular risk factors. For these men, a potency rate of 30% to 40% is more realistic. The surgeon must reconcile that providing unrealistic expectations will lead to dissatisfied patients.

Andrew McCullough, MD: Some degree of ED is almost universal after RP. One of the clear problems is the definition of ED after RP. RP is one of the most commonly performed open procedures during urologic residency, and it has become apparent that many factors are involved in a successful erectile outcome after surgery.

Preoperative, intraoperative, and postoperative issues all influence outcome.

Until 1992 and the National Institutes of Health (NIH) consensus position paper on ED,⁵ there was no uniformly accepted definition of ED. Many of the articles published on post-RP ED before and after 1992 did not use uniform or standard definitions or validated questionnaires in reporting their rates of erectile function preservation. The first simple and validated questionnaire used by urologists was introduced by O'Leary and coworkers⁶ in 1995. Krupski and colleagues⁷ reported a high level of variation in the erectile function rates depending on the specific definition used. In a longitudinally followed cohort of 260 patients, only 5% of men described their erections firm enough for intercourse, whereas 61% rated their ability to function sexually as *good* or *very good*.

As more standardized definitions are used, reported erectile function preservation rates have decreased. To add to the confusion, erectile function rates currently include men successfully using PDE-5 inhibitors, who by definition have ED. Very few men are as good postoperatively as they were preoperatively, and virtually none are better off. Most lose some degree of erectile function.

Herbert Lepor, MD: An excellent point. We had some men who do not regain potency, yet have excellent orgasms and are very happy with their intimacy. Others are potent by definition because they can achieve penetration, yet they are unhappy with the quality of their erections. It is not only about the erection.

What are some of the factors that predispose to ED after RP?

Jason D. Engel, MD: As Dr. McCullough has already mentioned, the role of erectile nerves in preserving erectile function after prostatectomy

is clearly important. Unfortunately, predisposing factors that exist prior to surgery play an equal if not more important role in determining whether erections return. The status of the patient's relationship with his partner, his personal interest in sex, and his partner's interest in sex are the strongest predictors of sexual outcome postprostatectomy. Along with motivation, blood flow and comorbidities that affect blood flow, such as obesity, cardiovascular status, diabetes, smoking, etc, are also strong predictors of outcome. And as we know, a patient must come to his prostatectomy with excellent erections and few signs of ED to expect erectile function to return after surgery.

Herbert Lepor, MD: In the article we presented at the American Urological Association (AUA) meeting in May 2008,⁴ we ascertained factors that influenced preservation of potency. Our univariate analysis revealed that age, prior history of hypertension, coronary artery disease, the quality of baseline erections, frequency of intercourse, prior use of PDE-5 inhibitors, and the number of cavernous nerves preserved all influenced return of erectile function.

Andrew McCullough, MD: A commonly held theory is that in the postoperative period the penis is in a constant state of hypoxia, which is detrimental to the health of the organ.

During erection, oxygen tension changes in the corpus cavernosum from 25 to 40 mm Hg in the flaccid state to 90 to 100 mm Hg in the erect state. There are acute and long-term effects of chronic hypoxia. Oxygenation of the cavernous tissue is an important factor in the regulation of local mechanisms of erection. Arterialization of blood flow during nocturnal erections is crucial to providing the free oxygen necessary for the formation of NO by both neuronal

and endothelial nitric oxide synthase (e-NOS). After crossing into smooth muscle cells, NO reacts with guanylate cyclase to catalyze the conversion of guanosine triphosphate (GTP) to guanosine monophosphate (GMP). The lack of free oxygen, transported to the penis by oxygenated hemoglobin, is theoretically detrimental to the synthesis of NO and cyclic guanosine monophosphate (cGMP) formation. Poor oxygenation prevents the synthesis of cGMP and predisposes to cavernous fibrosis due to increased synthesis of collagen via transforming growth factor beta (TGF- β), with resulting ED. The induction of collagen is related to decreased corporal oxygenation or hypoxia. Cavernous neurotomy was demonstrated to produce hypoxia and fibrosis in rat corpus cavernosum.⁸ In this study, ablation of cavernous nerves bilaterally was associated with increased TGF- β 1 mRNA expression and hypoxia-inducible factor 1 α , TGF- β 1, and collagen I and III protein expression. It was theorized that agents that decrease corporal hypoxia might improve erectile function after RP. Treatment of human corpus cavernosum smooth muscle cells with TGF- β 1 increased collagen synthesis⁹; this increase in collagen was attenuated by simultaneous administration of prostaglandin E1 (PGE1). In addition, PGE1 suppressed TGF- β 1 induction of TGF- β 1 mRNA.

Kim and colleagues^{10,11} showed that isolated human and rabbit corpus cavernosum tissue strips exposed to arterial-like PO₂ relaxed with acetylcholine and with electrical stimulation of the autonomic dilator nerves. Decreasing PO₂ to levels measured in the flaccid penis resulted in loss of the relaxation response. Normoxic conditions readily restored endothelium-dependent and neurogenic relaxation. In the rabbit corpus cavernosum, low PO₂ reduced basal levels of cGMP and

prevented cGMP accumulation induced by stimulation of dilator nerves. Furthermore, low PO₂ inhibited nitric oxide synthase activity in corpus cavernosum cytosol. The investigators concluded that physiological concentrations of oxygen modulate penile erection by regulating NO synthesis in corpus cavernosum tissue.

Limited invasive blood gas studies in human models have shown decreased oxygen tension in vasculogenic impotence and a hypoxic cavernosal state in the flaccid penis. Corporal and penile flaccid oximetry was examined in a comparative study of 101 men (22 potent, 26 non-RP ED, and 53 RP ED).¹² Although there was no significant difference in StO₂ among ED patients, RP ED patients had significantly lower corporal StO₂ than potent patients.

Histomorphological studies in men suggest there are changes in cavernous smooth muscle and collagen content after RP.¹³ As soon as 2 months after surgery, trabecular elastic fibers and smooth muscle fibers were decreased, and collagen content was increased, in the corpora cavernosa compared with presurgical levels; these changes were exacerbated after 1 year. This fibrosis appears to be due to denervation and/or ischemia. These findings suggest that ED after RP may be associated with increased cavernous fibrosis and may account for the observations that a program of regular corporal oxygenation with intracorporal PGE1 may reduce the degree of postoperative ED.¹⁴

Herbert Lepor, MD: Does nerve-sparing surgery improve outcomes?

Jason Engel, MD: At this point, I do not think that anyone would argue that sparing the erectile nerves does not improve outcome. There is abundant literature that shows improvement in erection rates after prostatectomy when both versus 1 versus neither nerve bundle is spared. However, the quality of a nerve-sparing operation remains a subjective as-

essment, so there will always be inexactness to this claim. Robotic dissection and visualization allows surgeons to spare the nerve bundles in a more comprehensive and consistent manner. However, linearity between my subjective assessment of nerve sparing and whether erectile function returns cannot be proved. The importance of blood flow and the revascularization of the penis via collateralization are central to the recovery of erectile function after prostatectomy. Finding the best penile rehabilitation protocol is the highest priority in improving sexual outcomes after prostatectomy. In highly experienced hands, surgical technique cannot be refined much further in terms of nerve sparing.

Herbert Lepor, MD: Does robotic prostatectomy improve outcomes?

Jason D. Engel, MD: Dr. McCullough and I have just finished the MUSE RP-01 trial, which has provided some insight. As a multisite penile rehabilitation trial comparing daily MUSE® (alprostadil urethral suppository; VIVUS, Inc, Mountain View, CA) versus daily Viagra® (sildenafil citrate; Pfizer Inc., New York, NY) in both the open and robotic surgical setting, it has allowed a comparison of open versus robotic sexual outcomes within the same protocol. This makes MUSE RP-01 truly unique, particularly given the fact that nearly 200 patients were enrolled prospectively and randomized.

We found no differences in International Index of Erectile Function (IIEF) scores between open and robotic surgery, although we did show some significant differences favoring robotic surgery when looking at stretched penile length and intercourse success. Whether stretched penile length is a surrogate for penile health and eventual return of erectile function has not been fully established, so we are not sure of the significance of this finding. Whether the observations are real or

due to intersite variability is not clear. This significant finding warrants further study. Nevertheless, although certainly not definitive, MUSE RP-01 has strengthened my own personal belief that there are inherent advantages of the robotic approach that lead to improved sexual outcomes.

Herbert Lepor, MD: As far as penile length, it is important to note that the difference in outcome may simply be due to the fact that the penis was stretched more vigorously at the robotic surgical site than at the open surgical site. There is no good explanation to support the observation that open surgery causes the penis to shrink in size more than robotic surgery does because initial postoperative measurements and potency rates were not different. The minimal observed difference is most likely due to interobserver variability. A study presented at the AUA meeting in 2007¹⁵ that compared potency outcomes between open versus robotic RP using the same self-administered instrument and definition of potency showed a slight but not statistically significant advantage of open versus robotic surgery. The study that Dr. Engel referred to earlier, where robotic RP was performed at George Washington University and open RP was performed at New York University, also failed to show an advantage of either technique.

What is the timeline for natural return of erectile function after RP?

Jason D. Engel, MD: Patients should not expect appreciable return of natural potency until 6 months postprostatectomy, and, if lucky enough to start to recover at that point, erectile function will typically continue to improve over a 2- to 3-year span. Erection rates are most commonly reported at 1 year, but in fact a very small minority of patients will have natural, spontaneous erections at 1 year. This has led many major centers to start reporting their rates at

18 months to 2 years. A great study would follow a cohort for 5 years. Such a study would show that several men have their first spontaneous intercourse between years 2 and 3. This is exactly why I push my patients to have artificial erections as early as possible because they will typically wait a long time for spontaneous recovery.

Herbert Lepor, MD: My group just published an article¹⁶ that queried men whether their erection changed between 2 and 4 years postoperatively. Approximately 20% of men indicated that their erections improved moderately or markedly. Therefore, we should not tell men their maximal return of erectile function occurs by 18 months. Men who have good function seem to be the ones who improve the most after 2 years.

What is the concept of penile rehabilitation?

Andrew McCullough, MD: The concept of end-organ rehabilitation after a nerve injury is not new. Every neurologist and orthopedist quickly refers a patient for muscle rehabilitation after a nerve injury. Why should it be different for the penis? Montorsi¹⁴ was the first to show that pharmacologic intervention could affect the outcome of nerve-sparing surgery. Animal models have likewise shown the benefit of pharmacologic intervention with PDE-5 inhibitors and immunophyllin ligands. Padma-Nathan and colleagues¹⁷ showed a 7-fold benefit with nightly sildenafil over placebo at 1 year. Despite the mounting evidence and general agreement that penile rehabilitation is important, urologists are still lacking a consensus as to the right regimen.

Herbert Lepor, MD: Do PDE-5 inhibitors improve recovery of erectile function? If so, what is the mechanism?

Andrew McCullough, MD: The advent of PDE-5 inhibitors revolution-

ized the treatment of post-RP ED, and PDE-5 responsiveness has been incorporated into the definition of successful ED outcome after RP. However, post-RP patients remain one of the most PDE-5 inhibitor refractory groups, with intercourse success rates of approximately 40% in placebo-controlled studies.¹⁸⁻²⁰ An intact cavernous nerve-smooth muscle relationship is optimal for maximum PDE-5 effectiveness. Any reduction in the number of firing nerves or smooth muscle responsiveness decreases the effectiveness of the PDE-5 inhibitors. The responsiveness to PDE-5 inhibitors after RP is clearly dependent on the time from surgery, with the maximum recovery taking place at 18 to 24 months,²¹ within the time frame expected for nerve recovery.²² That being the case, what rationale is there for the use of sildenafil in penile rehabilitation? Indeed, the early use of PDE-5 inhibitors has been questioned as providing little to no value.²³

A randomized, placebo-controlled study of 76 men after bilateral NSRRP found serial NPT (1, 4, 8, and 12 months) and unassisted erectile function satisfactory for vaginal penetration at 1 year in men who took 50 or 100 mg of sildenafil citrate nightly for 9 months postoperatively.¹⁹ The investigators found a 7-fold improvement in normalization of erectile function in the treatment group over placebo at 1 year. NPT was better in the treatment group, with most of the benefit demonstrated in the first 4 months and a profound loss of Rigi-Scan® (Timm Medical Technologies, Inc., Eden Prairie, MN)-detected NPT at 1 month postoperatively.¹⁷

The purported mechanisms to explain the results are reduction in postoperative corporal hypoxia enhanced endothelial function and possible neurotropic mechanisms. Montorsi and colleagues²⁴ showed in a placebo-controlled study that the use of sildenafil citrate taken nightly enhances NPT. It is

possible that the nightly sildenafil citrate enhances corporal oxygenation in a suberectile state, much like PGE1 was shown to enhance corporal StO₂. The administration of nightly sildenafil citrate was shown to decrease penile fibrosis in the human after RP.¹³ In patients in whom vascular endothelial function is impaired by conditions such as aging, diabetes, hypertension, or hyperlipidemia, administration of sildenafil citrate improved endothelium-dependent vasodilation.²⁵⁻²⁷ As endothelium-derived NO synthase (e-NOS) is important in the maintenance of erections, it is possible that sildenafil citrate is potentiating the pro-erectogenic effect of e-NOS. In rats treated within 24 hours of stroke, sildenafil citrate increased neurogenesis and reduced neurological deficits,²⁸ suggesting the capacity to promote recovery of nerve function. Sildenafil citrate may be accelerating or enhancing cavernous nerve regeneration. Comparable studies have not been carried out with the other PDE-5 inhibitors.

A recent, large, placebo-controlled penile rehabilitation study²⁹ with another PDE-5 inhibitor, vardenafil, demonstrated no advantage of rehabilitative nightly or on-demand vardenafil over placebo in terms of return of erectile function at 11 months, or of PDE-5 inhibitor responsiveness. Differences in methodology and endpoints make it impossible to reconcile the sildenafil citrate and vardenafil penile rehabilitation studies but do underscore the need for more rigorously performed studies.

Herbert Lepor, MD: Is there evidence that MUSE has a role in penile rehabilitation?

Jason D. Engel, MD: This is precisely what the MUSE RP-01 trial set out to examine. In this trial, patients undergoing robotic and open radical prostatectomy were randomized 2 to 1 to either 9 months of daily 250 µg MUSE versus daily 50 mg sildenafil, with test doses of 100 mg of sildenafil

for on-demand use at prescribed times within this 9-month period or after a washout period. Spontaneous intercourse was also recorded after the 9-month period ended. The IIEF-30 was used as the primary measurement of potency, with Sexual Encounter Profile (SEP) diary data and global assessment questionnaires collected as well.

The 2 groups were similar in terms of IIEF success, although there was significant superiority favoring MUSE over sildenafil at 6 months after prostatectomy. Thus, MUSE RP-01 establishes MUSE as at least as efficacious in the setting of penile rehabilitation after prostatectomy as sildenafil. What surprised me, however, was that the dropout rate was no higher in the MUSE group than the sildenafil group, and that penile pain usually resolved if the patient continued with daily dosing for at least 1 week. The dropout rate was approximately 25% in both groups, with sildenafil patients most commonly dropping out due to vision changes, nasal stuffiness, and dizziness.

What also became quite clear during this 1-year study was that although the daily MUSE patients did not necessarily have more success with on-demand 100 mg sildenafil throughout the year, several of the patients that failed at this on-demand dose of sildenafil were regularly using their 250- μ g MUSE dose to achieve satisfactory intercourse. I had previously never considered 250 μ g of MUSE to be an erectogenic dose. MUSE RP-01 did not call for SEP data to be collected with on-demand 250 μ g of MUSE, but nevertheless patients would regularly turn in SEP data that showed failure with 100 mg of sildenafil and many successful intercourse attempts with 250 μ g of MUSE. I eventually began to ask patients to report SEP diary data using 250 μ g of MUSE as well as 100 mg of sildenafil, and my impression only became stronger.

I should note that nearly every patient who had been taking 250 μ g of MUSE daily that succeeded with 100 mg of sildenafil would preferentially continue taking on-demand MUSE after the 1-year period of the trial. In other words, patients who had been using MUSE for rehabilitation would typically ask for MUSE prescriptions in addition to or instead of sildenafil for on-demand usage after 1 year, even if they had reported success with both medicines at the end of the study period.

These observations, coupled with my lack of confidence in PDE-5 inhibitors as a useful on-demand solution for erections during the first year of recovery after prostatectomy, have led to my preferential use of MUSE as part of a penile rehabilitation program. I think MUSE RP-01 would have been even more informative if patients had been given both MUSE at the 1000- μ g dose and/or sildenafil at the 100-mg dose for on-demand intercourse. I anecdotally witnessed 60% on-demand success with 250 μ g of MUSE during RP-01. This is the success rate typically reported with much higher doses of MUSE, so I suspect such a higher dose would have shown even higher success within the confines of a trial.

Herbert Lopor, MD: There are men who do not achieve an erection with PDE-5 inhibitors during the early recovery phase after RP. Many of these men will not embark on a penile injection regimen. For these men, MUSE is an excellent alternative for achieving erections adequate for intercourse. I believe it is underutilized in the management of post-RP ED.

What is the mechanism for MUSE in penile rehabilitation?

Andrew McCullough, MD: Costabile and colleagues³⁰ evaluated the erectile response to intraurethral PGE1 in 384 men with ED after RP, with treatment beginning no less than

3 months after surgery. This was a multi-institutional study before the approval of PDE-5 inhibitors and included men at differing times from surgery and with both NSRRP and NNSRRP. Initial doses were 125 or 250 μ g, which were increased to 500 or 1000 μ g if the erectile response was inadequate. When treatment was administered in the clinic, 70% of the participants developed an erection sufficient for intercourse. These subjects were then randomized to a 3-month at-home trial with either PGE1 or placebo. During this phase 57% of the PGE1 subjects had successful intercourse at least once at home, compared to an intercourse rate of 6.6% of men treated with placebo. These rates compare favorably with PDE-5 inhibitor response rates in younger men with bilateral NSRRP. Adverse events included penile pain and urethral pain/burning. This placebo-controlled study supported the use of a less invasive treatment modality in men who might not otherwise respond to PDE-5 inhibitors.

More recently, Raina and coworkers³¹ reported the results of a study in 54 prostatectomized men who used transurethral PGE1 (250, 500, or 1000 μ g). Subjects experienced ED for at least 6 months after surgery before initiating treatment. Fifty-five percent of the subjects were able to achieve and maintain erections sufficient for intercourse while on treatment, and 48% continued long-term therapy with a mean use of 2.3 years. There were no significant differences in responses between those subjects who had a nerve-sparing surgery (34 patients) and those who had a NNSRRP procedure (20 subjects).

A recent report demonstrated the efficacy of early intervention with transurethral PGE1 in men with prostatectomy-associated ED.³² In this nonrandomized study, 56 men who had a bilateral nerve-sparing

operation began treatment with 125 μg PGE1 3 times a week within 4 weeks of surgery; another 35 men served as an observational control group. Treatment was continued for approximately 6 months, with the dose of PGE1 increased to 250 μg after 6 weeks. In the PGE1 group, 38 of 56 men (68%) continued treatment for the entire 6 months. At 6 months, 28 of 38 men (74%) resumed sexual activity; 15 (39%) had natural erections sufficient for vaginal penetration without treatment, and 13 (34%) used PGE1 as an erectile aid when having intercourse. In the observation group, 13 out of 35 men (37%) resumed sexual activity, 4 (11%) had natural erections sufficient for vaginal penetration, and 9 (25%) used adjuvant treatments. This encouraging but nonrandomized small study suggests that postoperative transurethral PGE1 is well tolerated and may be beneficial in penile rehabilitation in the ED that accompanies RP. The ability of PGE1 to increase smooth muscle relaxation and blood supply, even in the presence of local nerve trauma, suggests that the drug may rehabilitate nerves and blood vessels that are damaged during surgery.

One possible mechanism of nerve rehabilitation is through cyclic adenosine monophosphate (cAMP), which is reported to play a role in regeneration in both the peripheral and central nervous systems.^{33,34} In an *in vitro* model of axotomy using adult retinal ganglion cell axons, increasing cAMP promoted growth cone regeneration under conditions that normally would result in low regenerative potential.³⁵ Jiang and associates³⁶ demonstrated that endogenous levels of cAMP are higher in young neurons, which are able to regenerate after injury, as compared to older neurons, which lose the ability to regenerate.

Kogawa and colleagues³⁷ reported on nerve regeneration in dorsal root gan-

glia (DRG) of diabetic rats. Prior to nerve crush injury there were no apoptosis-positive DRG neurons observed; subsequent to axonal injury, apoptosis-positive neurons were seen in diabetic but not in nondiabetic animals or in rats treated with a PGE1 analog. The regeneration distance at day 7 after injury was shorter in diabetic rats than in animals in the other groups. The cAMP content of DRG on day 7 was higher than that at day 0 in nondiabetic and PGE1-treated animals, whereas it was not increased after 7 days in diabetic rats. The results suggest that PGE1 is able to rescue DRG neurons from apoptosis and that it improves axonal regeneration in diabetic rats.

The beneficial effect of PGE1 on corporal oxygenation was demonstrated by Padmanaban and colleagues.³⁸ In 101 patients with ED, the administration of PGE1 intra-urethrally or intracorporally resulted in a 37% to 57% increase in corporal oxygen saturation (StO_2). The increase in oxygenation occurred in the MUSE patients at a dose of 125 μg and despite marginal tumescence. Hence, PGE1 may not only rehabilitate penile function after a RP by directly relaxing cavernosal smooth muscle, thereby enhancing blood flow, but also may stimulate regeneration of local nerves, thereby increasing NO release. Such a dual mechanism of PGE1 would shorten recovery time and hasten the return of spontaneous erections and PDE-5 responsiveness. These results indicate that PGE1 is able to reverse some of the deleterious effects of RP that result in ED. Further, it appears that the earlier after surgery PGE1 is initiated, the better the erectile response. The ability of PGE1 to directly induce smooth muscle relaxation and increase blood supply, even in the presence of local nerve trauma, as well as stimulate regeneration of damaged nerves, suggests that the drug may rehabili-

tate nerves and blood vessels that are traumatized during surgery.

Herbert Lepor, MD: What is your penile rehabilitation program?

Jason D. Engel, MD: In the past, my program centered on either daily sildenafil or tadalafil 3 times per week, with on-demand PDE-5 usage at the highest approved dose. However, when enrolling patients in postprostatectomy trials other than MUSE RP-01, in which drugs are not provided to patients, I quickly learned that compliance to protocols using PDE-5 inhibitors is at best 50%. Cost continues to be the primary determinant as to whether a motivated patient will comply with a penile rehabilitation program. As previously stated, I am also not very impressed with the efficacy of PDE-5 inhibitors in the first 9 months postprostatectomy.

The on-demand success of 250 μg of MUSE in MUSE RP-01 taught me that a penile rehabilitation program must include, at least within the first year, an on-demand solution other than a PDE-5 inhibitor if one wants happy patients. I have increased my usage of vacuum devices, and although this is useful in perhaps 50% of patients for on-demand intercourse, complaints of pain due to the band are frequent. I find introduction of penile injections, even for on-demand usage, to be a very hard sell to patients until they are convinced there is no other way to achieve success.

My preferred postprostatectomy rehabilitation program has evolved into daily or every-other-day MUSE at the 250 μg strength for approximately 9 months, with on-demand use of 1000 μg of MUSE. I layer in on-demand PDE-5 inhibitors at the 6-month point, and encourage use of either MUSE or a PDE-5 inhibitor for on-demand intercourse. Patients are far more willing to use MUSE after a prostatectomy than in general practice as long as the patient is given a

realistic expectation of success prior to surgery, with the clear understanding that the patient and his partner will have to work at success. I liken this process to a knee reconstruction—it will take sometimes painful and hard work after surgery to ensure the best outcome possible. Thus, I find my patients do not seem reluctant to try MUSE after prostatectomy, and view taking it daily as simply a part of their recovery. It is for this reason that those with penile pain are willing to work through it until it resolves. Patients with ED for other reasons are typically not willing to work through the pain, or to overcome their fear of a penile suppository.

The main impediment to this regimen is cost, of course, as is common to all medicines used for penile rehabilitation. However, VIVUS has introduced the services of a third-party precertification company that ensures that the patient gets up to 12 doses per month fully covered. I have found this to be extremely helpful, and although not perfect, this service does succeed without any imposition on the patient, me, or my staff 70% to 80% of the time. I am not aware of any such service provided by the makers of PDE-5 inhibitors. Using MUSE in my penile rehabilitation program is often the most economical approach for the patient and the most hassle-free approach for me and my staff.

Andrew McCullough, MD: The recovery of erectile function after nerve-sparing prostatectomy begins with a good nerve-sparing operation. Despite our best surgical efforts, all men will experience a decrease in erectile function after surgery. Our goal is to help the patient minimize the extent and duration of the dysfunction. With our current “bag of tricks,” there is no reason for a man not to resume assisted penetrative sexual activity within 6 weeks of

surgery, if he and his partner are so motivated. The need for early intervention cannot be overemphasized. Every man has heard the expression “use it or lose it.” There is increasing evidence that sexual rehabilitation regimens after prostate cancer surgery help prevent irreversible long-term functional damage to the penis. The best patient is an informed patient. Sexual rehabilitation begins before surgery. Key to the success of any program is the man’s understanding of the rationale and the need. Both he and his partner will meet with me or another physician. We become their rehabilitation coaches prior to prostate surgery. We discuss realistic goals and expectations for the recovery of sexual function and plan an individualized rehabilitation plan. The penile rehabilitation program begins prior to surgery, and includes:

- Viagra 50 mg nightly starting the week before surgery
- A vacuum erection device (VED) prescription (provided preoperatively)
- Viagra 50 mg nightly after discharge from the hospital
- Once a day usage of the VED after the removal of the catheter
- Follow-up visit with rehabilitation coach 1 week after catheter removal
- MUSE 500 or 1000 μg 2 \times per week (VED and Viagra not used on those days)
- Follow-up visit at 3 months; injection therapy initiated if inadequate erections for intercourse

Our rehabilitation plan helps maintain sexual satisfaction and overall quality of life for the man and his partner as they head into prostate cancer survivorship. Although sexual dysfunction may not be their first concern as they contemplate surgery, it is potentially the single most common long-term problem after curative surgery, open or robotic. We are ded-

icated to helping the patient and his partner retain sexual function after prostate surgery.

Herbert Lepor, MD: Thank you for a very informative discussion on advances in the treatment of post-prostatectomy ED. Over the past decade there have been many new options for rehabilitation and treatment of ED following RP. We have available a host of interventions for enhancing on-demand erectile function. You have provided compelling arguments in favor of aggressive penile rehabilitation strategies. The challenge we face now is defining the optimal penile rehabilitation protocol and convincing our fellow urologists to offer this regimen following RP. ■

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