Pharmacologic Penile Rehabilitation

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Introduction

Excellent long-term results have been obtained with radical prostatectomy (RP) for low-grade organ-confined adenocarcinoma of the prostate. Han et al. [1] reported a 15-year overall actuarial cancer-specific survival rate of 90% in patients with Gleason 6 or 7 (3 + 4) prostate cancer treated with RP. Although RP is an excellent therapy for prostate cancer, it is associated with several quality-of-life issues.

The most prevalent sequelae of RP are erectile dysfunction (ED) and urinary incontinence. A recent review reported that 93.4% of men who had undergone RP used no pads or one pad for urinary incontinence at 1 year [2]. This study highlights the acceptable percentage of patients who regain urinary continence. Unfortunately, the same cannot be said for erectile function. Prior to a series of anatomic discoveries about 20 years ago, ED was expected after RP. Today, the percentage of patients who regain potency after surgery varies greatly, even with the application of nerve-sparing techniques. At academic institutions with experienced surgeons, the rate of recovery for patients with ED after RP varies from 60% to 85%, although this number has been reported to be as low as 15% at other institutions [3,4].

Rationale for Postprostatectomy Penile Rehabilitation

Numerous factors can predict recovery from ED after RP. Factors that promote erectile function recovery include normal preoperative erectile function, lack of phosphodiesterase type 5 (PDE5) inhibitor use, younger patient age (< 60 years), absence of vascular disorders (eg, coronary artery disease, diabetes, hypertension, and dyslipidemia), and nonsmoking status [5,6].

The majority of patients who have undergone nerve-sparing RP have ED. Some patients may take up to 3 years to reach their new baseline erectile status [3]. Researchers believe that neurapraxia causes the ED. Neurapraxia can result from mechanically induced nerve stretching that may occur during prostate retraction, thermal damage to nerve tissue caused by electrocautery, ischemia of the nerves secondary to disruption of blood supply in attempted control of surgical bleeding, and local inflammatory effects associated with surgical trauma [7].

During the period of neurapraxia, low oxygen tension ensues in the cavernosal tissue. In an experimental model, significant overexpression of such hypoxia-related substances as tumor growth factor-β1 (TGF-β1) and collagens I and III was found in rats that had undergone bilateral incision of their cavernosal nerves, compared with control rats [8•]. In human cavernosal tissue, low oxygen tension inhibits production of prostaglandin-E (PGE). PGE inhibits collagen formation by inhibiting TGF-β1, which induces collagen synthesis [9]. With the inhibition of PGE, TGF-β1 can induce connective tissue synthesis. The trabecular smooth muscle is then replaced with collagen, which leads to the loss of the cavernous elastic mechanism and results in venogenic ED [10,11,12•].

With the finding that PGE inhibits TGF-β1, Moreland et al. [13] sought to assess the role of cyclic adenosine monophosphate (cAMP) in the regulation of connective tissue biosynthesis in human corporal smooth muscle cells in culture. They found that cAMP synthesis in human corpus cavernosum smooth muscle cells inhibits TGF-β1–induced collagen synthesis. These data suggest that agents causing...
an increase in cAMP or a decrease in phosphodiesterase activity, which would lead to increased levels of cAMP, could result in a decrease in collagen deposition [13]. In 2004, Schwartz et al. [14] assessed the effect of sildenafil on the intracorporeal smooth muscle content of patients who had undergone RP. Group one received 50 mg of sildenafil and group two received 100 mg of sildenafil every other night for 6 months following catheter removal. A percutaneous biopsy of the intracorporeal smooth muscle was performed prior to incision for RP and under local anesthesia 6 months later. The authors found a statistically significant increase in smooth muscle content in group two, but not in group one. This suggests that higher doses of sildenafil may increase smooth muscle content.

Apoptosis may also play a role in ED following prostatectomy. User et al. [15] performed bilateral neurotomy of the rat penis and found significant apoptosis in the subbulcineal smooth muscle cells. Apoptosis in the region of the subthunical venular plexus causes a defect in the vasoocclusive mechanism of the corpus cavernosum, which leads to ED. McVary et al. [16] recently confirmed that both intrinsic and extrinsic apoptotic pathways were activated in rats with disrupted cavernous nerves.

Despite the implications that venous leakage causes ED after RP, Mulhall et al. [17,18] noted a reduction in arterial inflow, possibly due to the ligation of accessory internal pudendal arteries during prostatectomy.

Pharmacologic Penile Rehabilitation
Postprostatectomy penile rehabilitation can include pharmacologic rehabilitation, a vacuum erectile device, and possibly programmed cavernous nerve stimulation. This paper only reviews the pharmacologic rehabilitation programs.

Intracavernosal injection
Based upon the pathophysiology of ED after RP, one should be able to alter the sequence of events that leads to ED. Montorsi et al. [19] were the first to attempt to alter this pathway. In 1997, these authors randomized 30 patients who had undergone bilateral nerve-sparing RP for clinically localized prostate cancer to either group one, in which subjects received an intracavernosal injection (ICI) of alprostadil three times a week for 12 weeks, or group two, in which no erectogenic therapy was administered. At 6 months, 67% of the patients in group one reported a return of spontaneous erections satisfactory for sexual intercourse, compared with 20% of the patients in group two. Based on Doppler sonography at 6 months, failure in two patients (17%) in group one was secondary to cavernous venoocclusive dysfunction, compared with eight patients who failed (53%) in group two. In two patients (13%) in group two, failure was secondary to cavernous artery insufficiency. The authors concluded that the injections of alprostadil decreased the hypoxia-induced tissue damage, subsequently leading to a higher possibility of spontaneous erectile activity at 6 months [19]. However, long-term follow-up results with scheduled ICI are lacking. Also, our recent prospective study demonstrated that long-term compliance with penile injection rehabilitation is problematic. Only 52.3%, 25.9%, and 35.3% of the patients were performing penile injection for rehabilitation as prescribed at 4, 8, and 12 months respectively upon follow-up [20].

PDE5 inhibitors
With the advent of PDE5 inhibitors, Montorsi et al. [21] sought to assess the effectiveness of sildenafil for increasing nocturnal erections in men with ED of various causes. Patients randomized to receive 100 mg of sildenafil had a significantly better overall quality of nocturnal erections, as recorded by the Rigiscan (Timm Medical Technologies, Inc., Eden Prairie, MN) device, when compared with patients in the control group. The question then followed: would an increase in postprostatectomy nocturnal erections as a result of sildenafil lead to a higher incidence of spontaneous erectile function?

With PDE5 inhibitors, Padma-Nathan et al. [22] presented the first study for penile rehabilitation at the 2003 annual meeting of the American Urological Association. Seventy-six men with normal preoperative erectile function who had undergone bilateral nerve-sparing RP were randomly assigned to receive sildenafil or placebo nightly. Treatment began 4 weeks after surgery and consisted of 50 or 100 mg of sildenafil or placebo every night for 36 weeks, followed by 2 months without therapy. At the end of the trial, 27% of men in the sildenafil group, compared with 4% of men in the placebo group, reported the return of spontaneous normal erections. Additionally, the duration and amplitude of nocturnal erections progressively increased in the sildenafil-treated group. Although the results of this study are modest, it is the first study to correlate the return of nocturnal erections with the return of spontaneous sex-stimulated erections sufficient for intercourse.

Interestingly, a recent retrospective study by Montorsi et al. [23] showed no significant difference in erectile function in patients taking on-demand PDE5 inhibitors and those using PDE5 inhibitors as rehabilitative treatment after bilateral nerve-sparing RP. The International Index of Erectile Function (IIEF) Erectile Function (EF) domain at the mean 12-month follow-up was 19.5 ± 9.4 out of a total possible score of 30 for patients using on-demand PDE5 inhibitors, compared with 18.3 ± 4.0 for patients using PDE5 inhibitors as rehabilitation. Multicenter clinical trials are needed before the cost-effective and therapeutic benefits of daily use, compared with on-demand use, of PDE5 inhibitors in restoring spontaneous erections can be determined.

Combination of ICI and PDE5 inhibitors
In 2002, Montorsi et al. [24] randomized patients to receive three ICIs of alprostadil per week for 3 months, followed by oral sildenafil as needed for 3 months, com-