

## Erectile Dysfunction Following Radical Prostatectomy

a report by

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Radical prostatectomy (RP) is the most common treatment for organ/specimen-confined prostate cancer. The surgical techniques used to perform RP have been refined and improved over time to the extent that fewer than 10% of patients develop problems with urinary incontinence. However, most patients still experience erectile dysfunction (ED) following RP.<sup>1-2</sup>

Fortunately, ED is amenable to treatment. A number of safe and effective treatments are available, such as vacuum constriction devices (VCDs), transurethral vasodilators, intracorporeal (IC) injection of vasoactive drugs, oral therapy, and penile implants. New research suggests that early penile rehabilitation with non-oral erectoids can aid in the return of normal penile function by improving tissue oxygenation and preventing penile fibrosis. In the future, new therapies, such as sural nerve grafting and the administration of growth factors that stimulate cavernous nerve regeneration, may enable surgeons to help their RP patients avoid the emotional devastation caused by post-operative ED.

### VCDs

A basic VCD model consists of a cylinder with a pump, which is attached to the end of the penis. The pump is used to expel air out of the cylinder, creating a vacuum. This forces blood to flow into the penis, which, as a result, swells and becomes erect. A constriction ring is then placed around the base of the penis to maintain the erection.

Current models are safe and produce penile rigidity that is sufficient for vaginal penetration and intercourse in most patients. Efficacy rates range from 60–80%, and satisfaction scores are generally high for both patients and their partners. Cookson and Nadig, for example, found that 80% of patients with RP-associated ED who were using a VCD were satisfied with the treatment.<sup>3</sup> Compliance after one year of activity decreases from 70 to 50%,<sup>4</sup> partly due to tightness or pain from the constriction ring and diminished sensation of the phallus and glans.<sup>5</sup>

### Transurethral Vasodilators

Intraurethral alprostadil was introduced by Padma-Nathan et al. in 1997. With this therapy, a medicated pellet containing alprostadil is inserted directly into the penis via the urethra (medicated urethral system for erection (MUSE)). An erection generally occurs within 10–15 minutes of application, and will last for up to one hour.

The Cleveland Clinic studied the efficacy and compliance of MUSE in 27 patients who developed ED after undergoing RP between 1996 and 2000.<sup>6</sup> Patients completed the abridged version of the International Index of Erectile Function (IIEF)-5 questionnaire, which is also known as the Sexual Health Inventory for Men (SHIM). The results showed that MUSE was effective in 13 of the 27 patients (48%) after a mean of 2.2 years; however, the other 14 patients (52%) had discontinued treatment after only a mean of eight  $\pm$  1.4 months, mainly because of an inadequate response or side effects. This study concluded that, although MUSE is effective in patients who undergo either nerve-sparing or non-nerve-sparing RP, one of every two users will discontinue therapy because of an insufficient erectile response.

### Intracorporeal Injection

Patients using this type of therapy inject prostaglandin E1 (PGE1) or alprostadil in combination with papaverine and phentolamine (triple mixture) directly into the cavernosal blood vessels via a syringe.<sup>7-8</sup> Phentolamine is a direct adrenoceptor blocker, whereas alprostadil and papaverine modulate levels of cyclic 3', 5'-adenosine monophosphate (cAMP) in the cells. All four of these drugs work by increasing penile blood flow by relaxing the arterial and trabecular smooth muscles.<sup>9</sup> An erection occurs within 10 minutes of the injection, and generally lasts up to one hour.

A number of studies have documented the efficacy of IC therapy in patients with ED caused by RP. Dennis and McDougal reported a success rate of 85%.<sup>10</sup> Rodriguez Vela et al. found that IC PGE1 injection resulted in adequate rigidity in 95% of patients.<sup>11</sup>

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Mulhall et al. found that 75% of their patients with ED had a good response to IC injection.<sup>12</sup> However, dropout rates in many series exceed 40% due to injection pain (14%), difficulty in reproducing a successful injection (10–20%), and penile fibrosis (2–15%).<sup>13</sup> In addition, many patients find it difficult (both physically and emotionally) to use a needle. In fact, the non-compliance rate ranges between 40% and 60% after one year, simply because of this fact.<sup>12</sup>

The authors' group conducted a study to evaluate the long-term efficacy and compliance of IC injection therapy in 102 patients who had undergone RP.<sup>14</sup> They found that 69 (68%) of the 102 post-prostatectomy patients were satisfied with IC injection therapy and that 49 (48%) chose to continue using the therapy in the long term (mean 3.5 years). However, the compliance rate was 70.6%, partly because the patients had either lost their partners or experienced a return of natural erections. The primary reasons for discontinuation in the study included inadequate erections.<sup>15</sup> Future studies should assess whether other injectable agents (e.g. forskalin, vasoactive intestinal peptide, and moxislyate) alone or in combination can increase efficacy and long-term compliance.

### Oral Therapy

In 1998, the first effective oral treatment for ED—sildenafil citrate (Viagra® Pfizer Pharmaceutical)—became available. Currently, oral therapy is the first treatment option for patients with ED caused by a variety of organic and psychogenic causes.<sup>16</sup>

The Cleveland Clinic was among the first to investigate the effects of sildenafil in patients following RP and to assess whether the presence or absence of the neurovascular bundles affects treatment outcomes. The initial publication concerned 15 patients who underwent bilateral nerve-sparing RP. Of these, 12 reported vaginal penetration at the one-year follow-up.<sup>17</sup> An update to this series, which consisted of 91 patients,<sup>18</sup> suggested that the presence of one or both of the neurovascular bundles does indeed affect outcomes. According to the authors, sildenafil can improve ED in as many as 70% of RP patients when a bilateral nerve-sparing procedure is performed, but only in half of patients when a unilateral nerve-sparing procedure is performed.

A three-year follow-up study showed that most patients who responded to sildenafil at one year (72%) continued to do so at three years.<sup>19</sup> SHIM scores were comparable between both follow-up points. The degree of neurovascular preservation continued to affect outcomes, with those undergoing bilateral nerve-sparing RP having the highest response rates. The study

concluded that sildenafil can restore normal penile function in 76% of pre-operative sexually potent men when bilateral nerve-sparing surgery is performed.<sup>19</sup>

Another Cleveland Clinic study found that four factors were statistically significantly associated with successful outcome:

- the presence of at least one neurovascular bundle;
- a mean pre-operative SHIM score  $\geq 15$ ;
- age of  $\leq 65$  years; and
- interval from RP to drug use of more than six months ( $p < 0.001$ ).<sup>20</sup>

This study also found that pre-operative erectile function and the interval between surgery and initiation of the drug therapy were associated with a successful outcome.

### Combination Therapy

A number of studies have looked at whether combination therapy can salvage penile function when individual therapy fails to correct ED.

#### VCD and Sildenafil

In one such study, 31 men who were unsatisfied with VCD alone as a treatment for ED after RP (mean follow-up 4.5 months) were instructed to take 100mg of sildenafil one to two hours before using the VCD for sexual intercourse. Of the 31 patients, seven (22%) reported no improvement with the addition of sildenafil and discontinued the drug, whereas 24 (77%) reported improved penile rigidity and sexual satisfaction. The latter group of patients also reported that sildenafil enhanced their erections 100% of the time. The authors concluded that adding sildenafil to VCD can improve sexual satisfaction and penile rigidity in some patients who are unsatisfied with VCD alone.

#### MUSE and Sildenafil

Nehra et al. reported that a combination of sildenafil (100mg) and intraurethral PGE1 (1,000 $\mu$ g) salvaged a refractory population of men with ED.<sup>21</sup> Recently, Jaffe et al. reported that five of 10 patients who did not respond to sildenafil treatment successfully responded to a combination treatment with MUSE and sildenafil.<sup>22</sup> The Cleveland Clinic also examined the effectiveness of MUSE-sildenafil combination therapy in patients who were unsatisfied with sildenafil citrate alone for ED following RP. Of 23 patients, 19 (83%) reported improved penile rigidity and sexual satisfaction. The other four patients did not improve and discontinued taking sildenafil. The authors concluded that the addition of MUSE to sildenafil therapy

improves sexual satisfaction and penile rigidity.

### Sildenafil and IC Injections

One study showed that combining IC injections with oral therapy in patients who do not respond to sildenafil alone is effective. Thirty-six patients who wished to switch from IC injections to sildenafil were included in this study.<sup>23</sup> Of the 36 patients, seven were not satisfied with sildenafil alone. These seven patients used IC injections with sildenafil to enhance the response. IC injections produce cAMP-mediated vasodilatation and enhance the sildenafil response.

### Penile Implants

Penile prostheses are generally reserved for patients who do not respond to any systemic medication and who are not interested in using conventional erectaids. Gerstenberger et al. reported a 75% satisfaction rate after penile prosthesis.<sup>24</sup> McLaren et al. reported that 83% of the men were satisfied with the results of implant surgery.<sup>25</sup> A study comparing penile prosthesis (n=65) with injection therapy (n=115) demonstrated that 70% of the implant patients were having coitus on regular basis, whereas only 41% of injection patients were sexually active in the follow-up period.<sup>26</sup>

The main concern is post-operative infection of the prosthesis. Infection rates range from 1.7% to 1.8%.<sup>27</sup> The mode of insertion does not affect the rate of infection.<sup>28</sup>

### Future Directions

#### Early Penile Rehabilitation

After RP has been performed, a period of neuropraxia occurs, which can last as long as 12 to 18 months. During this time, erectile activity is not possible and, thus, persistent penile hypoxia occurs. This, in turn, may lead to the formation of lacunar fibrosis and, ultimately, a decline in erectile capacity.<sup>29</sup> The use of erectogenic agents during this period of neuropraxia may improve tissue oxygenation and prevent penile fibrosis.<sup>30</sup> Initial data have been very encouraging and support this hypothesis:

- Padma-Nathan et al. reported that daily sildenafil preserved erectile function in 27% of patients following RP compared with 4% in a control group (no treatment).<sup>31</sup>
- Montorsi et al. found that 67% of patients who used IC injections thrice-weekly post-operatively experienced a return of natural erectile function after six months.<sup>30</sup>

- The Cleveland Clinic evaluated the role of early MUSE in a prospective study consisting of 91 patients (n=56 in the MUSE group and n=35 in the no-treatment [control] group). In the MUSE group, 38/56 (68%) continued MUSE treatment. At six months, 28/38 (74%) of the patients regained partial erections and 15/28 (53%) had natural erections sufficient for vaginal penetration without MUSE. In the control group, 13/35 (37%) regained partial erections and 4/13 (30.7%) had erection sufficient for vaginal penetration. Nine of the 18 discontinued treatment because of inadequate erections—five due to loss of sexual interest and four for local pain/burning.<sup>32</sup> The authors concluded that early MUSE therapy after RP increases the incidence of natural erections sufficient for vaginal intercourse.
- Another Cleveland Clinic study found that daily use of VCD after RP was associated with a high compliance rate of 60/74 (80%) and few complications. In this series, 80% of the patients at six to nine months reported having sexual activity (vaginal intercourse) with the VCD at a frequency of twice weekly. At a mean interval of nine months, the early (daily) use of VCD resulted in natural erectile function in 32% (19/60) of patients, with 10 of these 19 patients (52%) having erections sufficient for vaginal penetration.<sup>33</sup> This potency rate (defined as vaginal penetration) of 52% at nine months is significantly higher than the potency with the authors' 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 were previously inactive for a year or more, waiting for the period of neuropraxia to resolve. However, further confirmatory studies are needed to support the concept of early penile rehabilitation.

### New Oral Therapies

Myriad new therapeutic agents are emerging for the treatment of sexual dysfunction. Apomorphine SL has a central mechanism of action, at the approved doses of 2mg and 3mg; it induces a significantly higher percentage of erections than placebo. At the 2–3mg dose, the main side effect of nausea was acceptable at 4.7%.<sup>34</sup>

Tadalafil (Cialis®), a phosphodiesterase type-5 (PDE5) inhibitor, is safe and well tolerated. The drug significantly improved erectile function at the 10mg and 20mg dose. Montorsi et al. reported that patients receiving tadalafil showed greater improvement in all primary and secondary end-points (p<0.001)

compared with placebo following RP.<sup>35</sup> Fifty-four per cent reported successful penetration attempts, and 41% had a successful vaginal intercourse.

Another PDE5 inhibitor, vardenafil (Levitra®), is a new selective PDE5 inhibitor.<sup>36</sup> 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 sufficient for vaginal penetration.<sup>37</sup> Further clinical trials are required to assess their potential benefits in the treatment modality of ED after RP.

The authors' center has conducted a prospective study comparing the efficacy and side effects of all the three oral PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). They found that the side effects determined the choice of PDE5 inhibitors in 60% of patients, and efficacy determined the choice in the remaining 40% of patients. The mean SHIM scores for all three drugs did not significantly differ among the users.<sup>38</sup>

#### Intraoperative Cavernous Nerve Stimulation

The CaverMap™ system identifies the location of the cavernous nerves during RP by monitoring tumescence response to intra-operative cavernous nerve stimulation (NS). It is still unclear if 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.<sup>39</sup>

#### 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 a non-NS RP or unilateral NSRP.

Kim et al. recently reported that 33% (4/12) of their patients who received a sural nerve graft had spontaneous, unassisted erections sufficient for sexual intercourse compared with one patient in the control group (no treatment).<sup>40</sup>

#### 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 the return of erectile function. Lee et al. 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 (VEGF) in rats with arteriogenic ED protects what erectile function is left.<sup>41</sup> The applicability of this concept to a human model remains to be determined.

#### Conclusion

Despite advances in surgical technique, ED is still a common complication after RP. Standard therapies—VCD, MUSE, and IC injections—are important therapeutic options, particularly in patients who do not undergo nerve-sparing RP. However, most patients prefer oral therapy because of its simplicity. Sildenafil citrate and the newer PDE5 inhibitors are only effective when functional nerve tissue is present. Even so, oral therapy does not appear to be effective within the first nine to 12 months after RP, when neuropraxia exists, and standard treatment options should be encouraged during this time to maintain good sexual health and promote recovery of penile function.

In any case, all patients receiving treatment for RP-associated ED should receive realistic advice when being counseled about their options and should be followed regularly. Such actions can increase patient compliance and lower the attrition rate. ■

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