

REVIEW

Early penile rehabilitation following radical prostatectomy: Cleveland clinic experience

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Erectile dysfunction is one of the most important quality of life issues following radical prostatectomy. The potency rates reported following nerve-sparing technique varies between 40 and 86%, and the time period required for complete recovery of erectile function varies from 6 to 24 months. The literature evidence suggests that lack of natural erections during this period of time produces cavernosal hypoxia. Prolonged periods of cavernosal hypoxia induce fibrosis, which later increases the incidence of venous leak. Recently, there is a growing interest among the physicians to interrupt these events by preventing cavernosal hypoxia during the period of neuropraxia. Initial studies using intracavernosal injection appears to be beneficial. In this article, we reviewed the pathophysiology of cavernosal hypoxia following radical prostatectomy with currently available evidence for the interventions to promote the nerve recovery and regeneration.

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Introduction

Radical prostatectomy (RP) has been the 'gold standard' treatment for organ/specimen-confined prostate cancer for several decades. The introduction of prostate screening programs with annual examinations and prostate-specific antigens (PSAs) has led to earlier detection of most prostate malignancies. Earlier detection has significantly improved the cancer cure, allowing us to redirect our focus toward the quality of life issues. As most patients regain continence in time, erectile dysfunction (ED) has emerged as the major long-term quality of issue in the recent times. Penson and Litwin¹ in 2003 reported that sexual dysfunction was the most important quality of life issue at 24 months from the time of primary prostate cancer treatment.

Walsh and Donker² has revolutionized the field of urology by delineating the periprostatic anatomy and by performing the nerve-sparing technique, advances which significantly improved postoperative sexual function. In the past two decades, many urologists in the world have mastered this technique. The outstanding potency rates of 70–86% are often limited to the centers of excellence with large single surgeon series.^{3–5} In general, potency rates from the community urologists range from 21 to 50%, even after bilateral nerve-sparing surgery.^{6,7} These results indicate that a significant proportion of men fail to achieve erectile function following nerve-sparing RP.

Following bilateral nerve-sparing RP, patients are generally unable to achieve spontaneous erections and nocturnal tumescence. This temporary loss of ED appears to be mostly related to some degree of operative injury and is referred as the period of neuropraxia. The period of neuropraxia may last as long as 24 months.⁸ Since further advances in surgical techniques are slow to develop, most urologists are currently concentrating on early rehabilitation protocols to promote nerve recovery and nerve regeneration.

Despite the landmark study by Montorsi *et al.* in 1997 reporting a higher incidence of spontaneous recovery with early penile injections, most urologists around the world have been hesitant to

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recommend some form of 'early rehabilitation' during the period of neuropraxia. The period of neuropraxia has not been studied sufficiently well either on physiologic or clinical levels. This article highlights the pathophysiology and current evidence for the early treatments including our experience at the Cleveland Clinic Foundation.

Pathophysiology of early rehabilitation: historical evidence

Goldstein *et al.*⁹ in 1982 first reported the role of the cavernosal smooth muscle in the normal erection. Since then, several authors demonstrated that normal smooth muscle content and function are essential in initiation and maintenance of the erection. The integrity and function of any smooth muscle is dependant on tissue oxygenation. This phenomenon has been well established in cardiac myocytes. Similarly, the cavernosal smooth muscle function has been reported to be dependent on the tissue oxygenation.

Historically, collagen accumulation (fibrosis) has been reported as the most probable cause of ED in patients with penile arterial insufficiency.^{10–12} However, the exact mechanism of collagen accumulation in patients with penile hypoxia has not been established. In 1995, Moreland *et al.*¹³ reported that penile hypoxia induces transforming growth factor- β_1 (TGF- β_1) in the culture of cavernosal smooth muscle, which was implicated in the collagen deposition. They also reported that prostaglandin E1 (PGE1), added to the cavernosal culture, suppressed the TGF- β_1 -induced collagen synthesis. Daley *et al.* in 1996 reported that the production of PGE1 in the cavernosal muscle, which suppress the TGF- β_1 -induced collagen accumulation was also oxygen dependant. These initial reports have shown that penile hypoxia is the key factor in collagen deposition in hypoxic cavernosal muscle and PGE1 reduced the expression of TGF- β_1 . This opened a new era of interest in the field of pharmacological prevention of ED following RP.

Nocturnal erections have been implicated in preserving normal erectile function by providing regular tissue oxygenation.¹⁴ The lack of any erections during the period of neuropraxia has been implicated to produce persistent penile hypoxia. The hypoxia in consistently flaccid penis may induce fibrosis. Recently, Leungwattanakij *et al.*¹⁵ reported that 3 months after cavernous nerve damage in the rat model, the penile tissue biopsy revealed significant overexpression of TGF- β_1 and collagen.

More than likely, an appropriate amount of circulation to the penis occurs after RP with sufficient oxygenation at the capillary level. While *in vitro* studies have created an artificial condition

of low oxygen tension, whereby experimental effects occur, for example, induction of TGF- β_1 , whether this truly occurs *in vivo* remains unclear.^{12–18} To date, the penile hypoxia explanation remains theoretical. In fact, other possibilities may explain the collagen replacement in the penis following RP. Further scientific work is needed to prove that hypoxia actually occurs in the penis following RP, and that this is the mechanism for tissue damage in the penis.^{12–15}

Similarly, User *et al.*¹⁶ in 2003 demonstrated significant apoptosis in the cavernosal smooth muscle and high proportion of trabecular smooth muscle has been replaced by collagen. Similarly in human models, Iacono *et al.*¹⁷ from Italy recently studied the changes in penile biopsy before and after RP (2 and 12 months). They reported a significant decrease in the elastic fibers and smooth muscle content, and a significant increase in the collagen content in the postoperative biopsies compared to the biopsy before surgery. This smooth muscle fibrosis has been implicated in reduction of penile length that occurs in significant proportion of men following RP. These studies have further confirmed that neuropraxia from transient cavernous nerve damage plays a central role in cavernosal fibrosis.

Progressive cavernosal fibrosis produced due to persistent penile hypoxia has been shown to produce veno-occlusive dysfunction. Mulhall *et al.*¹⁸ in 2002 reported the incidence of venous leak increases with the postoperative time interval. They showed that the incidence of postoperative venous leak was 14% at 4 months, which increased to 35% between 9 and 12 months. Similarly, Montorsi *et al.*¹⁹ in 1997 reported that the incidence of venous leak was much higher in control group (no treatment) compared to the treatment group (alprostadil injections three times/week), 53 vs 17%. These two studies revealed that postoperative venous leak was proportional to the time interval from the surgery, and early treatment could result in a considerable decrease in venous leak.

It is evident from the literature that ED after RP is multifactorial in etiology. Penile hypoxia has been the most important precipitating factor in the formation of cavernosal fibrosis. The formation of cavernosal fibrosis with the subsequent venous leak has been implicated as one of the most important causes for the long-term ED after RP.

Clinical evidence for early rehabilitation

Recently, there has been great enthusiasm in early interventions to prevent penile hypoxia, cavernosal fibrosis and its long-term complications. Montorsi *et al.* first demonstrated the advantage of early rehabilitation in 1997 in a randomized controlled study on patients after bilateral nerve-sparing RP.

Patients were randomized to treatment (receiving intracavernosal alprostadil 2–3 times/week for 12 weeks, $n=15$) and a control group (no treatment, $n=15$). After a minimum follow up of 6 months, 67% (8/12) in the treatment group were reported to have spontaneous erections sufficient for satisfactory sexual intercourse compared to the 20% (3/15) in control group. Penile Doppler studies revealed veno-occlusive dysfunction in 17% (2/12) in treatment compared to the 53% (8/15) in control group.¹⁹ This first landmark study has demonstrated the importance of early penile rehabilitation after RP. This study generated a great deal of interest and enthusiasm in the field of early penile rehabilitation. In the following sections, we discussed subsequent clinical evidences regarding the role of various pharmacological and non-pharmacological agents in early penile rehabilitation.

Role of oral medications in early penile rehabilitation

There is a growing interest among the urologists regarding the early use of daily oral sildenafil. Recently, Schwartz *et al.*²⁰ analyzed cavernosal smooth muscle content in postprostatectomy population. A total 40 patients were included in the study, and a first cavernosal biopsy was performed at the time of surgery. Patients were advised to take 50 mg (group 1, $n=20$) and 100 mg (group 2, $n=20$) sildenafil citrate every other night. After 6 months follow up, 11/20 in group 1 and 10/20 in group 2 underwent a second biopsy. At 6 months, group 2 (100 mg) had significantly more smooth muscle content in the second biopsy (56.85%) compared to the first biopsy (42.82%; $P<0.05$). However, in group 1 (50 mg), there was no significant difference observed in smooth muscle content in second biopsy (51.67%) compared to the first biopsy (51.52%; $P>0.05$). They concluded that early use of sildenafil (50 mg) following RP appears to preserve the smooth muscle content, and at higher doses (100 mg), it increases the smooth muscle content.

Recently, the benefit of early sildenafil has been reported by Padma-Nathan *et al.*,²¹ who conducted a randomized controlled study in 76 men (oral sildenafil daily (50 mg, $n=23$; 100 mg, $n=28$) and placebo = 25) who underwent nerve-sparing RP with normal preoperative erectile function. Sildenafil was given for 36 weeks in the study group. After 48 weeks (~11 months) follow-up, 14 of the 51 (27%) patients receiving sildenafil had natural erections sufficient for intercourse compared to one of the 25 (4%) in the placebo group. This study revealed that oral daily sildenafil increased the return of erections sevenfold compared with the placebo group and was well tolerated. However, this study has been criticized because the return of

spontaneous erections in the placebo group is only 4%, which was very low compared to the other reported series in the literature. In a subset of 54 patients (35 sildenafil group, 19 control group) from the same study, longitudinal measurement of nocturnal penile tumescence and rigidity evaluation revealed that 29% (10/35) of the sildenafil group demonstrated return of spontaneous erectile function compared to 5% (1/19) in the control group.²² They also reported that tip rigidity of >55% appears to be the most important parameter to discriminate between responders and non-responders.

Recently, Gallo *et al.*²² from Italy evaluated the role of vardenafil in the recovery of erectile function following pelvic urological surgeries (RP and cystectomy).²³ After 6 months, vardenafil therapy increased the mean International Index for Erectile Function-5 (IIEF-5) score of 12.9 points in bilateral nerve-sparing RP patients, of 8.0 points in unilateral nerve-sparing RP patients and of 11.3 points in nerve-sparing radical cystectomy patients. This study showed that vardenafil was well tolerated and effective for recovery of erectile function in patients undergoing pelvic urologic surgery. However, lack of control group may be a limiting factor in this study. Further multicenter randomized studies are ongoing to investigate the potential benefit of daily sildenafil following radical RP.

Cleveland Clinic experience of early penile program Patient information. The Cleveland Clinic Institutional Review Board approved this study, and written informed consent was obtained from all patients. We obtained and reviewed the records of preoperatively sexually active patients with localized prostate cancer who underwent nerve-sparing RP between August 2002 and October 2004, after a minimal follow-up of 2 weeks postoperatively. None of the patients was able to have erections sufficient for vaginal penetration and had experienced severe ED. These patients were not able to have erections sufficient for successful penetration, and their mean IIEF-5 Sexual Health Inventory of Men (SHIM) score had decreased from 19.65 (preoperative baseline) to 4.27 (2 months after RP). All these men had undergone nerve-sparing RP (PSA <10, Gleason score <6, tumor stages T1–T3) with the same surgeon (CZ). This subset of patients was younger (55.6 ± 3.78 years) and preoperatively sexually potent (mean baseline IIEF-5 (SHIM) score: 22 ± 4.27). The patients who sought treatment for ED were initially evaluated with a comprehensive sexual history, and physical examination and pertinent laboratory testing. At that time, the patients were offered standard ED treatments, including a vacuum constriction device (VCD), intracavernous injections (ICs), the medicated urethral system for erection and oral therapy with sildenafil citrate.

Role of intraurethral alprostadil (MUSE) in early penile rehabilitation

We recently completed a prospective non-randomized study of 91 patients on the use of early MUSE after RP at Cleveland Clinic Foundation.²⁴ To our knowledge, this is the only report in literature. We included total of 91 patients. Of the 91 patients, 56 received early MUSE and 35 (control group) did not receive any early treatment. Patients in the early MUSE group received 125 micrograms (mcg) three times/week for the first 6 weeks. At 6 weeks, the MUSE dose was titrated to 250 mcg, three times/week for 4 months. Patients who could not tolerate the 250 mcg doses remained at 125 mcg for 4 months. Treatment efficacy was analyzed by the patient's response to Sexual Health Inventory of Men (SHIM) questionnaire. In the MUSE group, 38/56 (68%) continued MUSE treatment. At 6 months, 28/38 (74%) of the patients resumed sexual activity; 15/38 (40%) had natural erections sufficient for vaginal intercourse without MUSE; 13/38 (34%) continue to use MUSE as an adjuvant treatment for successful intercourse. Overall, 40% (15/38) at 6 months achieved natural erections sufficient for satisfactory sexual intercourse. The MUSE discontinuation rate was 32% (18/56). Nine of the 18 (50%) discontinued because of inadequate erections, five (28%) due to loss of sexual interest, and four (22%) due to local pain/burning. In the control group, 13/35 (37%) regained spontaneous natural erections and 4/35 (11%) had natural erections sufficient for vaginal intercourse. Of the 13 sexually active patients, nine were dissatisfied with their erections and used oral therapy/erect aids as adjuvant treatments. Overall, 11% (4/35) at 6 months achieved natural erections sufficient for satisfactory sexual intercourse.

In our experience, early MUSE therapy following RP increased the frequency of sexual activity, increased the incidence of spontaneous erections sufficient for intercourse and appears to shorten the neuropraxia period.

Role of VCD in early penile rehabilitation

We recently completed a prospective non-randomized study on the use of early VCD after RP at Cleveland Clinic.²⁵ To our knowledge, this is the only report in literature. At Cleveland Clinic we conducted a prospective study, which included 109 patients following RP between August 1999 and October 2001. Of the 109 patients, 74 (group 1) patients used early VCD daily for 9 months and 35 (group 2) were observed without any erectogenic treatment. This control group was the same used for the early MUSE comparison. Treatment efficacy was analyzed by responses to the SHIM. Patient outcomes regarding the compliance, changes in the penile length and circumference, return of natural erection, and ability for vaginal intercourse were

also assessed. With the minimum follow-up of 9 months, 80% (60/74) in group 1 successfully used their VCD with a constriction ring for vaginal intercourse at a frequency of twice/week, with an overall spousal satisfaction rate of 55% (33/60). Nineteen of these 60 patients (32%) reported return of natural erections at 9 months with 10/60 (17%) having erections sufficient for sexual intercourse. The abridged IIEF-5 score significantly increased after VCD use in both the nerve-sparing and non-nerve-sparing groups. After a mean use of 3 months, 14/74 (18%) discontinued treatment. Overall in the early VCD group, 17% (10/60) had natural erections sufficient for sexual intercourse.

In group 2, 37% (13/35) of patients regained spontaneous erections at a minimum follow-up of 9 months after surgery. However, only 4/35 of these patients (11%) had erections sufficient for successful vaginal intercourse and rest of the patients (26%) sought adjuvant treatment.

Interestingly when assessing the penile length and girth after surgery, in the 60 compliant patients, only 14 (23%) reported a decrease in penile length and girth at 9 months (range: 4–8). In the non-compliant VCD patients, 12/14 (85%) complained decrease in penile length and girth. In the control group (no VCD), 22/35 (63%) reported decrease in penile length and circumference, demonstrating that routine early use of the VCD helps prevent the decrease in penile length and circumference.

We conclude that early use of VCD following RP facilitates early sexual intercourse, early patient/spousal sexual satisfaction and preservation of penile length and girth. However, further studies doubt the principles of early use of VCD can potentially help an earlier return of natural erections sufficient for vaginal penetration.

Role of IC in early penile rehabilitation

Montorsi *et al.*¹⁹ from Milan (Italy) first reported their experience using ICs in 1997. Of total 30 patients who underwent nerve-sparing RP, 15 were randomized into group 1 (alprostadil injections three times/week for 12 weeks) and another 15 patients were randomized into group 2 (observation without erect aids). The dose of PGE1 varied from 4 to 14 μ g, with mean dose of 8 μ g. At 6 months, 67% patients in the injection group reported to have return of spontaneous erections sufficient for satisfactory intercourse compared to 20% in the observation group. We initiated a similar study in 2001 with a dose of 10 μ g PGE1. Of the 8 patients, six discontinued because of pain, which prompted us to discontinue our early PGE1 program 3 years ago.

Recently, we re-examined the role of early intracorporeal injections, with a lower dose of PGE1 (4 μ g/2–3 times/week) starting after 2 weeks after RP, combined with oral sildenafil (50 mg/day).^{26,27} We reduced the injection dose to 4 μ g to get partial

erections with minimal if any pain. Our goal was to have a compliance of more than 90%. Further dose modifications have been made to achieve this goal. We included total 18 patients in this study. Of the total 18 patients, four increased the dose up to 8 μg without any pain (two had mild discomfort), six patients continued the same dose of 4 μg and the remaining patients decreased the dose. Of the eight patients who decreased the dose, six used 2 μg dose and two patients further reduced the dose to 1 μg . The compliance with this program is 100%.

After a mean follow-up of 6 months (3–8 months), 17/18 patients were sexually active, eight (45%) patients with injections alone and nine (55%) patients with the combination of injection and sildenafil citrate. In this follow-up period, 10/18 (56%) patients achieved spontaneous partial erections, but could not have sexual intercourse. One patient was sexually inactive because of significant incontinence. While our initial response was very encouraging, the ability to be sexually active required combination therapy. Fifty percent of our patients needed sildenafil to be sexually active with our low-dose PGE1 program. This oral dependence prompted us to use 30 U of low-dose Trimix (1 ml = 100 U of low Trimix contains, PGE1, 5.88 μg ; phentolamine, 0.59 mg; papavarine, 17.65 mg/2–3 times/week), which has provided comparable sexual activity without sildenafil. Early low-dose Trimix can produce more efficacious erections than early low-dose PGE1. All patients with the low-dose Trimix were sexually active without sildenafil citrate; and after a mean follow up of 4 months (3–9 months), one patient had partial natural erections. At a mean follow up of 6 months, 1/22 (4.5%) patient had venous leak on Doppler studies. This patient delayed using low-dose Trimix till 10 weeks after the surgery due to incontinence. Overall, combining all the patients on early injections (18 PGE1 and four low-dose Trimix) at 6 months all 22 (100%) patients were compliant, 96% (21/22) remained sexually active and 50% (11/22) regained natural erections.

We conclude from our early injection data that high compliance can be achieved if good counseling education was performed at the time of the initial dose, and proper dose modifications was made according to efficacy and side effects profile. A good early injection program should facilitate early sexual intercourse in addition to stimulating an earlier return of natural erections.

Summary

ED is a significant problem following nerve-sparing RP. The time period required for recovery of erectile function appears to vary from 6 to 24 months. During this period of neuropraxia, absence of natural erections predisposes to cavernosal hypoxia,

which plays a key role in postprostatectomy ED. Prolonged periods of cavernosal hypoxia and fibrosis predispose to venous leak, which further aggravates the ED. While the hypothesis is appealing that early pharmacological prophylaxis could prevent corporal fibrosis and subsequent venous leak, this question has not been never truly answered.

While initial clinical results reported in early 1997 showed advantage of early ICs,¹⁹ no confirmatory studies followed due to the lack of patient compliance (pain and fear of needles). Similarly, poor patient compliance using early penile injections led us to consider other early options such as early VCD and intraurethral alprostadil (MUSE).²⁵ Our clinical data using VCD was promising with 100% of patients returning to sexual activity and 32% of patients had some return of natural erections, but disappointing with regard to a 17% of return of natural erections sufficient for vaginal intercourse. Our clinical data using early MUSE was promising in that 74% of patients resuming sexual activity, 55% of patients had some return of natural erections and 40% of patients had return of erections sufficient for vaginal intercourse. This response, however, was still suboptimal, since 60% of patients were still erect aid dependant at 6 months to achieve sexual intercourse. While early daily sildenafil appears to improve the natural erections, it does not promote early sexual activity. Recent data using early daily sildenafil showed a significant advantage with return of natural erections at 11 months (27 vs 4%), but again 73% are still unable to have sexual intercourse at 1 year. When entered into a rehabilitation program, multiple uncontrolled factors including personal relationships, other health issues and simply variations in commitment and motivation to perform rehabilitation all have promoted patients' continued involvement in treatment arms.

These observations prompted us to revisit our early injection program in combination with early daily sildenafil following RP. We combine early daily sildenafil (50 mg) to promote daily vasodilatation with either early penile injections of PGE1 injections (mean 4 μg /2–3 times/week) or 30 U of low-dose Trimix (1 ml contains PGE1 5.88 μg , phentolamine 0.19 mg and papavarine 17.65 mg/2–3 times/week) to provide the strongest pharmacological stimulus to penis and to stimulate sexual activity. Our early combine program shows 100% compliance and has 50% return of spontaneous natural erections at 6 months. Injection of vasoactive agents provides the strongest stimuli to the neurovascular network of the penis. Our use of sildenafil combination with injection allows us to reduce the injection dose of PGE1 and lower penile pain considerably. The combination of daily sildenafil with penile injections appears to be safe and should prove to be effective early penile rehabilitation strategy.

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