Journal of Pelvic, Obstetric and Gynaecological Physiotherapy, Autumn 2015, **117,** 35–40

POGP CONFERENCE 2014

Erectile dysfunction following radical prostatectomy

I. Pearce
Department of Urology, Manchester Royal Infirmary, Manchester, UK

Abstract
Erectile dysfunction following radical prostatectomy for malignancy is a common and debilitating side effect of the procedure. This condition can have a significant negative impact on the quality of life of both the patient and his partner. Ideally, patients should be seen and counselled prior to their surgery, where possible, so that early conservative measures (e.g. weight loss, exercise and pelvic floor muscle training) can be instituted before or immediately after the operation. A full assessment is required in order to identify potentially reversible or modifiable concomitant risk factors, and management should follow a stepwise progression. Penile rehabilitation therapy with early daily phosphodiesterase type 5 inhibitors is gaining increasing acceptance because these drugs reduce penile fibrosis and loss of length, and also improve the response to treatment. Phosphodiesterase type 5 inhibitors, either daily or on demand, are the first-line therapy for erectile dysfunction, and have achieved excellent results in patients with good preoperative erectile function who received nerve-sparing surgery. Prostaglandin E_1 (alprostadil) therapy and vacuum devices for erection provide avenues for second-line treatment. Penile prosthesis implants provide an excellent third and final line of management that results in extremely high patient and partner satisfaction.

Keywords: erectile dysfunction, management, radical prostatectomy, therapy.

Introduction

Erectile dysfunction is defined as the persistent inability to achieve or maintain an erection sufficient for penetrative intercourse to the satisfaction of both partners (Feldman *et al.* 1994). The condition is a common and debilitating consequence following radical prostatectomy for prostatic malignancy, with a widely ranging reported incidence of 25–75% in men who have undergone this type of surgery (Sanda *et al.* 2008). Since curative prostatic carcinoma is being detected in an increasingly young age group, the issue of postoperative erectile failure is becoming, quite rightly, a very prominent issue.

Mechanism

With regard to the mechanism of post-radical-prostatectomy erectile dysfunction (PRPED), trauma to the cavernous nerves is central to the ensuing process leading to erectile failure. Such nerve damage leads to an increase in intracavernosal collagen and a loss of the smooth muscle (i.e. apoptosis) that is crucial to the erectile mechanism. Vascular compromise with a resultant reduction in the delivery of oxygenated blood results in corporal ischaemia, which further hinders the erection process and leads to greater fibrosis (Mulhall *et al.* 2002; Secin *et al.* 2007). As a consequence of this, erectile failure occurs, and the patient may also experience a degree of penile shortening that additionally hampers adequate function.

Predictors of erectile dysfunction following radical prostatectomy

Several characteristics have now been identified as risk factors for the development of PRPED that are independent of those found among the population in general; for example, age, hypertension and extremes of mood (Feldman *et al.* 1994).

The most influential factor in determining postoperative recovery of erectile function is

Correspondence: Mr Ian Pearce, Department of Urology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK (e-mail: ian.pearce@cmft.nhs.uk).

preoperative erection status. Therefore, it could be argued that nerve-sparing procedures should only be performed in patients with good preoperative erectile function.

Patient age remains a strong predictive factor, with increasing age signalling a higher risk of PRPED regardless of preoperative status.

Finally, in common with many complex surgical interventions, surgeon experience and volume are also related to the incidence of PRPED. Better outcomes are related to workload volume, with greater experience and workload being protective against the development of erectile dysfunction (Magheli & Burnett 2009; Vickers *et al.* 2011; Ficarra *et al.* 2012).

Assessment

In an ideal world, men with good erectile function who regard continued sexual function as important should be seen and counselled prior to their surgery, and this is an increasingly common mode of healthcare delivery.

Men should be advised about the likelihood of postoperative erectile dysfunction and instructed in the art of pelvic floor muscle training (PFMT) so that this may be performed both before and immediately after surgery. The International Index of Erectile Function (IIEF) questionnaire (Rosen *et al.* 1997) should be completed both before and after surgery, and at varying intervals during treatment so as to assess progress. The IIEF is a validated tool consisting of five questions relating to sexual function during the previous 6 months (Box 1). The questionnaire offers a sensitivity and specificity of 98% and 88%, respectively, for the clinical diagnosis of erectile dysfunction (Rosen *et al.* 1997).

While it is reasonable to assume that men with PRPED who experienced good erectile function preoperatively have iatrogenic erectile dysfunction, a thorough work-up should still be performed. This should include tests for serum cholesterol, random glucose and hormone profile (i.e. testosterone, leutinizing hormone and follicle-stimulating hormone) since previously undiagnosed risk factors for erectile dysfunction may be influential postoperatively and hinder efficacious treatment.

Management

Management of PRPED should progress in a stepwise fashion, beginning preoperatively and flowing through various stages of management from the least invasive approach to radical surgery. As well as PFMT, preoperative management involves lifestyle modification where necessary; for example, weight loss, smoking cessation and alcohol reduction (Derby *et al.* 2000; Esposito *et al.* 2004; Salonia *et al.* 2012). All of these should continue in the postoperative period.

First-line therapy

The development of phosphodiesterase type 5 (PDE-5) inhibitors has revolutionized the treatment of PRPED. Furthermore, following the recent lifting of National Health Service Schedule 2 restrictions on the prescribing of generic sildenafil citrate, another step forward has been taken. Immediate daily therapy with low-dose PDE-5 inhibitors is increasingly being utilized for men who have undergone nerve-sparing radical prostatectomy because this management approach allows them to make an earlier return to sexual function (Montorsi *et al.* 1997). This form of early penile rehabilitation is based on the premise that PRPED is, in part, secondary to ischaemia, which, if left unchecked, results in the loss of erectile smooth muscle and fibrosis, with a resultant reduction in penile length. Thus, the early resurrection of erectile function will improve the oxygenated blood supply to the corporal tissues, and hence, ameliorate any ischaemic changes (Schwartz *et al.* 2004).

Studies have reported success rates of 75% for daily doses of sildenafil in patients with erectile

Box 1. International Index of Erectile Function questionnaire

(1) How do you rate your confidence that you could get and keep an erection?
(2) When you attempted intercourse, how often were you able to penetrate (enter) your partner?
(3) During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
(4) During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
(5) When you attempted sexual intercourse, how often was it satisfactory for you?

Table 1. Pharmacokinetics of phosphodiesterase type 5 (PDE-5) inhibitor agents

Variable	PDE-5 inhibitor			
	Sildenafil	Tadalafil	Vardenafil	Avanafil
Avoid food (yes/no)	Yes	No	Yes	No
Avoid alcohol (yes/no)	Yes	No	Yes	No
Time to effect (min)	30–60	30	30	15–30
Window (h)	12	36	12–14	6
Start dose (mg)	50	10	10	50
Response rate	77%	67%	76%	40%
Other doses (mg)	25, 100	5, 20	5, 20	100, 200
Response rate	56%, 84%	81%	66%, 80%	57%
Launched (year)	1998	2003	2003	2012

dysfunction following nerve-sparing radical prostatectomy compared to just 15% in those who did not undergo this form of surgery (Raina *et al.* 2004; Bannowsky *et al.* 2008; Padma-Nathan *et al.* 2008).

Currently, Cialis (tadalafil) is the only daily PDE-5 inhibitor that is licensed in the UK.

The original on-demand method of administration of PDE-5 inhibitors may still be utilized, of course, with success rates, as defined by erectile quality and successful intercourse, in the region of 70% in men who have undergone nerve-sparing surgery (Brock *et al.* 2003; Montorsi *et al.* 2004). While some patients and clinicians prefer this model, in general, daily administration is associated with improved outcome, greater spontaneity and higher levels of patient satisfaction. However, early penile rehabilitation with PDE-5 inhibitors does not confer a greater chance of erectile function independent of therapy, but rather, an enhanced response to treatment. This is almost certainly a consequence of early oxygenation, less fibrosis and maintenance of smooth muscle integrity.

It is vital that patients receiving PDE-5 inhibitor therapy are given appropriate instructions regarding the manner in which the medication must be taken. In particular, it is necessary to avoid both fatty food and alcohol in order to prevent a delay in absorption and a reduction in the effects of sildenafil and vardenafil. Patients need to be informed that sexual stimulation is required, and that the tablet must be taken some time prior to this, as indicated in Table 1, which illustrates the pharmacokinetics of the four main PDE-5 inhibitors.

With regard to on-demand treatment, it has become apparent in recent years that several attempts may be required prior to achieving a satisfactory result, and hence, compliance relies on patients having a thorough understanding of this in order to avoid early discontinuation.

Finally, patients should be advised that they should only source their PDE-5 inhibitor treatment from their general practitioner or specialist clinician. This is because the regulation of the many online sources for directly purchasing these drugs may not be as robust as it should be.

The side effects of PDE-5 inhibitors are listed in Table 2.

Second-line therapy

Intracavernosal injections

For patients for whom PDE-5 inhibitor therapy is either contraindicated or ineffective, treatment with intracavernosal prostaglandin E_1 injection (5–20 μg) offers excellent results. Alprostadil is the only currently licensed intracavernosal therapy, but studies have reported success rates across a wide population cohort that are in the region of 90% for both erection quality and satisfaction with sexual intercourse (Linet & Ogrinc 1996; Porst 1996; Heaton *et al.* 2001). Once again, the early introduction of this form of treatment will help to reduce the degree of penile atrophy and enhance the response to therapy.

Patients should be warned of potential complications (Table 3), and instructed in the administration technique. Particular attention should be paid to ensuring that the injection is delivered into the lateral aspect of the penile shaft in order

Table 2. Side effects of phosphodiesterase type 5 inhibitor treatment (Hatzimouratidis *et al.* 2015)

Side effect	Rate of occurrence
Headache	12–16%
Flushing	4–12%
Dyspepsia	4–12%
Nasal congestion	1–10%
Dizziness	1–2%
Visual disturbances	<2%

Table 3. Side effects of intracavernosal prostaglandin E_1 injections (Hatzimouratidis *et al.* 2015)

Side effect	Rate of occurrence
Pain	11%
Prolonged erection	5%
Priapism	1%
Fibrosis	2%

to avoid both the ventrally positioned urethra and the dorsal neurovascular bundle.

Topical agents

Alprostadil may also be administered in a localized fashion in the form of the medicated urethral system for erection (MUSE), or as a topical cream (Vitaros).

With MUSE, a high-dose alprostadil pellet (1000 μg) is inserted into the distal urethra following micturition, and subsequent penile massage facilitates absorption. Vitaros is a topical cream application (0.5 mL containing 300 μg) that is administered to the glans penis over the external urethral meatus. Absorption is allowed to passively occur over 30 s before digitally enhanced absorption follows.

These agents have the benefit of being more acceptable than injection treatment, but in general, MUSE and Vitaros offer lower success rates (Shabsigh *et al.* 2000; Mulhall *et al.* 2001). In particular, MUSE is associated with a significant degree of urethral irritation, hindering its widespread uptake. The side effects of alprostadil therapy are listed in Table 4.

While there have been no robust studies into the effect of these treatments in the post-radical-prostatectomy patient group, it is likely that results slightly inferior to those obtained in the general population will be encountered following nerve-sparing surgery. The role of such local therapies is as a second-line optional alternative to injection treatment. Topical alprostadil can also be utilized for patients who are able to achieve decent erectile function but have a degree of distal flaccidity.

Table 4. Side effects of alprostadil therapy (Hatzimouratidis *et al.* 2015)

Side effect	Rate of occurrence
Pain	~30%
Dizziness	~10%
Fibrosis	<1%
Priapism	<1%
Urethral bleeding	5%
Infection	0.2%

Vacuum devices

Vacuum devices with or without the use of a penile constriction ring provide a non-physiological but pharmacology-free erection. This approach is based on the passive engorgement of the corporal tissue with deoxygenated blood, which is first drawn in via the utilization of a vacuum, and then trapped by a constriction device. While success rates vary enormously, some patients report greater than 90% satisfaction (Levine & Dimitriou 2001). However, the major drawback of vacuum devices is the absence of oxygenated blood to stem the degree of fibrosis and apoptosis of the penile smooth muscle.

This method of treatment is perhaps the most cost-effective for those who continue to suffer from erectile dysfunction. The initial cost of the device, which is between £200 and £400, is the only financial outlay.

Most discontinuation occurs early, i.e. within the first 3 months. This method is probably best suited to those patients who are only infrequently sexually active, and who prefer a pharmacologically independent means of treatment.

The side effects of vacuum devices for erection include:

- pain;
- inability to ejaculate;
- bruising;
- paraesthesia; and
- skin necrosis.

Third-line therapy

Regardless of aetiology, the third-line treatment for erectile dysfunction is the insertion of a penile prosthesis. Previously malleable or semi-rigid, the gold standard for these devices is now the three-piece inflatable prosthesis. This involves the placement of two corporal cylinders, a scrotal pump and a reservoir in the retropubic space. Patients achieve an erection on demand, but unlike a normal physiological erection, a penile prosthesis aims to make the penis rigid, and does not offer a significant increase in either length or girth.

Despite this, prosthesis implantation offers extremely high satisfaction rates for both patient and partner, usually exceeding 90% (Holloway & Farah 1997; Montorsi *et al.* 2000; Mulhall *et al.* 2003; Bernal & Henry 2012). This is probably

partly because of the long-term nature of erectile dysfunction, and the fact that most patients have previously endured several failed therapies.

Infection and prosthesis erosion are the two major complications of implant surgery. Both issues usually require the removal of the device, although salvage may be possible in cases of mild infection. The removal of a prosthesis as a result of a severe infection or erosion is typically followed by a significant period of time before attempting a reinsertion. This procedure is both difficult and associated with poorer outcomes, and therefore, it should only be within the remit of a specialist implanter.

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Ian Pearce graduated from the University of Nottingham Medical School, Nottingham, UK, in 1988, and subsequently trained in the West Midlands and North West England before being appointed consultant urological surgeon at Manchester Royal Infirmary in 2002. His specialist interests are andrology and bladder dysfunction, including incontinence, and he has previously served on the Executive Committee of the Female, Neurological and Urodynamics Urology section of the British Association of Urological Surgeons (BAUS), and the BAUS Specialist Advisory Committees for both Urology and Core Surgical Training. Ian is the current editor-in-chief of the Journal of Clinical Urology.