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PROSTATE CANCER (D PAREKH, SECTION EDITOR)

Penile Rehabilitation: The Evolutionary Concept in the Management of Erectile Dysfunction

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Abstract A compromise in erectile function is commonly experienced after radical prostatectomy and has been attributed to injury to vascular, neurogenic, and smooth muscle. The concept of rehabilitation after organ injury is not a novel concept and is one that has been applied to all aspects of medicine. Penile rehabilitation has been classically defined as the use of a device or pharmacologic agent to aid erectile function recovery after radical prostatectomy. Here we redefine penile rehabilitation as the use of any device, medication, or intervention to promote male sexual function as a primer before and after any insult to the penile erectile physiologic axis. We also review the epidemiology, rational and current literature on penile rehabilitation after prostatectomy.

Keywords Erectile dysfunction · Penile rehabilitation · Radical prostatectomy · Intracavernosal injections · Inflatable penile prosthesis · Phosphodiesterase inhibitors

Abbreviations

ED	Erectile dysfunction
RP	Radical prostatectomy
cGMP	3'5'-guanosine monophosphate
VED	Vacuum erection devices
ICI	Intracavernosal injection

Introduction

Tumescence is the result of a complex interaction among neurologic, vascular, endocrine, and psychological systems. In order for successful penetration and intercourse, this amalgam must all work in harmony. A temporary or permanent impairment in any one of these mechanisms can result in erectile dysfunction (ED). ED, as defined by the National Institute of Health, is the incapacity to achieve and sustain a satisfactory erection necessary for sexual intercourse [1, 2]. The incidence of ED is increasing worldwide and conservative projections put the number of new cases at 322 million by 2025. Recent data from the Massachusetts Male Aging Study (MMAS) of 1709 men estimated 52 % of American men aged 40-70 years experience some degree of ED in their lifetime [2, 3].

Prostate cancer is the most common malignancy among men in the United States, and according to the American Cancer Society, close to 240,000 new cases of prostate cancer will be diagnosed in 2013 [4]. There are many treatment options available for those diagnosed, but radical prostatectomy (RP) remains as one of the gold standard for locally invasive disease [3]. Unfortunately, radical prostatectomy

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carries with it the risk of inducing post-operative erectile dysfunction [5–7], regardless of the operative techniques used. The Prostate Cancer Outcomes study revealed 60 % of men experienced self-reported erectile dysfunction 18 months post-operatively, and only 28 % of men reported erections firm enough for intercourse at a 5 year follow-up [4, 5]. Additionally, the CaPSURE study reported that only 20 % of patients returned to their preoperative potency levels at one year following radical prostatectomy [6].

Post-RP ED pathophysiology is multifactorial, but has been attributed to factors related to a neurogenic, vasculogenic, and or smooth muscle injury [9]. ED secondary to RP may be neurogenic in origin as a consequence of a neuropraxia. Thermal injury to the cavernous nerves will permanently damage loss of erectile function after surgery. Less obvious is the possible injury to the nerves secondary to traction. Additionally, types I and III collagen, along with up regulation of fibrogenic cytokines have been demonstrated in neural related injuries after radical prostatectomy. Post-operatively, any neuropraxia can result in cavernosal tissue damage and atrophy [8, 9]. Smooth muscle and endothelial changes have been documented as a direct result of cavernous nerve injury. These structural changes are in response to smooth muscle apoptosis. Some researchers believe decreased oxygenation secondary to fewer nocturnal erections postoperatively, leads to the development of cavernosal fibrosis [8, 10]. Vascular injury in the RP can arise from damage to accessory pudendal arteries, which can be a major tributary to penile arterial flow. Other studies have demonstrated venous leak as a vascular injury based on penile Doppler ultrasound in the post-prostatectomy setting [9, 11]. Despite the implementation of a robotic approach to RP that boasts improved optics, removal of tremor, and superior surgical accuracy, a meta-analysis did not demonstrate any improvement in erectile function [9, 10]. This has led to a paradigm shift concerning ED after RP along with the development of penile rehabilitation programs.

Penile rehabilitation has been classically defined as the use of any pharmacologic agent or device after RP to maximize erectile function recovery. These programs are designed to improve long-term erectile function after nerve-sparing surgery. However, in addition to erectile dysfunction, the post prostatectomy patient is at increased risk of Peyronie's disease, penile shortening, and fibrosis [11]. We now formally redefine penile rehabilitation as the use of any device, pharmacologic agent, or intervention to promote male sexual function (including girth, length, curvature and, quality and longevity of tumescence) as a primer before and after any insult to the penile erectile physiologic axis. While this is commonly seen in RP, we advance the concept that this may also play a role in any instance of insult to erectile function, including Peyronie's disease, penile fracture, treatment after priapism, after radical cystectomy, and pelvic trauma. In the setting of RP, the timing of penile rehabilitation is of utmost importance, with strategies including monotherapy or combination therapy of phosphodiesterase 5-isozyme inhibitors (PDE5 inhibitors), vacuum erection devices (VED's), intracavernosal injection (ICI), intraurethral suppositories, and dietary supplements.

Timing of Rehabilitation

Prior to the consideration of which potential rehabilitation modalities may be appropriate, it is important to consider when a penile rehabilitation protocol should be initiated. It has been stated that the purpose of penile rehabilitation is the prevention of corpora cavernosa smooth muscle structural alterations, to limit venous leak development, and to maximize the chances of a patient returning to his preoperative level of erectile function [12••]. Iacono et al., demonstrated these structural changes as a progressive fibrosis of the corpora cavernosa. A total of 19 patients underwent corpora cavernosa biopsies at the time of radical prostatectomy, and at two and 12 months post-surgery had evidence of a time related, quantitative and qualitative decrease in elastic and smooth muscle fibers, and a progressive increase in collagen fibers after radical prostatectomy [13]. Although this study was small in number and no penile rehabilitative efforts were analyzed, it provided rare histologic evidence in humans post -prostatectomy. This correlates with rat cavernous neurotomy models with evidence of smooth muscle apoptosis as soon as day 1 after nerve injury[14]. Gontero et al., evaluated the hemodynamic parameter response to intracavernous PGE via color Doppler ultrasound in 72 patients after non-nerve sparing radical prostatectomy with normal preoperative International Index of Erectile Function (IIEF) scores. The patients who received intracavernous injection and Doppler within the first three months had improved erectile response to the injection. In the early group, only 22.2 % had peak systolic velocities of <30 cm/s compared with 51.3 % of those with injection at four to 12 months [15].

Mulhall et al., prospectively evaluated 84 patients post bilateral nerve sparing RP. Forty-eight patients initiated a penile rehabilitation protocol <6 months after surgery and were considered early rehab with 36 patients >6 months considered late rehab. At two years after surgery, the early rehab group was found to have a significantly better erectile function than the delayed group, with both unassisted and sildenafil assisted erections [12••]. A small series by Mosbah et al., randomized 18 patients after nerve sparing radical cystoprostatectomy into two groups, with therapy at two and six months post-operatively. They found a significant improvement in erectile function, intercourse satisfaction, and overall satisfaction in those started on early therapy compared to late therapy. There was also noted to be a significant improvement in end diastolic velocity compared to the pre-treatment levels in the early group only [16]. The Cleveland Clinic has presented its experience

with early penile rehabilitation with various therapies including intraurethral MUSE, VED, and ultimately with combination daily low dose sildenafil and low dose intracavernosal injections 2-3 times per week, starting as early as two weeks postoperatively. In the final group, there was 100 % compliance, with 17/18 patients sexually active after a mean follow-up of six months with either injections alone or combination therapy [17]. This data suggests that the timing of rehab is important, with an early initiation of penile rehabilitation after an injury resulting in improved outcomes. Ultimately this supports the idea that "time is tissue."

PDE5 Inhibitors

The phosphodiesterase enzyme can be categorized into eleven different subtypes (families) [18]. This enzyme is responsible for the degradation of 3'5'-guanosine monophosphate (cGMP), which results in the functional deactivation of cGMP. Most human tissue expresses several types of phosphodiesterase isozymes. However, the human corpus cavernosum smooth muscle cells predominantly express the phosphodiesterase 5-isozyme (PDE5) subtype [19, 20]. The vasodilation of blood vessels and dilation of smooth muscle in the penis that results in an erection are regulated by nitric oxide and guanylate cyclase. PDE5 inhibitors potentiate penile erections by increasing levels of cGMP (Fig. 1) [19, 20, 21••]. PDE5 inhibitors have been well established as the first-line therapy in the management of post-prostatectomy erectile dysfunction [2, 18, 19].

The advent of PDE5 inhibitors has changed the medical approach in the management of ED. The use of PDE5 inhibitors as a therapy in the management of post- prostatectomy ED has been studied in both animal and human studies. It has been well documented that the production of nitrous oxide is impaired after RP [20, 21••]. Since PDE5 inhibitors increase cGMP, which, in turn, increases levels of nitric oxide and guanylate cyclase, PDE5 inhibitors are able to exert an antifibrotic effect on cavernous tissue [22]. Because of their convenient oral administration and their ability to help prevent penile degeneration and corpus cavernosum fibrosis, PDE5 inhibitors have become a popular first-line treatment in penile rehabilitation following RP [23, 24].

The role that PDE5 inhibitors could play in penile rehabilitation was first demonstrated through experimental rat models. Klein et al., demonstrated that apoptosis of penile erectile tissue occurred after denervation of rat penis in 15 Sprague Dawley rats. This offered some explanation at the molecular level concerning the mechanism of decreased penile size and/or impotence after RP [25]. This was further validated when User et al., showed that DNA content was significantly decreased in bilaterally denervated rat penises and unchanged in rats that were unilaterally denervated [14]. Ferrini and colleagues concluded in their animal study that long-term vardenafil treatment may prevent corporal veno-occlusive dysfunction by preserving smooth muscle content and inhibiting corporal fibrosis after bilateral cavernosal nerve

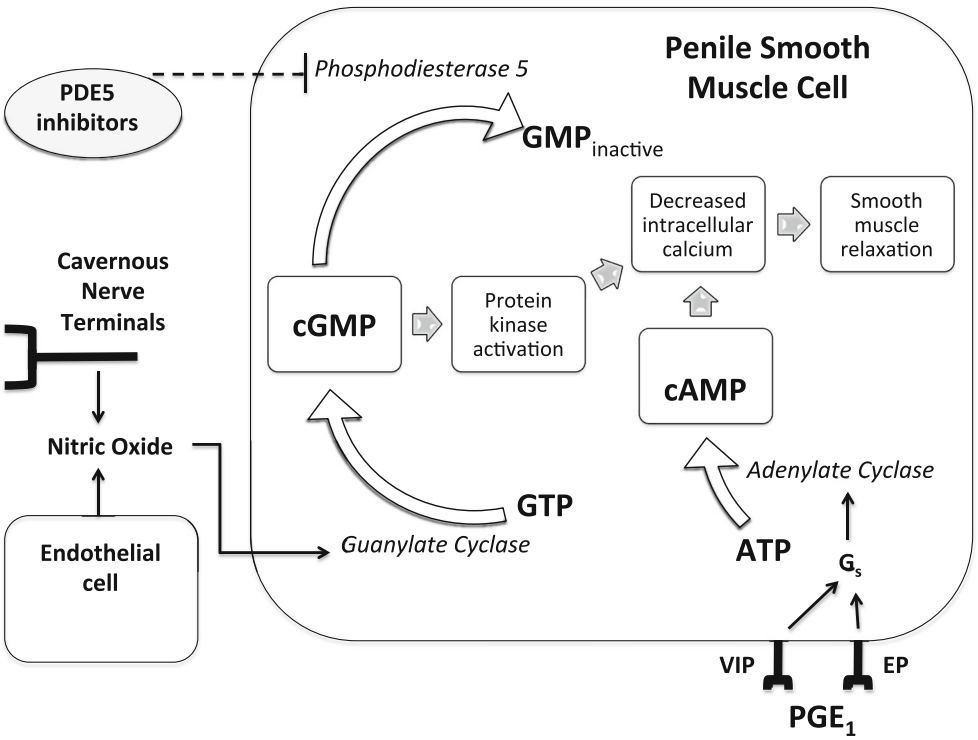

Fig. 1 Here we demonstrate the mechanism of action of erections from PDE5i and PGE1 therapies

resection [26]. Furthermore, Sirad et al., later proved in rats that sildenafil treatment after bilateral cavernous nerve resection activated genes related to smooth muscle preservation and down regulated genes related to fibrosis in the corpora cavernosum. This gave the first mechanistic justification for PDE5 inhibitor use as protective therapy after RP [22].

Recent published literature demonstrates the benefit that PDE5 inhibitors can have in penile rehabilitation in humans. In 2004, Schwartz, Wong, and Graydon evaluated males who underwent RP and were treated with either 50 mg or 100 mg sildenafil every other night for six months beginning on the day of catheter removal. In the 50 mg sildenafil group there was no significant change in the preoperative versus postoperative intracoporal smooth muscle content. In the 100 mg sildenafil group, there was actually noted to be an increase in smooth muscle content [27]. This was a small study without placebo control but showed a positive histologic (smooth muscle content) relationship with the group receiving the higher dose of sildenafil. In a study cohort of 238 patients, Padma-Nathan and colleagues concluded that nightly sildenafil administration for 36 weeks after radical prostatectomy markedly increases the return of normal spontaneous erections [28]. Montorsi et al., further evaluated the use of nightly versus on-demand vardenafil for penile rehabilitation and found no significant difference between the two groups of men after bilateral nerve sparing prostatectomy [29]. Bannowsky et al., separated 43 patients after nerve-sparing radical prostatectomy into a sildenafil group vs. a no PDE5 inhibitors treatment group and evaluated their recovery of erectile function. They determined that sildenafil leads to a significant improvement in the recovery of erectile function [30]. Furthermore, the Prostate Cancer Outcomes (PCO) study cited that only penile prostheses were more successful than sildenafil in helping patients achieve firm erections after RP [5]. Aydogdu et al., evaluated the use of tadalafil 20 mg three times per week starting on the day of surgery for six months compared to no tadalafil in the evaluation of penile size after prostatectomy. In the tadalafil rehab group, there was a non-significant tendency to decrease penile length and girth at month 3, but no significant difference changes from month 3 to month 6. In the no rehab group was there a significant decrease in all penile measurements at month 3, and from month 3 to month 6 [31].

While PDE5 inhibitors have been shown to be effective in the rat model and have benefit in human studies, more human trials are needed. Patient compliance can also be a barrier to a successful penile rehabilitation protocol, with high medication cost being a typical limiting factor for continued patient use. Lee, Cheetham, and Badani evaluated the compliance of patients on an oral PDE5 inhibitor rehabilitation protocol and found that 32 % of men discontinued therapy <2 months after prostatectomy and were deemed non-compliant. An additional 39 % discontinued therapy by six months with complaints of medication cost. Long-term compliance as well as pre-operative erectile function were noted to be independent predictors of the return of erectile function [32].

Vacuum Erection Devices

The use of VED's for the treatment of ED has been around for more than a century and is one of the safest, noninvasive, drug free and cost effective therapies [23, 24]. Having been eclipsed to a second line therapy by the emergence of PDE5 inhibitors, VED's are quickly becoming a favorite alternative ED therapy for patients that are unable to tolerate or are refractory to oral therapy [23, 24, 33]. These vacuum devices also have been used at times as first line therapy for patients with neurogenic, psychiatric and arteriogenic ED etiologies [33]. The majority of ED patients can successfully obtain an erection using a VED [34].

VED's are progressively being used as part of the treatment regimen in penile rehabilitation following RP. A novel animal study was performed to evaluate the possible molecular mechanisms involved in the use of vacuum therapy in penile rehabilitation. Yuan et al., demonstrated that in a rat model of bilateral cavernous nerve crush injuries, the use of VED therapy resulted in improved erectile with reduced HIF1α, TGF β1, and apoptosis indices, and increased smooth muscle/collagen ratios and preserved eNOS and α-smooth muscle actin [35].

In the RP patient, loss of penile length and girth has been shown to occur in the immediate postoperative period [33, 36••, 37, 38]. While PDE5 inhibitors are less effective at preserving penile length and girth; however, VED's can be used to fill this void. While neuropraxia may occur during RP due to cautery injury or nerve stretch, in which case PDE5 inhibitors may not have efficacy, this is where VED may augment the return of blood flow to the phallus to promote erections [33, 38]. Due to the mechanism of action of VED, they can target either temporary or permanent neuropraxias, which are independent of any erectile physiology. VED's create sub-atmospheric pressures that allow flow of blood restoring cavernosal oxygen. This is key to protecting smooth muscle integrity during the period of neuropraxia and can preserve penile length and girth if used as early as possible following RP [24, 37]. Kohler et al., prospectively randomized 28 men post-prostatectomy to rehabilitation with a VED at either one month or six months post-surgery. They demonstrated that the early VED rehab group had a significantly higher IIEF score with preserved stretched penile length [28]. In 2012, Shen et al., showed that early use (at three months) of VED's post RP preserved penile length and girth compared to late use (at 12 months) post RP [39]. Sellers et al., found that with routine VED use prior to penile prosthesis surgery, the average cylinder size placed in their

practice size increased by a length of 3.5 cm [40••]. The combination of VED and PDE5 inhibitors may minimize penile atrophy as well as decrease erectile function recovery time following RP. Recently, Basal et al., conducted a retrospective study with over 203 patients that showed a marked decrease in erectile function recovery periods with combined PDE5 inhibitors and VED compared to monotherapy (PDE5 inhibitors or VED only) by an average of five months [34].

The use of VED's in penile rehabilitation protocols has been limited by the fact that the available studies have not determined the optimum length of therapy. Studies have arbitrarily chosen between three and nine months for the length of VED use, despite the fact that full healing and recovery from RP can take up to one year [41].

Intraurethral / Intracavernosal Applications

Prostaglandin E1 (PGE_1), alprostadil, can be administered in two systems as an intracavernosal injection or as an intraurethral suppository. MUSE® is a single use intraurethral system for ED the delivery of alprostadil to the male urethra. It induces vasodilation and expansion of the corpora spongiosum. Local venous channels then transport the drug to the corpora cavernosa where it dilates the cavernosal arteries and relaxes trabecular smooth muscle via the cAMP pathway. This vasodilation causes rapid arterial inflow and the expansion of the lacunar spaces within the corpora. As the expanded corporal sinusoids are compressed against the tunica albuginea, venous outflow through subtunical vessels is impeded and then an erection is achieved [42].

The pioneering work of Montorsi et al., demonstrated in 1997 that the use of intracavernosal injection of PGE1 after nerve-sparing RP significantly increased the recovery rate of spontaneous erections. It was theorized that the mechanism of action of PGE1 improved cavernous oxygenation, which limited the development of hypoxia-induced tissue damage [36••]. The effectiveness of MUSE in a large randomized prospective study on penile rehabilitation for nerve sparing radical prostatectomy was published in 2010 by McCullough et al. It demonstrated no significant differences between intraurethral alprostadil and sildenafil in IIEF erectile function domain and intercourse success rates. In addition, a 6-month follow-up demonstrated a significantly better global assessment question for intraurethral alprostadil ($P<0.028$) compared to sildenafil [42].

Current AUA guidelines for intra-urethral suppositories and ICI recommend their use on select patients that are either not candidates for or have failed therapy with oral PDE5 inhibitors [43]. Currently, there are no definitive studies that provide guidance on the post-operative timing for penile rehabilitation utilizing intra-urethral suppositories. Intracavernosal injection (ICI) studies using alprostadil have shown to produce valid erectile responses in a significantly higher proportion of patients when started within month 3 after non-nerve sparing RP [15]. Injections given in the first month postoperative demonstrated the best response rate, but this method produced significant complications and poor patient compliance [15]. Studies assessing the combination of alprostadil suppositories with either a penile constriction device or oral PDE5 inhibitors have shown increased efficacy over alprostadil alone [44, 45•, 46]. Mulhall et al., evaluated 132 post-prostatectomy in a non-randomized fashion. Fifty-eight of these patients followed a penile rehabilitation protocol with initial challenge with oral PDE5 inhibitors within six months of surgery, and, if there was an inadequate response, they were encouraged for intracavernosal injection. Seventy-four patients were in the non-rehabilitation group. Seventy-seven percent of the rehabilitation group required use of ICI, either bimix or trimix. After 12 months, there was a significant improvement of IIEF scores in the rehabilitation group and at 18 months post-surgery, 52 % of the patients in the rehab group recovered spontaneous functional erections compared to 19 % of the non-rehabilitation group. In addition, patients who underwent rehabilitation were noted to have improved responses to sildenafil and ICI [46]. In patients who cannot tolerate or do not respond to ICI with alprostadil, papaverine and phentolamine may be utilized, typically in combination with each other or with the addition of alprostadil for PGE1 non-responders. Ultimately, patient compliance and medication side effects remain limiting factors in the use of these medications

Conclusions

Since its inception in 1997 by Montorsi, penile rehabilitation after RP has become an important if somewhat controversial component of post-RP ED therapy [36••]. The clinical paradigm of penile rehabilitation came to light based on the idea that induced early sexual stimulation and augmented blood flow to the penis would facilitate the return of the patient's natural erections. It has been convincingly shown that nerve injury results in changes in the smooth muscle architecture of the corpus cavernosum, including apoptosis and progressive fibrosis that lead to loss of the potential to recover erectile function. Although there has been a marked improvement in surgical technique during RP with the advent of robotic assistance, ED post-RP remains a major potential surgical complication.

Despite the evidence presented here, there is a lack of consensus in the literature as to the optimal rehabilitation protocol for rehabilitation in regards to modalities used,

timing of initiation of rehabilitation, and duration of treatment [47, 48]. While timing appears to be important, there is no definitive study that identifies the optimal start time for penile rehab. Based on the available research, we favor the initiation of a rehab protocol at the earliest possible date to attempt to minimize any potential penile tissue alterations. In Fig. 2 we propose our approach to penile rehabilitation. This includes the early initiation with a VED and oral PDE5 inhibitors. While there is some question in regards to the use of on-demand vs. regularly scheduled dosing of the PDE5 inhibitor, we favor a daily or at least 3-4 times per week use of the medications, especially during the early phase of recovery when the patient may not have any desire for sexual activity or may not have recovered enough erectile function for on-demand activity.

In penile rehabilitation of patients following RP early use of VED's have proven to be the most beneficial in the preservation of penile length and girth. This can be especially distressing for a male patient. Despite side effects such as numbness, pain, bruising, and petechiae, there are few contraindications to VED use. However, as with PDE5's, there is still a lack of data in regards to how often the VED should be used and for how long. Based on the work of Sellers et al., we favor a daily usage without constriction band for at least ten minutes at a time.

ICI and intraurethral Muse suppository typically remain second line agents. However, for those patients who are poor responders to oral medications or desire a stronger, on-demand medication during recovery, they remain feasible options and can be started as soon as the patient prefers if he has had inadequate tumescence with oral agents. The key advantage of using ICI is that a pharmacologically induced erection can be nearly 100 % of their preoperative baseline erection. Thus, the patient takes advantage of a modality that both complies with penile rehabilitation strategies and good on-demand erections for sexual activity.

Full recovery from the penile injury can take up to 12 months or more and as such the patient must be carefully counseled to avoid anxiety and frustration over the lack of function.

We acknowledge that the limitations of the available data result in an inability to provide formal standardized guidelines in regards to penile rehabilitation. However, we propose a penile rehabilitation protocol that extrapolates from the available data and clinical experience with a simple, common sense protocol (Fig. 2). We recommend the early initiation of chronic, oral PDE5 inhibitors at least 3-4 times per week as early as possible. In the case of prostatectomy, we would recommend initiation of VED therapy when the catheter has been removed to minimize changes in penile length and girth. This combination therapy is key to limiting damage to the cavernosal smooth muscle and preservation of penile length and erectile

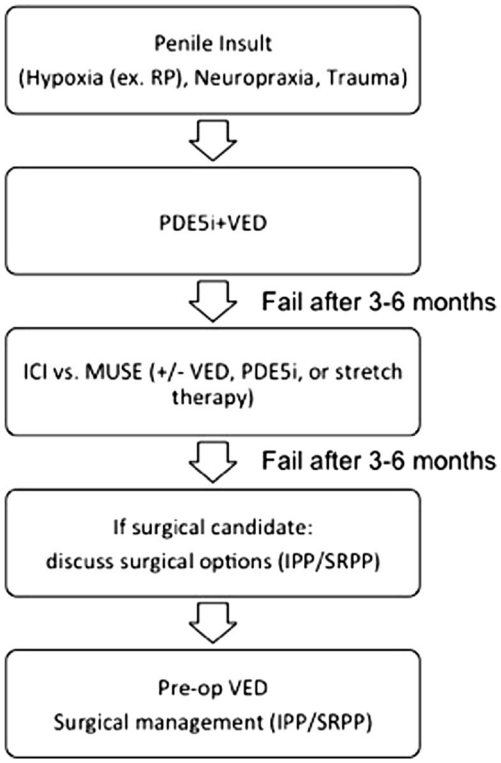

Fig. 2 Penile rehabilitation protocol

potential. If there has been no improvement in erectile function within 3-6 months, ICI or intraurethral Muse can be initiated; however, these may be utilized at any time in the recovery in an on demand fashion if the patient has inadequate response or oral PDE5 inhibitors. Rehabilitation therapy can continue for up to one year and, if the patient still has inadequate erectile function, then he may be considered for elective penile prosthesis placement.

We further propose that the concept of penile rehabilitation be extended beyond the scope of RP. Recovery of function through penile rehabilitation after sustaining an injury through any vehicle should be considered for any insult to the erectile physiologic axis including Peyronie's disease, penile fracture, after priapism, after cystectomy, and pelvic trauma.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Tariq S. Hakky, Dr. Adam S. Baumgarten, Dr. Justin Parker, Dr. Yin Zheng, Dr. Mike Kongnyuy, and Dr. Daniel Martinez each declare no potential conflicts of interest relevant to this article.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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