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Penile Rehabilitation: The “Up”-date

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Abstract

Purpose of Review: The purpose of this review is to review the penile rehabilitation literature published since the beginning of 2017. Specific emphasis was placed on determining how the new findings increase our understanding of the mechanisms leading to recovery of erectile function after pelvic surgery and to identify potential focus areas for future studies.

Recent Findings: A meta-analysis of penile rehabilitation after prostatectomy was published in early 2017 reporting that PDE-5 inhibitors, intracavernosal injection (ICI) therapy and vacuum erection devices (VED) improved erectile function; however, the benefit was not observed after a washout period. Preclinical studies have identified potential regenerative therapies after cavernous nerve injury.

Summary: While significant methodological challenges remain, recent literature suggests benefits to starting penile rehabilitation immediately after surgery, but not extending past 1 year post-operatively. The cost-benefit ratio of penile rehabilitation remains unclear; however, decreasing costs of PDE-5 inhibitors as well as improvements in characterizing post-surgical erectile dysfunction may help to personalize penile rehabilitation, improve outcomes and improve the cost-benefit ratio. Better and more consistent trial design is needed to develop the optimal regimen(s) for restoring sexual function in men. Finally, future studies to translate promising preclinical regeneration therapies to humans are also needed.

Terms:

erectile dysfunction; penile rehabilitation; radical prostatectomy; PDE-5 inhibitors; vacuum erection device; intracavernosal injection

Introduction

Erectile dysfunction (ED) is a common fear among men undergoing deep pelvic surgeries. Due to the number of surgeries performed for prostate cancer and the excellent 5-year survival rate, the vast majority of the literature has focused on the incidence of ED and the recovery of function after radical prostatectomy. Several decades ago it was assumed that virtually all men would have permanent ED after radical prostatectomy. The advent of “nerve sparing” surgery and phosphodiesterase-5 (PDE-5) inhibitors, however, has dramatically increased the number of men who recover erectile function after surgery. Thus, there have been increasing efforts to further expand the number of men who regain function

after surgery and the speed with which they regain it—the two main tenets of penile rehabilitation.

This review of the penile rehabilitation literature published since the beginning of 2017 will focus on rehabilitation after prostatectomy, mirroring the recently published studies. While penile rehabilitation can be offered to men undergoing any deep pelvic surgery, whether similar results will be seen is unclear, as there is considerable variation in attempts to spare the cavernous nerves and other parasympathetic fibers as a function of the type of surgery and surgeon experience.

Natural History

The vast majority of men will experience complete loss of erectile function immediately following radical prostatectomy, regardless of whether or not the nerves were spared during surgery. This has been attributed to iatrogenic neuropraxia from stretch, heat and other microinjuries sustained by the cavernous nerves running alongside the prostate. Nonetheless, many of these men will ultimately regain erectile function. The most significant predictors of who will regain function are erectile function prior to surgery, age, and nerve sparing status [1].

While many men will be able to engage in sexual intercourse, most will not recover to their preoperative level of erectile function. Indeed, Al-Ali and colleagues reported on the long-term effects of radical prostatectomy by comparing men who had undergone the procedure to healthy, age-matched controls [2]. Not surprisingly, mean IIEF-5 scores were significantly lower in the post-prostatectomy group, with risk of having moderate to severe ED (i.e., IIEF-5 < 18) being 2.2- to 4.7-fold higher depending on the age group.

Furthermore, the process can be quite protracted. For example, 40% of men with ED 12 months following surgery will regain function over the next three years and beyond [3]. While psychologically difficult, prolonged ED after surgery also results in physiological changes in penile tissue that can impact future erectile function and quality—fibrosis, loss of vascular smooth muscle cells and Peyronie's disease [4, 5•]. Thus, efforts to restore erectile function as soon as possible to minimize these changes has remained a critical focus.

Penile Rehabilitation up to 2017

Liu and colleagues published a meta-analysis of penile rehabilitation techniques after prostatectomy, examining the literature published up to February 2017 [6]. They reported on data pooled from 11 randomized controlled trials and 5 case-control studies, involving a total of 2,012 patients. While the majority of the literature focused on PDE-5 inhibitors, they found that all forms of penile rehabilitation (PDE-5 inhibitors, vacuum erection devices (VED) and intracavernosal injections (ICI)) were associated with significant improvements in erectile function. Overall, men who used PDE-5 inhibitors for penile rehabilitation reported improved erectile function twice as frequently as those who did not. These findings came with a significant caveat—studies that assessed erectile function after a washout period found no difference between PDE-5 inhibitor users and non-users.

Given the limited number of studies that assessed erectile function after washout, it remains unclear to what degree penile rehabilitation with PDE-5 inhibitors may improve the underlying, unassisted erectile function. Nonetheless, these data clearly indicate that PDE-5 inhibitors at a minimum can assist erectile function after prostatectomy—similar to the way they help improve erectile function in men who have not undergone surgery.

PDE-5 inhibitors appear to also have positive effects beyond simply achieving erections. Previous animal and human studies have demonstrated PDE-5 inhibitor use can decrease fibrosis and increase vascular smooth muscle in the penis after cavernous nerve injury [7–10]. Thus, even if PDE-5 inhibitors may not improve spontaneous erectile function, their use in penile rehabilitation may improve future response to PDE-5 inhibitors and other adjuncts (e.g., ICI) and reduce the incidence of Peyronie’s disease.

Challenges

In evaluating the literature covered by and published since Liu’s meta-analysis, several challenges become clear. First, each treatment center has a unique penile rehabilitation regimen. Different protocols use different PDE-5 inhibitors, different doses, different administration schedules, and different durations of therapy. Additionally, some investigators used VEDs or ICI, either alone or in combination with PDE-5 inhibitors. Some studies barred the control group from using any PDE-5 inhibitors, while others permitted on-demand dosing. A few studies assessed erectile function after a washout period. Thus, differences in rehabilitation regimens make applying findings from one study to another difficult.

Second, there is high variability in the inclusion and exclusion criteria of the studies. For example, most studies used healthy adults with no prior history of ED. The validity of these studies remains unclear, as many of the men undergoing radical prostatectomy would not meet eligibility for inclusion. The surgical modality varied as well, with some studies only including robotic/laparoscopic prostatectomies while others included open prostatectomy. Additionally, some studies excluded men who had not undergone nerve sparing surgeries, whereas others included non-nerve sparing surgeries.

Third, there was significant variation in the definition of “recovery” of erectile function. There was little agreement on IIEF-5 cutoff scores, and some studies used other questionnaires or patient self-reports.

Thus, extracting meaningful data from the literature can be challenging. Nonetheless, several papers published over the past 18 months have provided some additional insights that may help to refine future clinical trials.

New Insights-Timing

The sooner penile rehabilitation is started the better. Jo and colleagues reported that early initiation of penile rehabilitation after prostatectomy was better than delayed initiation [11]. In this study, patients were given sildenafil 100 mg twice per week for three months and then erectile function was assessed at the 12-month anniversary of their surgery. 120 patients

were randomized to either the early (treatment started at the time of catheter removal) or delayed (treatment started 3 months after surgery) treatment arms. Patients were allowed to continue taking sildenafil as needed after completing the three-month rehabilitation program. As such, there was no clear washout phase. Nonetheless, 41% of the early group reported an IIEF-5 score ≥ 17 (questions 2 and 3), compared to 18% of the delayed group. These data suggest that starting penile rehabilitation earlier improves response to PDE-5 inhibitors.

New Insights-Duration

While the above data indicate that starting PDE-5 inhibitor therapy sooner appears to improve outcomes, the optimal duration of therapy remains unknown. Kim and colleagues attempted to answer this question by retrospectively reviewing their data regarding duration of daily tadalafil use [12]. They found that men who used daily tadalafil for one year had significantly better erectile function than those who did not use tadalafil regularly; however, there were no significant differences in erectile function in those who had used tadalafil for 2 years or longer compared to only 1 year. As there was no washout period and other time points were not investigated, it remains unclear whether duration has a significant impact. For example, it may just be that men currently using tadalafil have better erections than those who do not—a conclusion supported by the meta-analysis. Nonetheless, these data suggest that prolonging penile rehabilitation beyond 1 year does not have significant benefit over on-demand dosing.

New Insights-Mechanisms

There is minimal blood flow within the flaccid penis resulting in penile blood oxygen saturation similar to that of venous blood. By contrast, the rapid inflow of arterial blood during penile erection drastically increases oxygen delivery to the tissues. It has, therefore, been hypothesized that prolonged tissue hypoxia due to the absence of erections may be a causative factor in permanent ED after surgery [13]. To address this, Chiles and colleagues randomized patients to hyperbaric 100% oxygen or hyperbaric air therapy shortly after radical prostatectomy [14]. Although they reported treatment to be safe, they did not find hyperbaric oxygen significantly improved erectile function. While on the surface this may appear to negate the hypoxia hypothesis, it should be noted that hyperbaric air therapy is still delivering elevated partial oxygen pressures to the patient, and thus, is still increasing blood oxygen delivery. Their study, therefore, investigated the difference between increased and highly increased oxygen delivery. Second, their therapy was short in duration relative to the period of recovery of erectile function. In the treatment group, men received hyperbaric oxygen every weekday for two weeks, beginning after removal of the catheter. While not reported in their cohort, most men—even those who will ultimately regain function—would still have several weeks to months of ED following their therapy. Thus, the duration of their therapy may not be sufficient to alter the natural course. Finally, while they overenrolled their study in order to accommodate dropouts, the number of men who completed the study ($n=83$) was lower than the target ($n=90$) needed to achieve sufficient power to detect differences. Thus, the contribution of prolonged tissue hypoxia to permanent ED remains open to further investigation.

Alternatives Beyond PDE-5 Inhibitors

As mentioned earlier, Liu's meta-analysis revealed that VED and ICI were also useful adjuncts for erectile function. If reducing tissue hypoxia-induced fibrosis and loss of smooth muscle cells is the main target of penile rehabilitation therapy, ICI and VED may be beneficial as they would permit erections earlier than PDE-5 inhibitors alone. ICI can give a rigid erection by increasing arterial inflow into the penis, similar to a natural erection, resulting in increased delivery of oxygenated blood and stretching of the penis.

VED therapy may be particularly appealing for several reasons. First, as highlighted in a review by Wang, the majority of blood entering the penis while using a VED is arterial in source [15]. Thus, in the absence of erectile function following surgery, VED (like ICI) could be used to stretch and oxygenate the penis earlier than PDE-5 inhibitors alone. VED can also be used for short periods, multiple times per day, which may be more physiologically relevant than ICI as men usually have several erections per 24-hour period. This may be more appealing to men who may not be sexually active and would prefer to avoid having a prolonged, ICI-induced erection. Finally, the cost of the VED is negligible compared to multiple doses of PDE-5 inhibitors and even compounded ICI medications.

The benefit of combination VED/PDE-5 inhibitor therapy was demonstrated in a study of men undergoing penile rehabilitation following total mesorectal excision for rectal cancer (which tends to be a younger age group than prostate cancer) [16•]. As seen in previous studies without a washout period, nightly low dose sildenafil was associated with significant improvement in IIEF-5 scores at 3, 6, and 12 months post-surgery compared to no intervention. Combination sildenafil with daily VED use had even greater improvements, particularly at the earlier time points. These data suggest that increasing blood delivery to and stretching the penis with VED is superior to waiting for spontaneous, PDE-5 inhibitor-assisted erections to take place.

Cost-Benefit Ratio

The unclear benefit of penile rehabilitation at improving unassisted erectile function raises concern about its cost-benefit ratio, particularly for PDE-5 inhibitor-based regimens. The predominant concern is financial due to the high cost of frequent and long-term dosing regimens—although the increasing availability of generic sildenafil and tadalafil may improve that ratio in future analyses.

While cost to the overall healthcare system remains a concern, medication cost may also be a significant deterrent for patients if it is not covered by insurance. In Italy, Tuscan citizens are given PDE-5 inhibitors free of charge following radical prostatectomy. By comparing Tuscan citizens to non-citizens living in the area, Siena et al were able to study the effect of cost to the patient as a factor in compliance with penile rehabilitation therapy [17]. Not surprisingly, those who received the PDE-5 inhibitors free-of-charge were more likely to start penile rehabilitation early, had fewer dropouts and had better overall compliance to the prescribed protocol compared to those who had to pay out-of-pocket. They also reported

better sexual function and satisfaction based on the UCLA Prostate Cancer Index-Sexual Function and Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire scores.

Another way to improve the cost-benefit ratio would be to determine who is likely to benefit from PDE-5 inhibitor-based penile rehabilitation, as there are subgroups of men who respond and subgroups who do not. Kim et al reported results of long-term tadalafil use after robotic radical prostatectomy [12•]. Notably, most patients underwent penile duplex ultrasound. Men with evidence of venous leak on ultrasound had poor response to PDE-5 inhibitor treatment compared to those with arterial insufficiency or normal studies (14.2% vs 55% vs 53.3%, respectively). Thus, penile duplex ultrasound soon after radical prostatectomy may be helpful in delineating who is likely to respond to the PDE-5 inhibitor-based therapy, and who may benefit more by starting other therapies sooner.

Furthermore, men with poor/absent erectile function prior to surgery may benefit from early penile prosthesis placement rather than using PDE-5 inhibitors, ICI or VED. Mondaini et al published a case series of ten men who underwent combined radical prostatectomy and penile prosthesis placement, with the hypothesis that early placement of the prosthesis might preserve penile length [18]. Indeed, penile length was maintained (although all the men had refractory ED and may have already experienced penile shortening prior to surgery). All the men—and their partners—were pleased with the results. For men with severe ED, this may prove to be a better option than attempting penile rehabilitation.

Preclinical Investigations

The previous clinical studies have largely focused on regaining erectile function after nerve damage has occurred. Many preclinical studies, however, have been focusing on preventing the nerve loss and regeneration in the immediate period following nerve damage. The regenerative properties of platelet-rich plasma (PRP) and stem cells have been investigated in animal models of bilateral nerve crush injury, a model of nerve injury that closely approximates radical prostatectomy. While the preclinical studies were performed before the range of this review, no studies have reported outcomes of PRP injection in men with post-surgical ED. One study investigated platelet-rich fibrin matrix injections in men with non-surgical ED and/or Peyronie's disease, and found injections were safe and feasible [19]. While they noted a 4-point improvement in IIEF-5 scores (p-value not reported), only 7 of the 17 patients completed the IIEF-5 and the authors didn't specify how many of the respondents had been injected for ED.

Injection of bone marrow-derived stem cells into the corpora of men with severe post-prostatectomy ED has previously been shown to improve erectile function and blood flow [20]. In an interesting extension of this finding was recently published, which demonstrated that corporal injection of exosomes from adipose- and bone-marrow derived stem cells at the time of nerve crush injury also improved erectile function and attenuated nerve, smooth muscle and endothelial cell loss [21].

Additionally, studies of regeneration have been performed in the absence of PRP or stem cells, with recent studies including roles for augmenting sonic hedgehog signaling and

inhibiting the LIM-kinase-2 pathway [22]. Sonic hedgehog treatment has previously been shown to improve erectile function in rats with crush injury [23]. Choe and colleagues probed the mechanisms of these findings by injecting sonic hedgehog protein embedded hydrogel onto the crushed cavernous nerves in rats [24]. Sonic hedgehog signaling supported the injured neurons allowing regrowth to take place, preventing neuronal loss and thereby maintaining downstream signaling. Many other compounds have been previously studied in the cavernous nerve crush injury model and have been recently reviewed by Haney and colleagues [25].

It should be noted, however, that nearly all of the regenerative therapies studied in the nerve crush injury models were administered at the time of injury. It therefore remains unclear whether most of these therapies are truly promoting regeneration or simply preventing loss of neurons, smooth muscle cells and endothelial cells. In most cases, the mechanisms underlying the benefits remain unclear; however, these findings do open the door for future clinical studies aimed at preventing and treating the underlying etiologies of post-surgical ED.

Future Directions

In summary, clinical studies published since the beginning of 2017 have focused largely on the use of PDE-5 inhibitors, ICI and VED in penile rehabilitation post-prostatectomy. Preclinical and forthcoming clinical trials in regenerative medicine therapies may expand rehabilitation and allow for the damage incurred by surgery to be reversed. As the regenerative studies reported to date have largely been preclinical, significant further investigation will be needed before their effects on post-surgical ED and their effectiveness compared to existing rehabilitation protocols will be known.

With regards to the recent data and ongoing penile rehabilitation protocols, it appears that starting penile rehabilitation with PDE-5 inhibitors sooner is better than later, and that combination therapy with ICI and VED may yield improved results. Nonetheless, limited studies investigating the clinical effectiveness of PDE-5 inhibitors in penile rehabilitation following a washout period, as well as few human studies investigating physiological changes as a result of penile rehabilitation significantly limit our ability to draw conclusions. Additionally, given very few studies have investigated penile rehabilitation after pelvic surgeries other than radical prostatectomy, its role in these scenarios remains unknown.

As reiterated throughout this review, significant differences between study designs have limited the conclusions that can be drawn from them. Well-designed, prospective clinical and basic science studies will be important to help optimize recovery of erectile function and sexual activity of men after pelvic surgery. Points to consider include:

1. *Standardization of protocols.* As the above studies have highlighted, there is significant variation in penile rehabilitation protocols throughout the world. Standardization of the protocols (e.g., inclusion criteria, medications and adjuncts, dosages, timing, outcome measures, etc.) will be important for allowing meaningful interpretation of the results and comparisons between studies.

2. *Better characterization of the men included in the studies.* Understanding and categorizing men by the physiologic mechanisms underlying their ED will help identify optimal rehabilitation options and help improve the cost-benefit ratio of treatment.
3. *Inclusion of a washout phase.* Several studies have reported no difference in unassisted erectile function after a washout period for PDE-5 inhibitors. As the goal of penile rehabilitation is to increase the number of men who will regain function, it will be important that erectile function be assessed both while on the treatment regimen and after a washout period.
4. *Standardization of outcome measures.* Clearly and consistently defining both subjective (e.g., IIEF-5 scores) and objective (e.g., penile blood flow, degree of fibrosis) outcome measures will be critical to allowing comparisons between regimens.
5. *Expanding studies into other populations* Significantly more research into men with suboptimal pre-surgical erectile function, medical comorbidities, non-nerve sparing surgeries (both prostatectomy and other pelvic surgeries) will be important to extend the validity of the findings to the general population. Additionally, determining meaningful rehabilitation protocols for non-sexually active men and men who engage in anal intercourse (which may require more rigid erections than vaginal intercourse and oral sex) will be important.

Clearly, there are ample opportunities for research to help hone penile rehabilitation therapy and allay the concerns of men facing deep pelvic surgeries. It should be remembered, however, that erectile function requires a combination of nerves, blood flow, hormones and psychological factors. While many studies have investigated the effects of surgery on nerve function and regulation of penile blood flow, there have been few studies that have addressed (or even checked) testosterone levels. Likewise, psychological factors that could contribute significantly to ED (e.g., depression, concern about recurrence, financial stress, poor body image, performance anxiety, etc.) need to be included in future studies.

Finally, while penile rehabilitation is peno-centric by definition, we must not forget that ED is only part of the sexual dysfunction that can occur after pelvic surgery. Problems with orgasm (i.e., anorgasmia, dysorgasmia, climacturia) and Peyronie's disease may also exist. Simply restoring erectile function may not be sufficient—or even necessary, for that matter—to restore sexual satisfaction after surgery. Further investigation into penile rehabilitation and other aspects of sexual rehabilitation will be critical to minimize the sexual, physical and psychological side effects of pelvic surgery in men.

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