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Prevention and Management of Postprostatectomy Erectile Dysfunction

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Abstract

Context: Erectile dysfunction (ED) is the complication associated with radical prostatectomy (RP) for clinically localized prostate cancer that has the most negative impact. Currently, several therapeutic options are available to improve sexual health after surgical treatment.
Objective: To critically analyze the factors affecting erectile function after RP and to evaluate the evidence suggesting the role of pharmacologic prophylaxis and treatment of ED after surgery.
Evidence acquisition: This article is based on the proceeding of the Risk Evaluation and Mitigation Strategy (REMS) meeting held in Madrid, Spain, in 2007.
Evidence synthesis: Several basic science reports have highlighted a potential role of phosphodiesterase type 5 inhibitors (PDE5-Is) in the prevention of endothelial damage related to ischemia–reperfusion and/or denervation following surgery. However, patient selection and preservation of both nerves and vascular supply integrity are the major determinants of postoperative erectile function. Pharmacologic treatment of postoperative ED, using either oral or local approaches, is effective and safe. Moreover, recent studies have shown that pharmacologic prophylaxis early after RP can significantly improve the rate of erectile function recovery after surgery. Use of on-demand treatments for treatment of ED in post-RP patients has been shown to be highly effective. In this context, pharmacologic prophylaxis may potentially have a significant expanding role in future strategies aimed at preserving postoperative erectile function.
Conclusions: Administration of pro-erectile drugs is the key factor of erectile function recovery after RP. Use of on-demand PDE5-Is in post-RP patients has been shown to be effective and safe, with better results seen in select young patients treated with a bilateral nerve-sparing approach. Pharmacologic prophylaxis may have a role in the future. Large, multicentric, placebo-controlled trials are urgently needed in order to identify the best regimen for treating postsurgery ED.

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1. Introduction

Radical prostatectomy (RP) is the most widely performed procedure for patients with clinical, localized prostate cancer (PCa) and a life expectancy of at least 10 yr [1–6]. This procedure may be associated with treatment-specific sequelae affecting health-related quality of life [7,8]. This topic is increasingly important because the diagnosis of PCa is becoming more frequent in younger patients [9]. Those patients are motivated to preserve their sexual function and the couple's sexual health, and, therefore, they are candidates for a bilateral nerve-sparing (BNS) procedure. In this context, the optimal outcome after BNSRP for clinically localized PCa is currently being defined as freedom from biochemical recurrence along with the recovery of continence and erectile function [10–12].

Erectile function impairment is certainly the most significant disorder that negatively affects the overall sexual health in patients who undergo RP. Research in post-RP recovery indicates that approximately 25–75% of men experience postoperative erectile dysfunction (ED) [12–18]. This broad range of postoperative erectile function impairment can be attributed to several study design factors, including differences in baseline tumor characteristics and sexual-health sample characteristics, surgical technique, surgical volume of the surgeon, length of follow-up after surgery, and the quality of study methodologies used to assess both prevalence and severity of male ED [16,18–22].

The aim of this review is to focus on the pathophysiology, the prevention and the treatment of postprostatectomy ED.

2. Evidence acquisition

This article is based on the proceeding of the Risk Evaluation and Mitigation Strategy (REMS) meeting held in Madrid, Spain, in 2007.

3. Evidence synthesis

3.1. *Pathophysiology of erectile dysfunction*

Preoperative potency is a key factor of erectile function recovery after surgery. Patients being considered for a nerve-sparing radical prostatectomy (NSRP) should ideally be potent prior to the procedure [23]. This is of utmost importance, since patients who complain to some degree of ED or patients who already use phosphodiesterase type 5 inhibitors (PDE5-Is) prior to surgery are at higher risk of developing severe ED postoperatively, regardless of the surgical technique used [23]. In this context, comorbid conditions identified at the time of the preoperative patient assessment (ie, such as diabetes mellitus, hypertension, ischemic heart disease, hypercholesterolemia, or history of cigarette smoking) also seem to negatively affect the recovery of spontaneous erections postoperatively because they may have an impact on baseline penile hemodynamics [23].

When debating post-RP ED, a number of intraoperative pathophysiological aspects deserve attention. Indeed, in suitable candidates, radical excision of the prostate should be performed with the objective of achieving total cancer control. This implies the accurate excision of all cancer present in the prostatic tissue, preserving the integrity of the anatomical structures on which urinary continence and erectile function are based. Therefore, to preserve erectile function, a rigorous nerve-sparing (NS) technique is mandatory [5,24–28]. The cavernous nerves follow a course adjacent to small vessels forming the so-called neurovascular bundle (NVB) along the posterolateral margin of the prostate bilaterally, and are located between the visceral layer of the endopelvic fascia and the prostatic fascia. However, a number of recent studies have demonstrated that the course of the NVBs might be more complex than historically thought and that a wide distribution of the nerve fibers belonging to the NVBs are spread all around the prostatic capsule [29–34]. These results have clearly shown huge amounts of fibers included in the NVB, which altogether contribute to a widely spread neural network instead of a real neural bundle. Based on the latter findings, some authors advocate a modification of the standard NS approach, suggesting an intrafascial RP aimed at maximizing nerve-fiber preservation [24,27,35].

A number of studies have also highlighted the potential role of hemodynamic impairment as a key factor in determining postoperative ED. While it is absolutely clear that preservation of the cavernous nerves is mandatory to obtain a spontaneous erectile function recovery after RP, the potential role of vascular insufficiency has increasingly gained interest as a contributor to postoperative erectile function impairment [36]. Indeed, several data have shown that erectile tissue requires oxygenation to maintain its integrity [23,37], which can be significantly affected if the arteries irrigating the cavernous bodies, such as the accessory pudendal arteries, are damaged intraoperatively. In this context, a rigorous preservation of the accessory

pudendal arteries has been advocated, although their role in functional outcomes still needs to be prospectively established [37,38].

Overall, both a postoperative denervation and/or an ischemic process (consequent to a ligation of anomalous pudendal artery branches or of venous plexuses that drain to or from the corpora cavernosa) may cause a progressive fibrosis in the corpora cavernosa [39–41]. Fibrosis and the subsequent loss in elasticity and function of erectile tissue together probably cause ED [39–41].

3.2. *Management of post–radical prostatectomy erectile dysfunction*

A key post-RP factor associated with erectile function improvement is administration of proerectile drugs. Historically, patients complaining of postoperative ED had several therapeutic options that may have increased the likelihood of obtaining erections sufficient for satisfactory sexual intercourse, including intracavernous injections [15,18,19,42], transurethral alprostadil [19,43], vacuum-device therapy, and penile implants [19,44]. At present, PDE5-Is are the first-line oral pharmacotherapy for the treatment of post-RP ED in patients who have undergone either a unilateral nerve-sparing radical prostatectomy (UNSRP) or a BNSRP [19]. Although this is still controversial, a key role for the preservation of postoperative erectile function is played by volume of the surgeon's surgical experience, which was even described as an independent predictor of erectile function recovery after surgery along with patient age and NS technique [45–47]. Indeed, PDE5-Is have the greatest effectiveness in patients who have undergone a rigorous NS procedure, which has been reported to be more commonly performed by the surgeons with the largest surgical volumes [45,46].

Although PDE5-Is are the first-line treatment option for the management of postprostatectomy ED, several treatments have been extensively studied. Intracavernous injections (ICIs) represent a valid alternative in patients that do not respond to PDE5-Is or who are not satisfied with the oral compounds. The main advantage of ICIs is an efficacy independent of the preservation of cavernous nerves [19]. A recent trial by Gontero et al showed a high satisfaction rate in patients treated with ICI after non–nerve-sparing RP [48]. According to the authors' conclusions, in order to obtain the largest adherence to therapy, ICI should be started 3 mo after surgery. Transurethral alprostadil may be a valid alternative to PDE5-I in patients who are not candidates for oral therapy. A recent report by Raina et al showed that transurethral alprostadil is effective and safe in treating postprostatectomy ED [43]. The same group identified the best results in terms of treatment-induced erections in patients with partially maintained erectile function after surgery [49].

3.3. *Rationale for phosphodiesterase type 5 inhibitor prophylaxis for prevention of post–radical prostatectomy erectile dysfunction*

The advent of PDE5-Is in the treatment of ED has clearly revolutionized the management of post-RP ED. This class of agents acts within the smooth-muscle cell by inhibiting the enzyme PDE5 which naturally degrades cyclic guanosin-mono-phosphate (cGMP), an intracellular nucleotide which acts as second messenger in the process of smooth-muscle cell relaxation. Increased levels of cGMP lead to the activation of cGMP-specific protein kinases which activate further intracellular events leading to the final reduction of intracellular calcium and, in turn, to smooth-muscle cell relaxation.

Several basic scientific studies have highlighted a potential role of PDE5-Is in the prevention of endothelial damage related to ischemia–reperfusion and/or denervation. Experimental data regarding the potential mechanisms involved in chronic administration of PDE5-Is have been published by Behr-Roussel et al [50]. Indeed, the effect of an 8-wk-long treatment with sildenafil (60 mg/kg per day subcutaneously) in male rats was evaluated on electrically induced erectile response in vivo before and after an acute injection of sildenafil (0.3 mg/kg intravenously). Interestingly, the authors found that endothelial relaxation induced by acetylcholine was significantly enhanced in rats treated chronically with sildenafil compared to untreated rats. This could imply that either muscarinic receptors or the transduction mechanisms leading to the activation of endothelial nitric oxide sintase are upregulated by a chronic sildenafil treatment. Moreover, functional in vivo evaluations showed that chronic administration of sildenafil significantly enhanced frequency-dependent erectile response and was associated with a greater response to an acute injection of sildenafil in treated rats compared to controls. Kovanecz et al demonstrated that a long-term single daily dose of tadalafil in the rat prevented corporal veno-occlusive dysfunction and the underlying corporal fibrosis caused by cavernous nerve damage [51]. The authors suggest that PDE5-Is may prevent ED through a cGMP-related mechanism that appears to be independent of inducible nitric oxide synthase induction. Those

findings are corroborated by Vignozzi et al, who demonstrated in vitro bilateral cavernous neurotomy-induced penile hypoxia by showing a dramatically increased hypoxyprobe labeling, a generally accepted probe of hypo-oxygenation after a 3-mo interval from surgical neurotomy. On histologic analysis, they found that chronic tadalafil treatment almost completely restored penile oxygenation and smooth-muscle/fibrous tissue ratio [52]. Similar results were obtained by the same group using sildenafil and vardenafil [53,54]. Very recently, Lysiak et al reported a protective role of chronic tadalafil administration on mice subjected to cavernous nerve resection or sham surgery. Their results demonstrated that the treatment with tadalafil decreased the number of apoptotic cells and increased the phosphorylation of the two survival associated kinases Akt and extracellular signal-regulated kinase 1/2 [55]. The authors conclude that their observations provide a rationale for the early use of PDE5-Is following RP or extensive pelvic surgery (during which there may be injury to the cavernous nerves) to aid in the return of erectile function.

Although basic scientific evidence may provide solid bases for a protective role of PDE5-I on cavernous tissue, the rationale for the use of these drugs as prophylaxis is not completely understood in human beings. However, recent studies have elucidated some mechanisms as being potentially involved. In an elegant study performed by Schwartz et al, a total of 40 potent volunteers with PCa underwent radical retropubic prostatectomy (RRP) and were divided into two treatment groups: group 1 received sildenafil 50 mg every other night for 6 mo beginning the day of catheter removal, and group 2 received sildenafil 100 mg every other night for 6 mo beginning the day of catheter removal. Percutaneous biopsy was performed using general anesthesia prior to incision for RRP and 6 mo later [56]. The authors reported a statistically significant increase in mean smooth muscle content 6 mo after RRP (42.82% vs 56.85%, $p < 0.05$) in group 2. The authors concluded that early use of a high dosage of sildenafil after RP seems to be associated with preservation of smooth-muscle content within human corpora cavernosa.

3.4. *Phosphodiesterase type 5 inhibitors for the treatment of post–radical prostatectomy erectile dysfunction*

PDE5-Is have acquired an established role in the treatment of post-RP ED. Because the mechanism of action of this class of drugs implies the presence of nitric oxide within the corporeal smooth-muscle cells, only patients undergoing a NS procedure should be expected to respond to them. To date, sildenafil, tadalafil, and vardenafil are approved for clinical use in the European Union and have also been utilized to treat post-RP ED.

Since their introduction in 1998, several studies have shown that PDE5-Is are significantly efficacious in ED patients after BNSRP, and several success predictors have been clearly outlined [19,23,57]. Historically, these predictors include patient age and rigorous preservation of the NVBs. Sildenafil is the drug which has been studied most extensively in this patient subgroup since its introduction in 1998. In general terms, sildenafil has been acknowledged to obtain the best results in young patients (<60 yr), in patients treated with a BNSRP, and in patients who show some degree of spontaneous postoperative erectile function. Typically, the response to sildenafil has been shown to improve as time passes after the procedure: best results are seen from 12 mo to 24 mo postoperatively. In different trials, the response rate to sildenafil treatment for ED after RP ranged from 35% to 75% among those who underwent NS surgery and from 0% to 15% among those who underwent non-NS surgery [57–59]. Furthermore, the effectiveness of both tadalafil and vardenafil as an on-demand treatment has also been evaluated these challenging patients. Tadalafil was also evaluated in a large multicenter trial conducted in Europe and the USA involving patients with ED following a BNSRP. Seventy-one percent of patients treated with tadalafil 20 mg on-demand reported an improvement of their erectile function, compared to 24% of patients who improved when treated with placebo ($p < 0.001$). The erectile function domain score of the International Index of Erectile Function (IIEF) was significantly higher after treatment with tadalafil 20 mg compared to placebo (21.0 vs 15.2; $p < 0.001$), and this difference was clinically significant. Patients receiving tadalafil 20 mg reported a 52% rate of successful intercourse attempts, which was significantly higher than the 26% rate obtained with a placebo ($p < 0.001$) [60]. Similarly, vardenafil has been tested in patients with ED following a UNSRP or BNSRP in a multicenter, prospective, placebo-controlled, randomized study in the United States and Canada. This was a 12-wk, parallel-arm study comparing placebo to vardenafil 10 mg and vardenafil 20 mg. Seventy-one percent of patients treated with a BNSRP reported an improvement of erectile function following the administration of vardenafil 20 mg and 60% reported an improvement of erectile function following the administration of vardenafil 10 mg. A positive answer to sexual encounter profile

question 2 (SEP-2; Were you able to insert your penis into your partner's vagina?) was seen in 47% and 48% of patients using vardenafil 10 mg and vardenafil 20 mg, respectively. A positive answer to the more challenging SEP-3 (Did your erection last long enough to have successful intercourse?) was seen in 37% and 34% of patients using vardenafil 10 and vardenafil 20 mg, respectively [61]. Recently an extended analysis focusing on the other domains of the IIEF of the same patients undergoing NSRP has underlined vardenafil's benefit over placebo regarding intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience ($p < 0.0009$ for each of the variable studied both at vardenafil 10 mg and vardenafil 20 mg) [62].

The adverse event profile of the three PDE5-Is has been very similar, and the discontinuation from treatment with one of the PDE5-Is is usually caused by lack of efficacy, while tolerability overall is more than satisfactory.

3.5. *Pharmacologic prevention of post–radical prostatectomy erectile dysfunction*

The increased understanding of pathophysiology of post-RP ED including the concept of tissutal damage induced by poor corporeal oxygenation paved the way to the application of pharmacologic regimens aimed at improving early postoperative corporeal blood flow. Montorsi et al [63] pioneered the concept of rehabilitation therapy for ED after RP. By using intracorporeal injections of alprostadil early after BNSRP, they demonstrated that the rate of recovery of spontaneous erections was significantly higher than observation alone. Similarly, Brock et al [64] showed that the continuous use of intracavernous alprostadil injection therapy was able to significantly improve penile hemodynamics and, in turn, the return of spontaneous erections (either partial or total) in patients with arteriogenic ED. These data have also been confirmed by Mulhall et al [65], who showed that the prophylactic use of intracorporeal injections of alprostadil in patients not responding to oral compounds resulted in higher rates of spontaneous functional erections and erectogenic drug response 18 mo after NSRP. In this context, prophylactic application of vacuum constriction device has also been proposed as an early penile rehabilitation approach aimed to promote an adequate cavernosal oxygenation and therefore to prevent penile fibrosis after surgery [66].

Despite great interest, only few clinical trials assessed the role of chronic (namely, continuous/prophylactic) PDE5-Is in men treated with RP. The basic concept would be to administer a PDE5-I at bedtime in order to facilitate the occurrence of nocturnal erections which are believed to have a natural protective role on the baseline function of the corpora cavernosa. Montorsi et al showed that when sildenafil 100 mg is administered nightly in patients with ED of various etiologies, the overall quality of nocturnal erections as recorded with the RigiScan device is significantly improved compared to those obtained after the administration of placebo [67]. Bannowsky et al evaluated the effect of low-dose sildenafil for rehabilitating erectile function after NSRP. Forty-three sexually active patients were randomized to receive either placebo or sildenafil 25 mg/day nightly. In the group taking sildenafil, 47% of patients achieved and maintained a penile erection sufficient for vaginal intercourse at 1 yr after NSRP, compared with 28% of patients in the control group with placebo. Clinically, those men who report some degree of spontaneous penile tumescence after surgery were the most likely to respond to PDE5-I [68]. Padma-Nathan et al [69] investigated the prospective administration of sildenafil 50 mg and sildenafil 100 mg versus placebo nightly in patients undergoing BNSRP who were potent preoperatively. Four weeks after surgery, patients were randomized to sildenafil or placebo for 36 wk. Interestingly, 27% of the patients receiving sildenafil responded, that is, demonstrated return of spontaneous normal erectile function, compared to 4% in the placebo group ($p = 0.0156$). Postoperative nocturnal penile tumescence (NPT) assessments were supportive. In 2005, Gallo et al [70] evaluated the role of vardenafil in the recovery of erectile function following pelvic urologic surgeries (RRP and cystectomy). After 6 mo of daily therapy, vardenafil therapy increased the mean IIEF-5 score to 12.9 points in the BNSRP group, to 8.0 points in the UNSRP group, and to 11.3 points in the BNS radical cystectomy group.

Surprisingly, the potential benefit induced by a continuously administered PDE5-I has rarely been compared to an on-demand PDE5-I administration schedule in methodologically rigorous studies. However, there are recognizable difficulties in carrying out such large placebo-controlled studies. The only report investigating the role of on-demand versus daily administration of PDE5-I after BNSRP has been published recently [71]. In this randomized, double-blind, double-dummy, multicentre, parallel-group study, 628 men were randomized to receive vardenafil nightly, vardenafil on-demand, or placebo for 9 mo. Surprisingly, in contrast to the prophylactic use of PDE5-Is for penile rehabilitation and treatment of ED in men following NSRP surgery,

this study suggested a paradigm shift toward on-demand dosing with PDE5-Is for the treatment of ED in patients who have undergone BNSRP.

4. Conclusions

Currently, the management of postprostatectomy ED relies on several available treatments that may help patients obtain erections sufficient for satisfactory sexual intercourses. Use of on-demand oral treatments in post-RP patients has been shown to be effective and safe, with better results seen in select young patients treated with a BNSRP. Pharmacologic prophylaxis, either with oral or intracavernosal drugs, may have a significantly expanded role in the future strategies aimed at preserving postoperative erectile function. Intracavernosal injections and transurethral alprostadil may represent a valid alternative to PDE5-I. Large, multicentric, placebo-controlled trials are needed in order to identify the best regimen able to provide the best strategy for the recovery of erectile function after RP.

Conflicts of interest

Francesco Montorsi is a paid consultant for American Medical System, Bayer-Schering, Mipharm, Pfizer, and Pierre Fabre Medicament.

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