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Tadalafil therapy for erectile dysfunction following prostatectomy

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***Abstract*:** Erectile dysfunction is a major complication affecting the quality of life of patients and partners after radical prostatectomy. Evolving evidence suggests that early penile rehabilitation may provide better erectile function after surgery. Phosphodiesterase type 5 (PDE-5) inhibitors are routinely considered a first-line treatment option in most algorithms for penile rehabilitation owing to their efficacy, ease of use, wide availability and minimal morbidity. Tadalafil is a long-acting, potent PDE-5 inhibitor for erectile dysfunction, with demonstrated effect in animal studies at preserving penile smooth muscle content and prevention of fibrosis of cavernosal tissue. This article evaluates the existing literature on tadalafil and critically analyzes its impact on erectile function following radical prostatectomy.

Keywords: erectile dysfunction, penile rehabilitation, radical prostatectomy, tadalafil

Introduction

Radical prostatectomy (RP) as a curative surgical approach for management of low–intermediate risk localized prostate cancer (PCa) among men with a life expectancy longer than 10 years in patients [Mottet *et al.* 2014] has seen dramatic growth over the past two decades. Adoption of aggressive prostate specific antigen screening programs, coupled with widespread media attention towards the issue of PCa detection worldwide, has led to 90% of patients with PCa now being diagnosed in the local or regional stages, for which the 5-year survival rate is almost 100%. Nearly six out of ten patients with PCa who are younger than 65 are treated with RP [Siegel *et al.* 2012]. RP is associated with an impaired quality of life resulting from erectile dysfunction (ED) and incontinence among large numbers of these men.

Despite numerous recent technological and surgical innovations, such as robotic and anatomic nerve sparing surgery, the rate of ED is reported to be between 30% and 87% [Tal *et al.* 2009; Alemozaffar *et al.* 2011]. While the range of ED after RP is extremely wide, as a consequence of patient factors (age, comorbidities, preoperative EF), surgical factors (robotic, nerve sparing, intrafascial technique) and selection biases/reporting techniques, there is no controversy related to the significant impact ED has on men and their partners undergoing this intervention.

Indeed in the accumulating literature, a lack of well-designed, randomized, prospective high-volume studies which report the true prevalence of ED after RP [Mulhall *et al.* 2013] is well recognized. Among the studies that are available, they consistently demonstrate rates of ED after RP at significant levels, which has led to the development of diverse penile rehabilitation (PR) programs aimed at reducing the rates of ED after RP. Interestingly, the proportion of patients treated for PCa who subsequently get treated for complaints of ED was only 15% according to a recent report by Frederick and colleagues [Frederick *et al.* 2014].

The optimal treatment approach to minimize ED following RP remains controversial. Numerous studies demonstrate that a PR program is useful to improve erectile function, particularly after nerve sparing surgery [Mulhall *et al.* 2010]. Montorsi and colleagues published the first clinical study in support of PR, and showed that intracorporeal alprostadil injection improved recovery of erectile function following RP [Montorsi *et al.* 1997]. However, the ideal form or components of a PR program does not currently exist. According

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to a survey by the International Society for Sexual Medicine, 87% of urologists use some form of PR. Notably, 95% of participants used PDE-5 inhibitors for ED as the foundation of their program [Teloken *et al.* 2009]. The current medical literature suggests that phosphodiesterase type 5 (PDE-5) inhibitors should be the first-line treatment modality for ED after RP. PDE-5 inhibitors are effective, easy to use, safe with minimal side effects. Patients who do not respond to PDE-5 inhibitors should be treated with intracavernosal injection or with a vacuum erection device as second-line treatment. Penile prostheses remain a viable option for the patients who do not respond or for those patients and partners who want a permanent solution [Hatzichristou *et al.* 2014]. In this article, we discuss the role of tadalafil in ED after RP based on the current literature (Table 1).

Materials and methods

A literature search for all original and review articles published in the English language was performed using a PubMed database over the past three decades ending November 2014. Search keywords were tadalafil, PDE-5 inhibitors, sexual dysfunction, radical prostatectomy and penile rehabilitation. The selected articles were reviewed by the authors and their contributions included in writing the manuscript.

Pathophysiology of ED after RP

Erectile function physiology and pathophysiology remains an area of active research and the true etiology of post-RP ED remains to be fully elucidated. Many theories have been suggested concerning the etiology of ED after RP. Given that vascular function, neural signaling and end-organ structures all need to be intact for function to be normal, any dysfunction of these components can be causative. Direct injury or stretching of cavernosal nerve fibers is a commonly cited cause of ED in this population. Cavernous nerves are essential structures in providing normal erectile function. Several basic science documents clearly demonstrate that the number of proapoptotic and profibrotic factors are increased in cavernosal tissue after nerve resection [Mulhall *et al.* 2013]. Cavernous nerve damage during surgery decreased the amount of Neuronal nitric oxide (nNOS) and nitric oxide (NO), thereby reducing penile rigidity and decreasing the number of nocturnal erection episodes [Carrier *et al.* 1995]. Arterial blood flow during nocturnal erections is believed to be essential to maintain normal erections and cavernosal smooth muscle function. An animal study showed that cavernosal nerve injury causes a flaccid penis, as well as cavernosal hypoxia which leads to decreased prostaglandin E-1 while increasing the local concentration of transforming growth factor β and endothelin 1 [Champion *et al.* 2003]. These mediators regulate the amount of smooth muscle and collagen in cavernosal tissue. As a result of tissue hypoxia, the smooth muscle content to collagen ratio is shifted in favor of collagen. This occurs as a result of increased amounts of collagen with simultaneous smooth muscle apoptosis and corporal fibrosis, leading to a dysfunctional penis and failure of veno occlusion [Klein *et al.* 1997]. As a consequence of the loss of smooth muscle, failure of the penile expansion with erection leads to veno-occlusive dysfunction of the perforating subtunical venules, ultimately leading to ED.

Effect of tadalafil on cavernosal tissue after cavernosal nerve injury

Tadalafil, a potent PDE-5 inhibitor, is effective from 30 min after administration and efficacy can be maintained for up to 36 h. The $T_{1/2}$ of tadalafil is 17.5 h, longer than several other PDE-5 inhibitors, and it is not affected by food [Porst *et al.* 2003]. Several animal studies investigated the effect of PDE-5 inhibitors on cavernosal tissue after cavernosal nerve injuries. Kovanecz and colleagues investigated the effect of chronic tadalafil on cavernosal tissue in rats undergoing a unilateral or bilateral cavernosal nerve resection. The authors showed that using 45 days of daily tadalafil restored intracorporeal pressure, preserved smooth muscle content, increased smooth muscle to collagen ratio, and reduced the penile apoptotic index [Kovanecz *et al.* 2008]. Lysiak and colleagues examined penile tissue at 2, 4 and 6 weeks after bilateral cavernosal nerve resection in an animal study. They found that using 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 *via* an apoptotic-related mechanism. In addition, they showed the amount of apoptotic cells further increased 4 and 6 weeks after nerve resection [Lysiak *et al.* 2008].

Role of tadalafil in PR

The primary goal of PR is to restore early oxygenation to the penile smooth muscle [Köhler

Table 1. Treatment options for erectile dysfunction after radical prostatectomy.

Rehabilitation program elements
Education related to causes of ED post RP and rationale for rehabilitation program
Review of operative report and nerve sparing status
Assessment of recovery potential
Information related to penile muscle preservation as the basis of rehabilitation
Use of on-demand or daily dose PDE-5 inhibitors
The benefits of early intervention and achieving an erection
Rates of response is wide (15–80%) depending on patient and surgical factors
Disadvantages of rehabilitation (cost, time and medication related side effects)
Second-line treatment
Intracavernosal injections, vacuum erection devices typically started at 3 months if useable erections are not restored with first-line therapy or a contraindication exists to PDE-5 inhibitors
ICI has high dropout rates, owing to invasive nature, lack of spontaneity
VED may preserve penile length
Third-line treatment
Penile prosthesis implantation
High patient and partner satisfaction
Significant cost and level of invasiveness

ED, erectile dysfunction; PDE-5, phosphodiesterase type 5; RP, radical prostatectomy; VED, Vacuum Erection Device; ICI, Intracavernosal injection.

Table 2. Characteristics of the selected studies in review.

Study	Design of study and size	Inclusion criteria	Treatment	Control	Treatment period	Outcome
Montorsi *et al*. [2004]	Multicenter, randomized, double blind, placebo controlled trial, BNSRP, $N = 303$	Patients with ED 12–48 months after Nerve sparing radical retropubic prostatectomy (NSRRP)	Tadalafil 20 mg on-demand	Placebo	3 months	IIEF score, SEP-GAQ success rates and EDITS score
Montorsi *et al*. [2014]	Multicenter, randomized, double blind, three arm, parallel, $N = 423$	Preop, IIEF $>$ 22, age $<$ 68 years, PCa (cT1c–T2c), no history of ED	Tadalafil 20 mg-on demand	Placebo	At the end of double-blind treatment (9 months), washout:(10.5 months), open label:(13.5 months)	IIEF score, SEP success rates, MCIDs and penile size
			Tadalafil 5 mg daily			
Seo *et al*. [2014]	Case-control retrospective study, UNSRP or BNSRP, $N = 92$	No history of ED, PCa $\leqslant T_2$	Tadalafil 5 mg daily	No treatment	12 months	IIEF score, SEP success rate

BNSRP, bilateral nerve sparing radical prostatectomy; ED, erectile dysfunction; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; GAQ, Global Assessment Question; IIEF, International Index of Erectile Function; MCID, minimal clinically important difference; PCa, prostate cancer; SEP, sexual encounter profile; UNSRP, unilateral nerve sparing radical prostatectomy.

et al. 2007]. Given the hypothesis that hypoxia induces a cascade of events culminating in cavernosal muscle loss and increased fibrosis, this is a logical target. Penile oxygenation is increased

with PDE-5 inhibitors *via* activation of the NO/cyclic guanosine monophosphate (cGMP) pathway and also *via* antifibrotic and antiapoptotic mechanisms [Fode *et al.* 2013]. There are three randomized, placebo-controlled studies investigating the effect of tadalafil on erectile function after RP. In the first of these, a multicenter study published by Montorsi and colleagues enrolled 303 patients with preoperative normal erectile function who had undergone bilateral nerve sparing radical prostatectomy. All patients were randomized (2:1) to tadalafil 20 mg or placebo. This study showed that tadalafil on demand produced significant improvement in both primary and secondary endpoints after 12 weeks of treatment compared with placebo. Mean improvement in International Index of Erectile Function (IIEF-5) scores was reported, 5.3 ± 0.5 and 1.1 ± 0.6 in both the tadalafil on demand and placebo groups respectively ($p < 0.001$). In addition, in the tadalafil group, no patients reported serious adverse events and the rate of severe adverse events in tadalafil and placebo groups was reported at 5% and 2.9% respectively ($p = 0.55$) [Montorsi *et al.* 2004]. Recently, a well designed multicenter three-arm, parallel-group study was published by the same author. This study included 423 patients randomized to a double-blind treatment period, followed by a washout period and then an open-label extension phase with tadalafil once daily. Selected patients were randomly treated with daily tadalafil ($n = 139$), on demand tadalafil ($n = 143$) and placebo ($n = 141$) after RP. The results of the study showed that the rate of patients reaching IIEF-EF less than 22 at 9 months after treatment was 25.2%, 19.7% and 14. 2% in the tadalafil once daily, tadalafil 20 mg and placebo groups, respectively. IIEF target (IIEF > 22) was significantly higher in the tadalafil once daily group than in the placebo group, although significance was not reached among the on-demand and placebo groups. After 6 weeks of drug-free washout (at 10.5 months) the primary endpoint showed no statistical difference between groups. At the end of study after the 3-month open-label phase with tadalafil 5 mg, the rate of reaching target IIEF-EF increased in all groups. Importantly, there was no statistically significant difference among all groups. However the secondary endpoint defining preservation of penile length was demonstrated to be statistically superior at the end of study (at 13.5 months) in the tadalafil once daily group compared with the placebo group but not in the tadalafil on-demand group [Montorsi *et al.* 2014].

A recent study investigated the efficacy of daily 5 mg of tadalafil on erectile function compared with placebo after robotic prostatectomy. A total of 92 patients were divided into the tadalafil ($n = 47$) and placebo ($n = 45$) groups. At 6 months following surgery, mean IIEF-5 score was 10.3 ± 3.4 and 7.0 ± 4.0 for the tadalafil and placebo arms respectively. Furthermore, in all five domain scores the daily tadalafil group demonstrated a significant increase compared with the placebo group, in which no significant increase in any of the domain scores at 1 year was reported [Seo *et al.* 2014] (Table 2).

At present there are no data which clearly suggest the optimal dose, duration and timing of tadalafil use for men hoping for PR. Animal studies and some early clinical experience have demonstrated that daily tadalafil may better preserve endothelial function of cavernosal smooth muscle, and erectile function. It would seem intuitive to start the therapy as soon as possible, perhaps even prior to the injury (time of surgery), although there are no data to support this approach at present.

The factors determining the success of tadalafil in PR are not different than the other PDE-5 inhibitors. Nerve sparing surgery, age and preoperative erectile status are independent parameters predicting postoperative ED [Ficarra *et al.* 2012]. The effect of the surgical approach on erectile function, such as robotic, laparoscopic and open surgery, has not been thoroughly demonstrated to be clearly related to outcomes. Recently several articles have been published in favor of the robotic approach compared with the others. The rate of ED after robotic prostatectomy has been reported to be as low as 10–15% compared with the open or a laparoscopic approach [Coelho *et al.* 2010; Ploussard *et al.* 2014]. However, there are no evidence-based studies that clearly demonstrate robotic surgery as being truly superior to laparoscopic or open surgery. Randomized, placebo-controlled, multicenter studies of appropriate length are needed for accurate results [Ficarra *et al.* 2009].

Surgical skill and technique is another parameter used to predict the effect of erectile function after prostatectomy. Potdevin and colleagues showed that the recovery rate of EF at 3, 6 and 9 months after surgery is higher using the intrafascial technique compared with an interfascial technique [Potdevin *et al.* 2009]. Additionally, Xylinas and colleagues reported robotic intrafascial surgery

provided an early return to EF [Xylinas *et al.* 2010]. Recently, a meta-analysis of the use of PDE-5 inhibitors for ED after RP was published by Wang and colleagues. The authors found that longer duration of treatment positively affected erectile function after RP [Wang *et al.* 2014]. Additionally some authors suggested PR should be maintained up to 4 years after nerve-sparing surgery [Salonia *et al.* 2012].

Conclusion

The likelihood of ED after RP remains high despite various treatment modalities and evolving surgical techniques. PDE-5 inhibitors are considered by most investigators and clinicians as the first-line treatment approach for ED after RP, and remain the common element in most rehabilitation programs. Tadalafil is a potent PDE-5 inhibitor, which can be used daily or on demand for ED after RP. Early intervention using a rehabilitation strategy with tadalafil or other PDE-5 inhibitors may prevent loss of penile length, preserve cavernosal smooth muscle and increase erectile function. The efficacy of tadalafil and the likelihood of maintaining erectile function post RP appears to depend on the patient's age, preoperative EF score, nerve-sparing surgery and the skill of the surgeon.

The availability of well constructed multicenter, prospective, double-blind, randomized clinical trials of adequate size and duration remains a high priority, and essential to dovetail with the evolving basic science data before a definitive statement of the value of rehabilitation will be possible. Until these studies are completed, the clinician will need to evaluate the existing data and provide men undergoing surgical curative therapy for PCa with the benefit of their knowledge and understanding in an attempt to reduce the rates of post-treatment ED.

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Conflict of interest statement

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. Dr Brock is on the speakers' bureau and advisory board for Lilly and owns stock in, and is on the speakers' bureau and advisory board for Pfizer.

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