Penile rehabilitation after nerve-sparing radical prostatectomy. A critical review of the literature

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Summary

Objective. To describe the pathophysiology of nerve injury and to evaluate critically the clinical evidence supporting the use of penile rehabilitation following nerve-sparing radical prostatectomy (RP).

Material and methods. A non-systematic literature search of MEDLINE was done. A "free text" search through the fields "Title and abstract" of the records was done, using the following key words: "penile rehabilitation" and "radical prostatectomy". The search was limited to the papers published in English language after 1997.

Results. The cavernous nerve neuropraxia can prevent erections during the initial 12-18 months after RP, initiating a cascade of events which can led to fibrotic remodelling of corpora cavernosa. The aim of penile rehabilitation is to prevent this cavernous tissue damage by providing an adequate oxygenation to the corpora cavernosa.

The advantages of penile injection were first shown in a small randomized controlled trial (RCT) evaluating the use of intracavernous injection of alprostadil. The study' results, however, have never been reproduced. More recently, another RCT suggested sildenafil (50 mg or 100 mg at bedtime) increased the recovery of spontaneous erections, compared to placebo. However, the study suffers of several methodological drawbacks. A recently published double-blind, multicentre RCT enrolling 628 men showed that nightly dosing of vardenafil did not allow significantly higher potency rates after nerve-sparing RP, compared to the on-demand dosing.

Conclusions. The exact etiology of the fibrotic changes in the corpora cavernosa following nerve-sparing RP remains unknown. No high level evidence support any program of penile rehabilitation following nerve-sparing RP, while recent data showed that on-demand dosing was effective in improving both erectile function and sexual intercourse completion rates after RP.

Keywords
Penile rehabilitation • Radical prostatectomy • Sildenafil • Vardenafil • Tadalafil • Alprostadil • Erectile dysfunction

Introduction

Radical Prostatectomy (RP) is a common treatment for patients with clinically localized prostate cancer and a life expectancy longer than 10 years [1]. Erectile dysfunction is one of the most important complication after RP. The improvements in the knowledge of the anatomy

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of periprostatic fascias and cavernous nerves led to significant updates of the nerve-sparing technique improving significantly the potency recovery rates following RP. Even after a meticulous dissection to preserve both neurovascular bundles, however, erectile function may take up to 12-18 months to return, as consequence of post-operative neuropraxia.

Data coming from referral centres showed 12 or 18 months potency rates ranging from 60 to 80% after nerve-sparing retropubic RP [2 3]; from 45 to 76% after pure laparoscopic RP [4 5] and from 70 to 80% after robot-assisted laparoscopic RP [6-8]. Significant poorer results were reported in community hospitals with lower operative volume, regardless of the surgical approach [9].

High survival rates in young and sexually active men undergoing RP mean that many patients lives for a long period of time with erectile dysfunction with a significant negative impact on quality of life, self-esteem, and self-image. These findings contributed to the development of an increasing interest in the pathophysiology of post-operative erectile dysfunction as well as in its potential prophylaxis and treatment [10].

Historically, after nerve sparing RP patients have been encouraged during the neuropraxia period to continue waiting for the return of erectile function without any active intervention. With the aim of speed up the recovery of spontaneous erections after RP, since 1997 some Authors proposed the use of specific protocols of penile rehabilitation to prevent the cavernous tissue damage that occurs during the period of neural recovery, providing adequate oxygenation to the cavernous tissues.

Although a lot of experimental and clinical studies supported the use of penile rehabilitation after bilateral or unilateral nerve-sparing RP, the rationale and mechanism for their use in penile rehabilitation programs have not been fully elucidated [11]. Moreover, a recent randomised, double-blind, double-dummy, multicentre, parallel group study conducted at 87 centres across Europe, Canada, South Africa, and the United States showed that in men with ED following bilateral NSRP, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on demand dosing with phosphodiesterase 5 inhibitors (PDE5-I) in this patient group [12].

The aim of this non systematic review of the Literature is to describe the pathophysiology of nerve injury and to evaluate critically the clinical evidence supporting the use of penile rehabilitation following nerve-sparing RP.

Material and methods

The literature search was performed using MEDLINE, including only “free text” protocol and using the following terms “penile rehabilitation” AND “radical prostatectomy” across the fields “title and abstract” of the records. We selected only papers published in English after 1997, the year of the publication of the first randomized comparative study concerning penile rehabilitation [13]. The information obtained from the retrieved papers were inserted in the following sections of the article: pathophysiology of cavernous nerve injury; clinical evidence for early use of intracavernosal penile injections; clinical evidence for early use of oral therapy with 5-phosphodiesterase inhibitors; clinical evidence for on demand therapy after nerve-sparing RP.

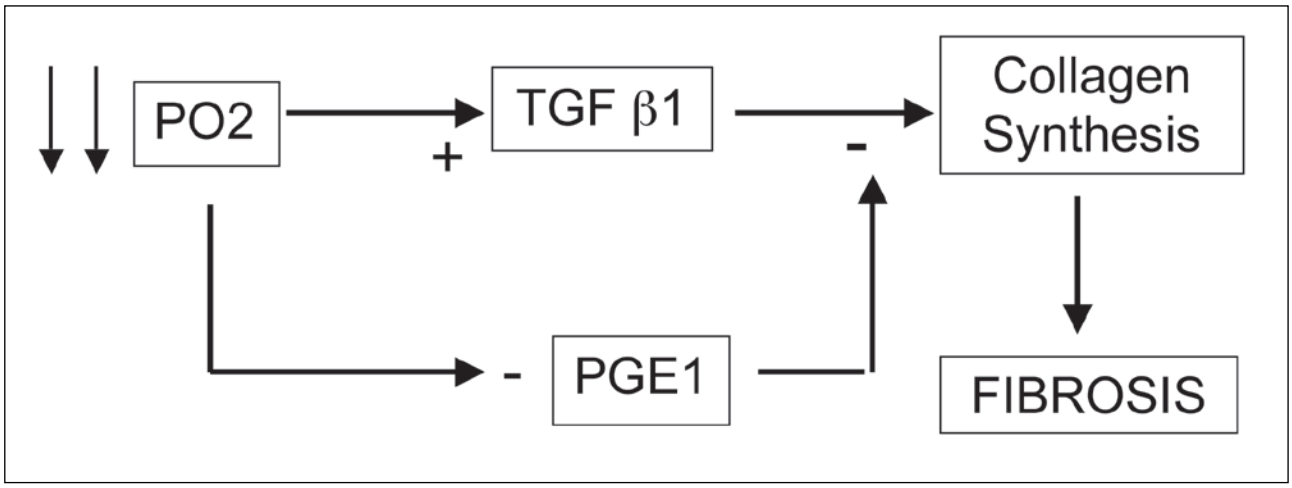
Pathophysiology of cavernous nerve injury

Several investigators demonstrated that normal smooth muscle content and function were essential in initiation and maintenance of erections. The integrity and function of any smooth muscle cell was usually related to the tissue oxygenation and fibrosis has been suggested to be the most probable cause of erectile dysfunction in patients with arterial insufficiency. However, the exact mechanism of collagen accumulation in patients who have penile hypoxia has not been established [14].

In vitro studies showed that penile hypoxia induced transforming growth factor-beta1 (TGF-β1), which is implicated in the collagen deposition. At the same time, prostaglandin E1 (PGE1) is able to suppress the TGF-β1-induced collagen synthesis [15]. However, the production of PGE1 in strips of rabbit cavernosum tissue was also oxygen dependent [16]. These studies suggest that the collagen content in the corpus cavernosum was regulated by oxygen tension through the increased or decreased expression of TGF-β1 and PGE1 (Fig. 1). Although elegant in the design, however, the “in vitro” studies of hypoxic environments should be correlated to the situation of a flaccid penis with caution. In fact, to date, no studies have proven any “in vivo” derangement of endothelial or smooth muscle cell metabolism secondary to a prolonged flaccid state. Therefore, the role of hypoxia in penile fibrosis after nerve-sparing RP remains a controversial issue.

Regardless of the previous critical issues, in patients who underwent a nerve-sparing RP a key role in the cause of erectile dysfunction is represented by initial neuropraxia. The etiology of cavernous nerve neuropraxia include mechanical stretch injury during retraction, ischemia from accessory vessel disruption

Figure 1. Penile hypoxia induces transforming growth factor-beta1 which is implicated in the collagen synthesis and decreases the production of PGE1 that is able to suppress the TGFβ1-induced collagen synthesis.



during the dissection, thermal injury from electrocautery use, and inflammation from surgical trauma. Neuropraxia can prevent erections during the initial 12 to 18-month period after nerve-sparing RP, initiating a cascade of deleterious events characterized by the reduction of blood flow to corporeal bodies, ischemic and hypoxic injuries, fibrotic remodelling, and apoptosis [17 18]. Using penile biopsy in human models before, 2 and 12 months after RP, Iacono et al. showed a significant postoperative decrease in the elastic fibers and smooth muscle content, compared to the preoperative biopsy [19]. Cavernosal apoptosis and collagen deposition can lead to veno-occlusive disease. Specifically, the incidence of venous leak increases with the post-operative time interval. Mulhall et al. reported that the incidence of veno-occlusive dysfunction was 14% 4 months after nerve-sparing RP and raised to 35% at 9 to 12-month follow-up evaluations [20] (Fig. 2). Therefore, in any patient undergoing RP, the insult can be primarily neurogenic (neuropraxia), vasculogenic (veno-occlusive mechanism) or mixed and it should be considered a dynamic process from surgery to recovery.

Penile Rehabilitation following nerve-sparing radical prostatectomy

The goal of penile rehabilitation is to prevent the cavernous tissue damage that occurs during the period of neural recovery providing an adequate oxygenation to the corpora cavernosa. Moreover, restoring nocturnal erections must be considered an alternative way to increase oxygenation of the cavernosal bodies using oral PDE5-I.

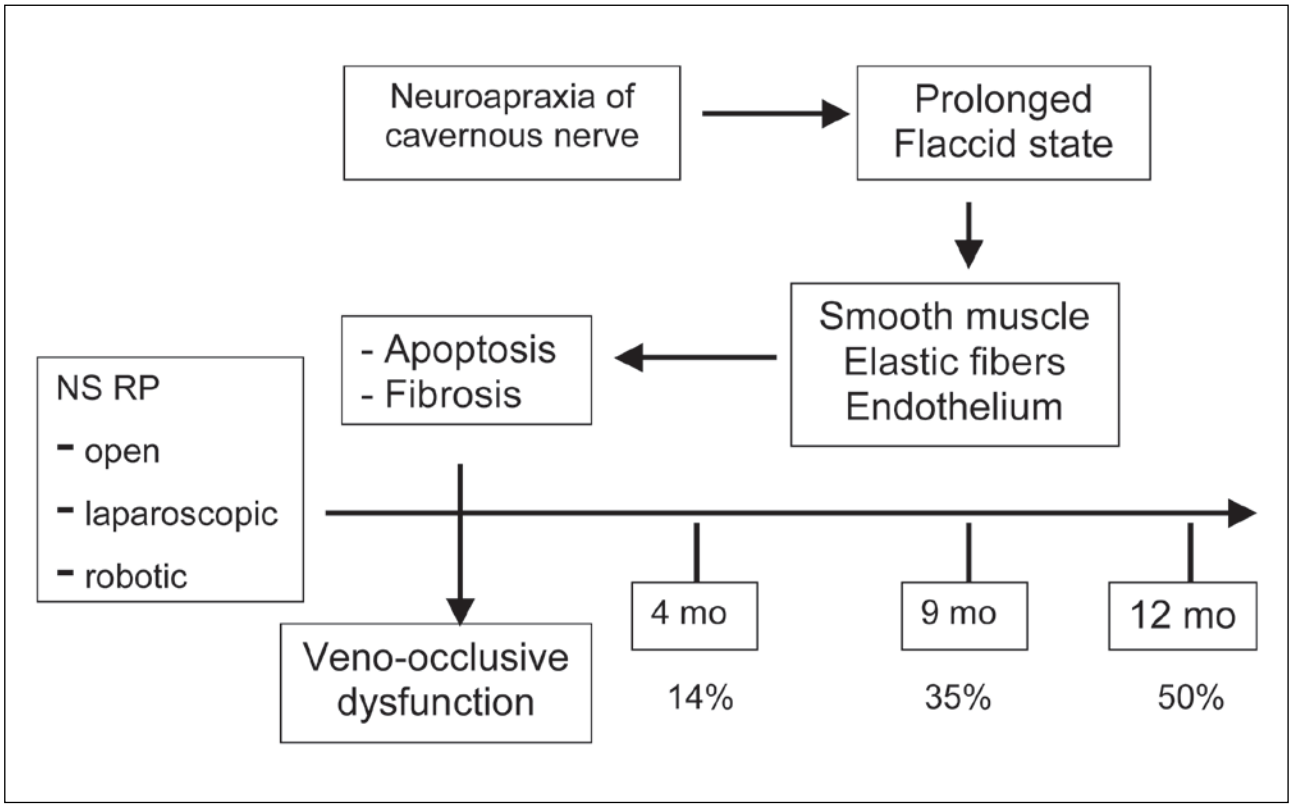
The potential options for early treatment of erectile dysfunction following nerve-sparing radical prostatectomy encompass pharmacologic and non-pharmacologic agents. The first group includes the oral PDE5-I (sildenafil, vardenafil and tadalafil), intracavernous agents (alprostadil, papaverine and phentolamine) and intraurethral agents (alprostadil). The main non-pharmacologic tools used for early penile rehabilitation are vacuum constriction devices (VCDs).

Clinical evidence for early use of intracavernosal penile injections

Intracavernosal injection of Alprostadil allows the activation of an alternative pathway to induce the relaxation of smooth muscle fibres in the cavernous tissue. Specifically, PGE1 actives the adenylate cyclase transforming ATP in AMPc, which, similar to GMPc, reduces cytoplasmatic concentration of Ca^{++} allowing relaxation of the smooth muscle fibres and, consequently, erections.

Montorsi et al. first demonstrated the advantages of penile injection of Alprostadil as an early intervention strategy in a randomized, controlled study, including 30 patients undergoing bilateral nerve-sparing RP [13]. One month after surgery, 15 patients were randomized to intracavernous alprostadil 2-3 times/week for 12 weeks, while 15 received no treatment. After a minimum follow-up of 6-month, 8 of 12 patients (67%) had spontaneous erections sufficient for intercourse, compared to 3 of 15 (20%) of those who were not injected. Moreover, penile Doppler ultrasonography revealed veno-occlusive dysfunction in only 2 of 12 patients (17%) included in the treatment group, compared to 8 of 15 (53%) in the control group. This study must be considered as one of the most original and impor-

Figure 2. Pathophysiology of cavernous nerve injury following nerve-sparing radical prostatectomy.



tant contribution in the urologic and andrological literature. However, it suffers of some important limitations. Firstly, the study was neither blinded nor placebo controlled. Secondly, the number of patients enrolled in the trial was limited. Thirdly, only 12 of the 15 patients randomized to treatment were evaluated at the 24-week follow-up. The analysis "per protocol" limited to those 12 patients showed a statistically significant advantage in favour of the treatment group but the "intention-to-treat analysis" failed to show any statistically significant difference (chi-square 3.589 – p = 0.06). However, in our opinion, the most important issue is that the data of this study were never confirmed. In the everyday clinical life, however, the use of PGE1 for penile rehabilitation following nerve-sparing RP did not become a mainstream option due to the limited patient compliance. Penile pain due to intracavenous injection and the throbbing penile discomfort secondary to long-lasting prostaglandin effects are two important limitations in the routine acceptance of this early treatment. Moreover, the logistic administration of an early injection program in most of the normal office practice is sometimes prohibitive because multiple visits are required to find the correct dose and to make sure that injections are done properly. However, in our opinion, the most relevant limitation to the diffusion of intracavernous therapy was the advent of PDE5-I.

Clinical evidence for early use of oral therapy with 5-phosphodiesterase inhibitors

These drugs act within the smooth muscle cell by inhibiting the enzyme PDE5 which naturally degrades cGMP, which acts as the second messenger in the process of smooth muscle cell relaxation. Increased levels of cGMP lead to the activation of cGMP-specific protein kinases that activate further intracellular events, finally leading to reduction of intracellular calcium and relaxation of the smooth muscle cells.
It had long been believed that PDE5-I needed an intact neural pathway to be effective, which is a doubtful issue during the neuropraxia period after nerve-sparing RP. Some proponents for the use of this class of agents in penile rehabilitation protocols, however, argue that this drugs might act through a separate, neural-independent mechanism, affecting the endothelium cell function. Several studies in the last few years showed an overall improvement in endothelium cell function after use of PDE5-I. However, theses studies were performed in diabetic patients [21] or in patients with vascular (arteriogenic)

erectile dysfunction [22 23]. In our opinion, this global improvement in endothelial cell function might suggest a possible role for PDE5-I during the period of neuropraxia after nerve-sparing RP.

Another basic concept related to the mechanism of action of PDE5-I in the patients who underwent RP is the bedtime administration, 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. Bannowsky et al. using the NPT recorded a residual erectile function the first night after catheter removal in 25 of the 27 patients (93%) who underwent nerve-sparing RP. Conversely, in a small control group of 4 patients treated with non nerve-sparing technique, no nocturnal erections were reported early after catheter removal [24]. According to the Authors, patients with residual nocturnal erections should be enrolled in a penile rehabilitation program with PDE5-I, while, on the contrary, patients without residual erections should be treated early with alprostadil intracavernous injection. The absence of the randomization and the limited number of patients evaluated in the study are relevant limitations, while the number of patients with residual erectile seems really high. In our opinion, further studies are needed to confirm the rationale of this approach.

The most relevant clinical evidence in favour of the nightly use of PDE5-I in a rehabilitation protocol is represented by the randomized controlled trial published by Padma-Nathan et al. For many years we had only the possibility to evaluate the data of this randomized, double-blind, placebo-controlled, trial in the abstract format [25]. Recently, the Authors published also the final version of the study on a peer-review journal [26]. In this study, 4 weeks after nerve-sparing RP, patients entered a 36-week double-blind, treatment during with sildenafil 50mg or 100 mg (once daily at night time), or placebo. After the end of the double-blind treatment and a 8-week wash-out period, erectile function, nocturnal penile tumescence and, in a subgroup, rigidity were assessed. Although the authors randomized 125 patients in the three arms, only 82 men completed the 36-week double-blind treatment and only 76 patients the subsequent 8-week drug-free period. Specifically, 23 patients in the sildenafil 50 mg group, 28 in the sildenafil 100 mg group and 25 in the placebo arm. Limiting the analysis to these 76 cases, the study showed a statistically significant advantage in those patients receiving sildenafil in terms of spontaneous erections sufficient for intercourse, compared to those taking placebo. Specifically, 27% of the patients in treatment arm reported erections sufficient for intercourse, compared to 4% in the placebo group ($p = 0.02$) [26]. The trial, however, presents many important drawbacks. Firstly, it is not possible to know the real allocation of the 125 randomized patients in the three arms of the study, which make impossible any intention-to-treat analysis. Secondly, the conclusions of the study were limited only to 76 of the 125 randomized patients. Finally, the 48-week potency rate detected in the placebo arm of the study (4%) seems to be unusually low following nerve-sparing RP. Therefore, in our opinion, the results of this study cannot be extrapolated to the general population of nerve-sparing patients.

Clinical evidence for on demand therapy after nerve-sparing RP

The most critical issue to accept the opportunity to prescribe in our patients a penile rehabilitation protocol after nerve-sparing radical prostatectomy is represented by the positive results observed with “on demand” PDE5-I administration schedule.

In 2006, Montorsi et al. reported a prospective non-randomized study evaluating the potency recovery following bilateral nerve-sparing RP. Specifically, those patients were subdivided in four different groups: 1) those receiving no erectile therapy; 2) those having intracavernosal injection of PGE1 on demand; 3) those taking PDE5-I on demand; 4) those having a rehabilitative PDE5-I therapy. After 12-month follow-up, the authors showed no significant difference in the mean International Index Erectile Function scores between patients who received “on demand” or those treated with a “rehabilitative” protocol [27]. Obviously, the main limit of this study is the lack of randomization.

The efficacy of “on demand” therapy in this particular and difficult setting of patients has been recently confirmed by a randomised, double-blind, double-dummy, multicentre, parallel group study which enrolled a total of 628 men aged to 18-64 years. The study design consisted of a 9-month double-blind treatment period, a 2-month single-blind washout period, and an optional 2-month open-label period. The results showed that nightly dosing with vardenafil did not have any effect beyond that of on-demand use. Moreover, the data of this study indicated that the use of on-demand vardenafil is of greater benefit than nightly treatment in patients following nerve-sparing RP, and support the on-demand use of PDE5-I following nerve-sparing surgery over a daily dosing regimen [12].

Conclusions

In our opinion, the critical issue in preservation of erectile function in patient who underwent RP is the quality of nerve-sparing procedure. A better technique is fundamental to reduce the period of neuropraxia and enhance the probability to reach spontaneous erections. The exact etiology of the fibrotic changes in the corpora cavernosa following nerve-sparing RP remains unknown.

This critical analysis of the literature highlighted that no high level evidence support any program of penile rehabilitation following nerve-sparing RP. However, the use of drugs during the early post-operative period reduces the time of potency recovery and improves the long-term results in terms of spontaneous or PDE5-I assisted erections. Recent data showed that on-demand dosing is more effective in improving both erectile function and sexual intercourse completion rates after RP. These data prompt reconsideration of the current practice of prescribing PDE5-I rehabilitation protocol. At the same time, the prescription of a rehabilitative protocol or an early "on demand" therapy following nerve-sparing RP can be considered an excellent strategy to give our patients the feeling that we are doing something to improve their probability to recover erectile function. In our opinion, however, patients should be aware that the exact benefit of rehabilitative protocols will remain highly controversial until better data become available.

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