

·Review·

Rehabilitation of erectile function following radical prostatectomy

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Abstract

The concept of muscle rehabilitation after nerve injury is not a novel idea and is practiced in many branches of medicine, including urology. Bladder rehabilitation after spinal cord injury is universally practiced. The erectile dysfunction (ED) experienced after radical prostatectomy (RP) is increasingly recognized as being primarily neurogenic followed by secondary penile smooth muscle (SM) changes. There is unfortunately no standard approach to penile rehabilitation after RP because controlled prospective human studies are not available. This article reviews the epidemiology, experimental pathophysiological models, rationale for penile rehabilitation, and currently published rehabilitation strategies. (*Asian J Androl* 2008 Jan; 10: 61–74)

Keywords: erectile dysfunction; penile rehabilitation; radical prostatectomy

1 Introduction

Prostate cancer is the most common type of solid cancer affecting American males [1]. According to the American Cancer Society, there were approximately 232 000 newly diagnosed cases diagnosed in the United States in 2005 (American Cancer Society Surveillance Research, 2005). The incidence of prostate cancer appears to be increasing worldwide, and is the second leading cause of cancer death in the US, with estimates of over 30 000 deaths during 2005. Men are diagnosed at increasingly younger ages. On the positive side, the 10-year survival rate is estimated to be as high as 92%. This high survival rate means that men will be living for a longer period of time with side effects that develop as a result of treatment.

Curative treatment of localized prostate cancer includes radiation therapy and radical prostatectomy (RP), with roughly equal numbers seeking each therapy. RP is the most common treatment for localized prostate cancer, with over 60 000 men undergoing RP every year [2]. Sexual dysfunction is the most common long term complica-

tion from surgery. The sexual dysfunction, encompasses universal loss of ejaculation, erectile dysfunction (ED), decreased orgasmic pleasure and diminished libido. The reported incidence of ED after RP varies from study-to-study, depending upon the age of the patient, erectile function prior to surgery, pre-existing medical conditions, the nature of the operation (i.e., nerve-sparing, unilateral or bilateral), and the experience of the surgeon.

It is important to understand the prevalence of ED in the population before undergoing RP and cover realistic outcomes in this regard. There have been numerous reports on the prevalence of ED in the elderly population. However, the occurrence of ED in healthy men without prostate cancer participating in prostate cancer screening programs has been poorly studied. Knowing the prevalence of ED in this group is important because it can be used as a baseline to determine the incidence of ED caused by prostate cancer and its related treatments. In a multinational study, 1 273 men without prostate cancer completed the International Index of Erectile Function (IIEF) questionnaire [3]. The mean age of this cohort was 57.6 years (range, 40–56 years) and 50.1% reported some ED. Of the men in this cohort, 8.8% had mild ED, 10.4% had mild-to-moderate ED, 9.4% had moderate ED, and 21.7% had severe ED. Older age (> 56 years), lower socioeconomic class, income, and education, and absence of a partner were all statistically

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more common in men with ED. The fact that 20% of men had severe ED in this older age group should be kept in mind when analyzing erectile function status in prostate cancer patients.

Penson *et al.* [4] reported that, while 81% of post-RP participants indicated that they had erections firm enough for intercourse prior to surgery, only 9% had strong erections 6 months after surgery. By 60 months after surgery, 55% of men reported an inability to achieve any erections and only 28% of the subjects reported erections sufficient for intercourse. The degree of sexual bother decreased over the 5-year period with 46% indicating that sexual function was a moderate or major problem at the end of this interval. It is unclear whether the decrease in sexual bother was due to improved function or resignation and acceptance of their ED. Other studies have reported ED rates after surgery of 50%–80% [5–8], while Kendirci and Hellstrom [9], in a review on management of ED after RP, reported an incidence ranging between 16% and 82%.

The introduction of the nerve sparing RP (NSRRP) [10] has improved postoperative results, but there remains tremendous variation in published rates of preservation of erectile function. The discrepancy between the reported preservation of nerves and recovery of erectile function leads to several important questions. What is the mechanism for ED after RP? Are the nerves damaged? Do we truly identify all the nerves at the time of RP? Since the time course of recovery is consistent with nerve regeneration or repair, can something be done to enhance neural regeneration? Is something else being damaged during surgery? Is there arterial injury? Does a secondary cavernosal smooth muscle (SM) injury occur from the nerve injury? Is the ED a result of corporal hypoxia? What is the benefit of penile rehabilitation after injury that occurs due to the surgery? If so, what kind, and when should it be started?

Many of these questions remain unanswered despite a history of over 100 years for this curative surgery for prostate cancer [11]. It is beyond the scope of this article to address all these questions. The need for erectile rehabilitation is being increasingly recognized. The concept of end-organ rehabilitation after nerve injury is not foreign to the urologist. Urologists have been rehabilitating neurogenic bladders after spinal cord injury for over 40 years. Yet, there is no standard penile rehabilitation protocol after RP similar to bladder rehabilitation or muscle rehabilitation after any injury in other areas of the body. This article will limit its review to the experimental and clinical literature on rehabilitation of erectile function after cavernous nerve injury in an animal model and radical surgery in the human.

2 ED after NSRRP: the problem

Why doesn't this consensus exist? There are many reasons but foremost was the lack of uniform acceptance that the problem even exists. With initial reports of postoperative "potency" rates in excess of 90% [12], ED post-RP was blamed on poor surgical technique and inexperience. RP is now one of the most commonly performed open procedures during urologic residency and it has become apparent that many factors are involved in a successful erectile outcome after surgery: preoperative, intraoperative and postoperative issues.

In order to address a problem it has to be defined, recognized, and accepted. Until 1992 and the National Institute of Health (NIH) consensus position paper on ED, there was no uniformly accepted definition of ED [13]. Many of the papers on post RP ED before and after 1992 did not use uniform or standard definitions or validated questionnaires in reporting their rates of erectile function preservation [14–17]. The first simple and validated questionnaire to be used by urologists was first introduced by O'Leary in 1995 [18]. Krupski [19] reported a high level of variation in erectile function rates depending on the specific definition used. In a longitudinally followed cohort of 260 patients, whereas only 5% of men described their erections firm enough for intercourse reported, 61% rated their ability to function sexually as good or very good [19]. As more standardized definitions are used, reported erectile function preservation rates have decreased [4, 20]. To add to the confusion, current erectile function rates include men successfully using phosphodiesterase 5 inhibitors (PDE-5*i*), who by definition have some form of ED. Very few men claim erectile function is as good postoperatively as it was preoperatively and virtually none are better off.

3 Mechanism of erection

Penile erection is a neurovascular event that depends on relaxation of trabecular and vascular SM in the corpora cavernosa and corpus spongiosum. During the flaccid state the SM of the trabeculae in these tissues and in the blood vessels of the penis are contracted and blood flow is reduced. Tumescence depends upon SM relaxation mediated by cholinergic and non-adrenergic non-cholinergic (NANC) mechanisms involving the release of nitric oxide (NO) and other mediators, which stimulate production of the intracellular cyclic GMP [21]. This second messenger causes SM relaxation through a variety of mechanisms, including reduction of intracellular calcium [22]. The vasodilator prostaglandin E1 (PGE-1) also causes SM relaxation but by increasing the concentration of the cyclic AMP via stimulation of adenylate cyclase [23, 24]. The end result again is a decrease in intracellular calcium. In either case, relaxation of corporal SM occurs, resulting in rapid arterial filling and en-

gorgement of the sinusoids within the cavernosal, as well as veno-occlusion, which results from compression of the subtunical venules against the tunica albuginea (Figure 1).

Synthetic exogenously administered PGE-1 (alprostadil) reproduces the hemodynamic effects observed in a natural erection. The vasodilatory effects of alprostadil on the cavernosal arteries and the trabecular SM of the corpora cavernosa result in rapid arteriolar inflow and expansion of the lacunar space within the corpora. As the expanded corporal sinusoids are compressed against the tunica albuginea, venous outflow through the subtunical vessels is impeded and penile rigidity develops. The fact that alprostadil has a direct vasodilatory effect on SM in the penis is the basis for its efficacy in the treatment of non-nerve-sparing or nerve-sparing post-RP ED, where nerve damage prevents the normal erectile stimulus from occurring. By improving blood supply to the damaged tissues, healing may occur and can be considered rehabilitative.

4 Animal models of cavernous nerve injury

In 1983 Lue and associates [25] described an animal model that closely approximates the effect of RP. The cavernous nerves in the dog are readily visible as discrete nerve trunks coursing postero-laterally to the

prostate. As the prostate is an intra-abdominal organ, its removal with nerve preservation is relatively easy. The acute (three dogs) and chronic (three dogs) effects of canine RP on erectile function was investigated. Acutely, all dogs responded to nerve stimulation after prostatectomy, equally to unilateral or bilateral nerve stimulation, but failed to respond after complete nerve transaction. In the chronic dogs (two months), one dog lost erectile function acutely and all dogs lost their erectile response by 2 months. This study supports the concept that unilateral nerve stimulation is sufficient for an erectile response and ED can develop over time after prostatectomy, without transaction of the nerves. These observations corroborate the anecdotal reports of men post-RP describing erections around their catheter but eventual complete loss after catheter removal.

In 1991 Quinlan [26] examined the effect of bilateral nerve ablation and genito-femoral nerve grafting, in effect grafting a peripheral nerve to an autonomic nerve. The results were effective restoring vaginal intromission after electrically induced erections in rats with bilateral nerve ablation after grafting. There was a notable time-dependent return of function consistent with nerve re-growth (Table 1).

In 1995 Carrier and associates [27] demonstrated the pacate loss (3 weeks) of erectile function and nitric oxide synthase (NOS) staining in the cavernous nerves of rats undergoing unilateral and bilateral cavernous nerve ablation. At 6 months the unilateral group regained function and NOS containing nerves, whereas the bilaterally ablated group had absolutely no return of erectile function or NOS staining.

In 1997 Klein [28] attempted to characterize the early molecular events after penile denervation and to investigate whether cavernous nerve injury causes apoptosis. He utilized a rat model of penile denervation in which penectomy was performed at specific time intervals after nerve damage. DNA was extracted for DNA fragmentation studies, tissue was stained for apoptotic nuclei, and mRNA was analyzed on a northern blot for sulfated glycoprotein-2 (SGP-2) expression. SGP-2, also known as clusterin, is a gene product that has been postulated to play a role in programmed cell death and its induced synthesis has been shown to accompany apoptosis in many urogenital tract systems [29]. Clusterin analysis was done

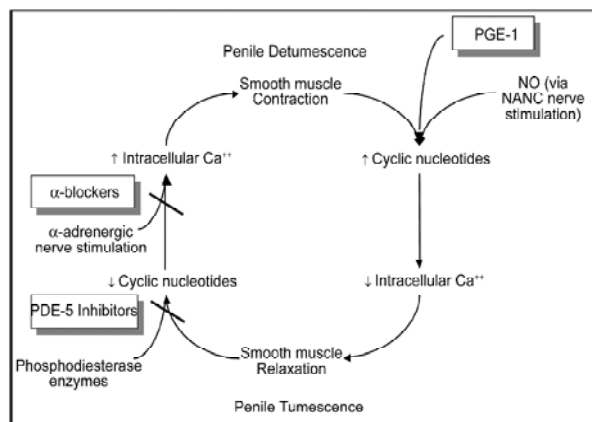


Figure 1. Schematic of molecular mechanism of erection. NO, nitric oxide; NANC, non-adrenergic non-cholinergic; PGE-1, prostaglandin E1; PDE-5, phosphodiesterase 5.

Table 1. The effect of genito-femoral nerve grafting in rats with bilateral nerve ablation. Reproduced from Quinlan *et al.* [26]. S, sham; NG, nerve grafted; A, nerve ablation without grafting.

	Two months			Four months		
	S	NG	A	S	NG	A
Vaginal intromission/Unsuccessful mounts (%)	100	14	5	91	89	18
Electrical stimulated erections (% with erections)	100	0	0	100	50	10

on five groups of three rats undergoing cavernous nerve injury followed by penectomy at days 1, 2, 3, 6 and 10 with a control group of 15 rats undergoing sham surgery.

DNA fragmentation was employed using *in situ* end labeling (ISEL) on a separate group of rats at day 2. DNA fragmentation and condensed cell nuclei characteristic of apoptotic cells were seen in the glans penis and the corporal bodies. However, the erectile tissue nuclei of sham operated controls did not stain and there was no evidence of apoptosis in any cells.

Figure 2 demonstrates the concomitant increase in clusterin in the neurectomized animals versus the sham group in the first two days, returning to sham levels at day 10 [28]. Clusterin levels have an increased expression in the rat ventral prostate after castration, in the rat kidney after vascular injury or unilateral obstruction, and in the cavernous tissue of castrated rats. This was the first animal study to experimentally support the concept of post cavernous nerve ablation induced penile apoptosis and the clinical phenomenon of decreased penile size after RP. Human longitudinal and cross sectional studies have shown significant loss of stretched penile length as early as one week post-RP [30–32].

The results by Klein were supported by User *et al.* [33] using a rat model of unilateral and bilateral nerve ablation. Penile weight, DNA content, total protein content, were measured at days 7, 14, 28 and 60. An apoptotic index was measured at days 1, 2, 7, 14, 28 and 60. In the bilateral nerve ablation group there was a significant decrease in penile weight at all time points between 7 and 60 days and a decreased DNA content after day 14. In the unilateral group, weight changes were observed at day 60 without any significant changes in DNA at any time. Significant apoptosis was seen as early as day 1 until day 28, even in the unilateral group. The corporal cells staining most intensely for apoptosis were those directly under the tunica albuginea. This may be significant in view of the recognized increased incidence of Peyronie's disease in men after RP [34] and the loss of stretched penile length after RP.

In order to attenuate apoptotic and functional changes that occur after nerve injury, Burnett *et al.* [35, 36] demonstrated the benefit of the neuroprotective molecule, FK506, administered before and after the nerve injury. Immunohistochemical and erectile function testing demonstrated preserved cavernous tissue histology and erectile function in immunophilin ligand treated rats. Such encouraging results were unfortunately not witnessed in human placebo controlled trials with FK506 [37].

Rajfer *et al.* [38, 39] examined the effect of sildenafil and vardenafil administration after bilateral cavernous nerve ablation (BCNA). Both studies demonstrate a benefit from PDE-5i administration after cavernous nerve ablation in preventing cavernous SM fibrosis and pre-

venting corporal veno-occlusive dysfunction. These investigations hypothesized that PDE-5i increased SM cell replication through increased intracellular cGMP concentration and inducible NOS (iNOS) upregulation.

Vigozzi *et al.* [40] demonstrated penile hypoxia, fibrosis, PDE-5 down regulation, resistance to tadalafil, sodium nitroprusside hypersensitivity and loss of penile NO, neuronal NOS (nNOS), endothelial NOS (eNOS), after BCNA in rats at 3 months. Chronic tadalafil administration reversed all these findings except the loss of penile NO, eNOS and nNOS. iNOS was not measured.

McVary and associates [41] showed that the decreased sonic hedgehog protein (SHH) signaling (derived from the cavernous nerves) is the cause for penile morphologic changes after cavernous nerve injury. The SHH signaling pathway is critical for establishing embryologic sinusoid morphology of the corpora cavernosa, and continues to regulate and maintain penile morphology in the adult organ [42]. In two rat models of ED, the diabetic bio-breeding/worcester rat (BB/WOR) and in the cavernous nerve (CN)-injured Sprague Dawley rat, SHH protein was significantly decreased [43]. In these same models there are significant morphological changes in the corpora cavernosa, including increased apoptosis and decreased SM and endothelial staining [42, 43]. In an elegant series of experiment these investigators demonstrated that SM and endothelial apoptosis in the cavernous nerve injury rats were similar to that induced in non neurectomized rats given an SHH inhibitor. Here they establish reversibility of the penile apoptosis in nor-

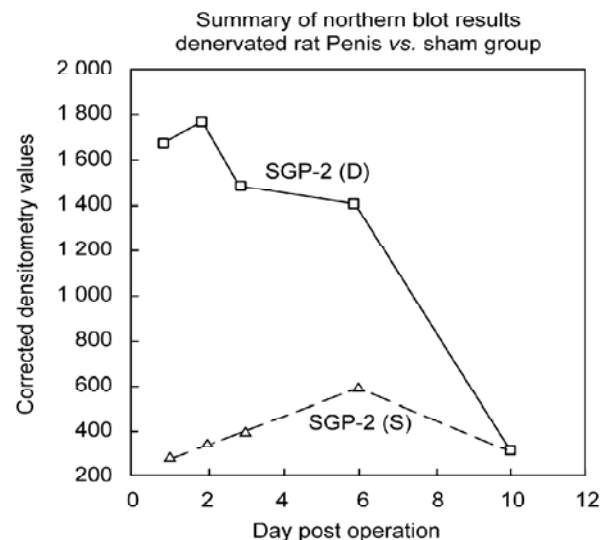


Figure 2. Increase in clusterin gene product as a marker of penile apoptosis after cavernous nerve ablation in the rat. Reproduced from Klein *et al.* [28]. SGP-2, sulfated glycoprotein-2; SGP-2 (D), denervated group; SGP-2 (S), sham group.

mal rats given a short term course of intrapenile SHH inhibitor and prevention of apoptosis by the administration of SHH at the time of cavernous nerve injury. They suggest a role for intrapenile SHH administration in the prevention of penile cavernous SM and endothelial apoptosis while the nerves are recovering after injury.

In summary, these animal studies demonstrate that cavernous nerve injury can occur with manipulation alone, cavernous nerve regeneration does occur, nerve grafts can be effective after nerve transaction, penile shrinkage and cavernous SM fibrosis occurs after nerve injury, and the administration of neuroprotective agents, PDE-5i or SHH protein can decrease or prevent cavernous SM fibrosis and preserve erectile function in neurectomized rats.

5 Nerve damage in post-RP ED

The etiology of ED after surgery for prostate cancer is likely multifactorial. Prostate cancer strikes men in their seventh decade of life when many are already experiencing ED [44]. While pre-surgical erectile function is a significant factor in determining erectile function after surgery [45] other invoked mechanisms include vascular injury and nerve injury [12]. The role of arterial injury as a cause of ED is unclear. In a large series of preoperatively potent men with postoperative ED undergoing penile dopplers after RP the incidence of arterial injury was less than 10%. In men with no arterial disease the most common finding was veno-occlusive dysfunction [46]. For this reason, one can postulate an initial neurogenic injury as the most likely initial cause of post RP ED.

Damage to the nerves after cavernous nerve injury and prostate reduces the amount of nNOS and NO that can be released during sexual activity, thereby reducing erectile function [27]. Consistent with the importance of surgical technique, there appears to be an advantage to nerve sparing over non nerve sparing ablation and bilateral to unilateral nerve ablation. Gralnek *et al.* [47] reported on 129 men who responded to a questionnaire, 83 of who had non NSRRP (NNSRRP) and 46 of who had a unilateral NSRRP (UNNSRRP). The sexual function score, which included questions regarding spontaneous erections and the use of erectile aids, showed a statistically significant difference in sexual function in men with a unilateral vs. a non nerve sparing surgery.

In a series of almost 3 500 men Kundu *et al.* [48] reported erections sufficient for intercourse in 76% of preoperatively potent men treated with bilateral NSRRP (BNSRRP) and 53% of men with UNNSRRP. In men less than 70 years of age the response rates were 78% and 53%, respectively. This series unfortunately retrospectively included men from 1983, prior to standardized ED questionnaires, and men currently taking PDE-5i.

These data suggest that preservation of local nerves is important for maintenance of erectile function. Decreased or loss of innervation within the erectile tissues has a number of deleterious effects; it prevents the release of NO from NANC nerves; decreases the production of cyclic nucleotides within the vascular SM; and reduces the subsequent relaxation of these tissues. As a result the intermittent increased blood flow and tumescence that would normally occur during nocturnal penile tumescence (NPT) or sexual stimulation is abolished or greatly diminished.

To complicate the question of nerve preservation, the exact location of the nerves that need to be preserved has recently been brought into question [49]. In an MRI study of men undergoing NSRRP performed by a single surgeon, attempts were made to visualize the neurovascular bundle (NVB) in men preoperatively. In 38% of men the NVB were not visualized on MRI (Group 1) whereas 41% had the NVB clearly visualized (Group 3). At 1 year there was almost a two-fold improvement in Sexual Health Inventory for Men (SHIM) score in men in whom the NVB was visualized. The percent change from baseline SHIM score was 44% (8.2% to 19.7%) in Group 1 and 24% (15.0% to 21.9%) in Group 2.

These findings were also seen when the men were categorized by age greater or less than 60 years of age. No systematic penile rehabilitation was used in any of these men. Though the results were statistically significant, obviously missing is histologic documentation that the structures seen on MRI were the NVB responsible for penile erections. Not reported was the ability to have erections satisfactory for sexual function.

6 NPT after RP

Data on NPT testing after RP are inconsistent and contradictory. Bannowsky [50] described 70% axial rigidity for 10 min in 17 out of 18 men at 15 days from surgery after NSRRP. This is consistent animal data and anecdotal experience of men having erections around their catheter postoperatively.

Kawanishi [51] described nine out of 21 (42%) with normal NPT at 4–6 weeks, as defined by an increase in diameter of > 20 mm for at least 5 min.

In a retrospective self selected group of 11 potent patients after RP, Lerner [52] reported that only two were mostly satisfied with their sex life according to a validated quality of life questionnaire. Rigiscan™ testing revealed that eight of the 11 patients had nocturnal erections which were adequate for vaginal penetration. Three of the five patients, who stated that they were mostly dissatisfied with their sexual functioning, had objective evidence of adequate erectile ability as documented by Rigiscan™. Three of the four patients who were am-

bivalent with respect to their sexual function also demonstrated objective evidence of normal erectile function. Lacking in all the previous small series was exact quantification of the nocturnal tumescence and statistical analysis.

In a retrospective comparative study of men with non surgical and surgical ED by Fraiman [53] a significant and profound loss of nocturnal erections was seen in men after RP at an average time from surgery of 9 months. In a prospective longitudinal 12-month NPT study of fully sexually functional men pre and one month post operatively, NPT was virtually eliminated [54] (Table 2). Follow-up with serial NPT testing demonstrated a time dependent return of NPT with the biggest improvement occurring 16 weeks post operatively [55] (Figure 3, personal data). Figure 4 (personal data) demonstrates the actual scan of a man preoperatively and post-operatively.

6.1 Penile hypoxia after RP

During erection, oxygen tension changes in the corpus cavernosum penis from 25–40 mmHg in the flaccid state to 90–100 mmHg in the erect state. There are acute and chronic effects of chronic hypoxia. Oxygenation of the cavernous tissue is an important factor in the regulation of local mechanisms of erection. Arterialized blood flow during nocturnal erections is believed important to provide the oxygen necessary for the formation of NO by both nNOS and eNOS. NO after crossing into the SM cell reacts with guanylate cyclase to catalyze the conversion of GTP to GMP. The lack of free oxygen, transported to the penis by oxygenated hemoglobin, diminishes the synthesis of NO and cGMP formation. Poor oxygenation stimulates TGF- β and results in a predisposition to cavernous fibrosis by increased synthesis of collagen [56]. Increased collagen deposition is caused by decreased corporal oxygenation or hypoxia [57]. Cavernous neurotomy was demonstrated to produce hypoxia and fibrosis in rat corpus cavernosum [28, 56, 58]. In this study, ablation of cavernous nerves bilaterally was associated with increased TGF- β 1 mRNA expression and hypoxia-inducible factor-1 α , TGF- β 1 and collagen I and III protein expression. It was theorized that strategies that improve corporal hypoxia might ben-

efit erectile function after RP. Treatment of human corpus cavernosum SM cells with TGF- β 1 increased collagen synthesis [59]; this increase in collagen was attenu-

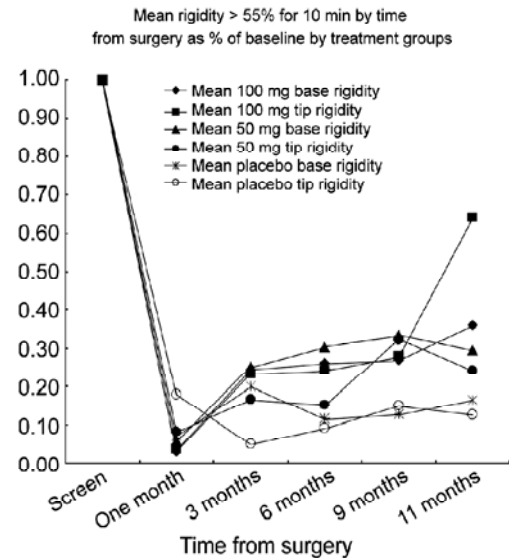


Figure 3. Recovery of nocturnal penile tumescence (NPT) in time.

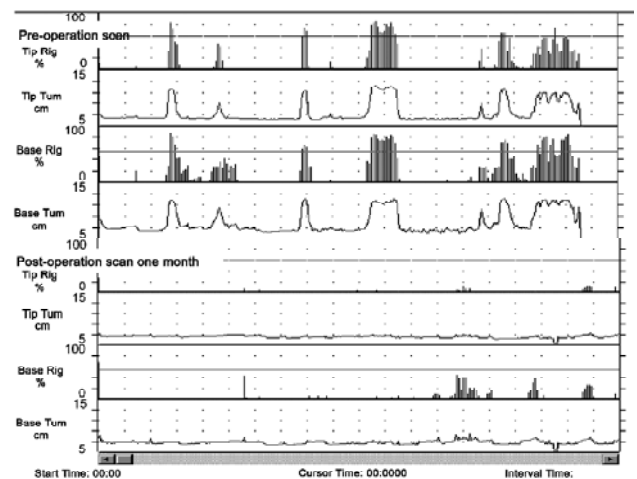


Figure 4. Pre- and one month post-operative nocturnal penile tumescence (NPT) testing (personal data). Rig, rigidity; Tum, tumescence.

Table 2. Prospective comparison of pre and one month post operative nocturnal penile tumescence (NPT) in 54 preoperative potent men.

	Duration of rigidity > 55% base (min)	Duration of rigidity > 55% tip (min)	Area under the curve (AUC) base rigidity	AUC tip rigidity	AUC base tumescence
Pre-operation	69	50	68	55	52
One month postoperation	3	5	5	4	7
P-value	0.0001	0.0001	0.001	0.0001	0.001

ated by simultaneous administration of PGE-1. In addition PGE-1 suppressed TGF- β 1 induction of TGF- β 1 mRNA.

Kim *et al.* [60, 61] showed that isolated human and rabbit corpus cavernosum tissue strips exposed to arterial-like pO_2 , relaxed with acetylcholine and to electrical stimulation of the autonomic nerves. Decreasing pO_2 to levels measured in the flaccid state resulted in a diminishing relaxation response. Normoxic conditions readily restored endothelium-dependent and neurogenic relaxation. In the rabbit corpus cavernosum, low pO_2 reduced basal levels of cGMP and prevented cGMP accumulation induced by electrical stimulation and similarly inhibited NOS activity in corpus cavernosum cytosol tissue [60, 61].

Blood gas studies in human models have revealed decreased oxygen tension in vasculogenic impotence and hypoxia in the flaccid penis. Corporal and penile flaccid oximetry was examined in a cross sectional comparative study of 101 men (22 potent, 36 non-RP ED, and 32 RP ED). Although there was no significant difference in StO_2 among ED patients, RP ED patients have significantly lower corporal StO_2 than potent patients (Table 3) [62].

Histomorphological studies in men after RP suggest there are changes in cavernous SM and collagen content [63]. As soon as two months after RP surgery, trabecular elastic fibers and SM fibers were decreased, and collagen content was increased, and these changes were accentuated after one year. This fibrosis is believed to have both denervation and ischemic etiologies. ED after RP is often associated with increased cavernous fibrosis and allows us to consider programs of regular corporal oxygenation with intracorporal PGE-1 to reduce post-operative ED [64].

7 Penile rehabilitation

7.1 Vacuum erection device (VED)

The VED is a longstanding effective erectogenic aid.

Though the effectiveness with ED is unquestionable, its role in penile rehabilitation is unclear. It is known that a proximal constriction band causes some penile ischemia while in use [65, 66]. The inflow of blood becomes non arterial and there is no SM relaxation [67].

In a randomized prospective study of 109 patients both nerve sparing (NS) and non-NS (NNS), 74 patients were instructed to apply the VED daily for 9 months *vs.* 35 men with no treatment. The duration of the VED application was not specified though the constriction band was used only for intercourse. Sixty of the 74 completed the VED arm. Men and their partners were mailed questionnaires. The results were inconclusive as 19/60 (32%) of the VED group reported spontaneous erections and 10/60 (17%) reported vaginal penetration (Table 4) [68]. In the “no treatment” group, 13/35 (37%) reported spontaneous erections and 4/35 (11%) reported erections satisfactory for vaginal penetration. The VED men stated subjectively that they had less penile shrinkage, but no objective measurements were made. 76%–86% of men were able to have sexual intercourse with the vacuum device regardless of the nature of the NS surgery. No long term follow-up or PDE-5 responsiveness was reported [68]. Though VED is effective in the treatment of post RP ED it has not yet been proven to be effective in penile rehabilitation protocols. That VED induces corporal ischemia, acidosis and lack of SM relaxation may theoretically be detrimental to longterm penile rehabilitation [69].

8 Intracavernosal alprostadil PGE-1 (ICT)

As indicated previously, PGE-1 induces erections by directly stimulating the production of cyclic AMP within the SM cells [23] and therefore does not require a functioning nerve to induce SM relaxation. By contrast, oral PDE-5is, which work by preventing the breakdown of cyclic GMP [70] require the presence of a functional

Table 3. Penile oxygen saturation in men with and without erectile dysfunction (ED). RRP, radical retropubic prostatectomy.

Site	Non-ED StO_2 (% , <i>P</i> value)	RRP ED StO_2 (%)	Non-RRP ED StO_2 (% , <i>P</i> value)
Right corpora	55.5, 0.02	46.1	46.5, 0.90
Mid-glans	72.4, 0.18	75.2	72.2, 0.09
Left corpora	61.0, 0.045	52.1	51.0, 0.79

Table 4. Comparison of satisfaction with VED between patients with NS and NNS RP in response to early use of vacuum erection device (VED). Reproduced from Raina *et al.* [68]. VED, vacuum erection device; BNS, bilateral nerve sparing; UNS, unilateral NS; NNS, non-NS.

	BNS (<i>n</i> = 31)	UNS (<i>n</i> = 22)	NNS (<i>n</i> = 21)
VED for sexual intercourse	81%	90%	76%
Return of Natural function with VED at 9 months	29%	32%	14%
Natural, erection sufficient, for intercourse at 9 months	16%	18%	5%
Spouse satisfaction	42%	50%	43%

nerves and NO to produce this second messenger and hence facilitate erections. These latter agents are in theory unlikely to be active until nerve function is at least partially restored.

There is much support for the early use of rehabilitative ICT [64]. At a time when surgical technique and expertise and patient age were considered the prime determinants of erectile function outcomes, this was the first study to suggest that pharmacologic intervention during the postoperative period could impact the results. The study suffers from methodological flaws. Thirty patients were randomized either tri-weekly ICT (Group 1) or no therapy (Group 2), starting one month after surgery for a total of three months. They were then evaluated after 3 months or at 4 months from surgery. Twelve of the 15 ICT patients completed the study whereas all 15 of the observation group completed. The evaluation consisted of a non-validated questionnaire, penile doppler testing and three nights of nocturnal penile tumescence testing. No preoperative testing was done, and no doppler or NPT data were included in the article, only summary data. The authors report erections satisfactory for intercourse in 67% group 1 and 20% of group 2. Contemporary placebo controlled studies using validated questionnaire report much lower erectile function rates at 4 months. Normal penile hemodynamics were reported in 83% group 1 vs. 33% group 2. Veno-occlusive dysfunction was seen in 17% of group 1 vs. 53% of group 2. NPT testing was "normal" in 58% of group 1 and 20% of group 2. No clear definitions were made of normal Doppler score or NPT testing. This early study was completed in the pre-PDE-5 era when validated sexual function questionnaires were not routinely used. Though intuitively appealing the results need to be interpreted cautiously as the results have yet to be duplicated in a placebo controlled fashion or on a larger scale.

In a small non placebo controlled series of 22 men initiated on ICT 2–3 times a week [71] and on immediate nightly sildenafil 50 mg, at a mean follow-up of 6 months (3–8 months), 50% of men reported weak spontaneous erections, though none sufficient for intercourse (SHIM score 8.1 ± 0.3). Ninety-six percent of the men were sexually active with injection therapy or a combination, similar rates to the VED. A deficiency of the study is its short term follow-up and lack of a randomized non-treatment control arm. The psychological benefit of being able to resume earlier sexual intercourse is a positive attribute.

In a non randomized observational study of post-RP men presenting for treatment with sildenafil refractory ED, patients were either offered ICT rehabilitation (R) ($n = 58$) or no rehabilitation (NR) ($n = 78$) [72]. The men self selected their therapy. ICT was suggested tri-weekly. Only patients who presented within 6 months post RP, who completed the IIEF questionnaire, and who

had been followed for at least 18 months were included. At 18 months post RP, there were statistically significant differences between the two groups in the percentage of patients who were capable of having medication-unassisted intercourse (R = 52% vs. NR = 19%); mean erectile rigidity (R = 53% vs. NR = 26%); mean IIEF erectile function (EF) domain scores (R = 22 vs. NR = 12); the percentage of patients with normal EF domain scores (R = 22% vs. NR = 6%); the percentage of patients responding to sildenafil (R = 64% vs. NR = 24%); the time to become a sildenafil responder (R = 9 ± 4 vs. NR = 13 ± 3 months); and the percentage of patients responding to ICI (R = 95% vs. NR = 76%). Though supportive of the concept of early penile rehabilitation, this study suffers from a strong patient self selection bias and lack of a placebo arm.

In support of early penile rehabilitation, the effects of intracavernosal PGE-1 in men were examined in men who had undergone an NNS RP. In this trial 36 patients initiated treatment within three months of RP, and 37 received it beginning 4–12 months after surgery. Color duplex Doppler ultrasound was conducted at various points over 12 months after the operation. Patients who initiated therapy within three months of surgery had a significantly better erection grade and a higher peak systolic velocity in at least one cavernosal artery, than those who initiated treatment later. In addition those subjects who received treatment the first month after surgery had a better erectile response than those who started receiving it 2–3 months after surgery. There was a higher incidence of painful erections in the group initiating treatment earlier [73]. In this author's opinion, due to the perceived invasiveness of intracavernosal therapy, it is difficult to convince patients to self inject frequently enough to benefit from the penile injections in rehabilitative fashion.

9 Intraurethral alprostadil (IUA)

Costabile *et al.* [74] evaluated the erectile response to intraurethral PGE-1 in 384 men with ED after RP, with treatment beginning no less than three months after surgery. This was a multi-institutional study before the approval of PDE-5i and included both men at differing times from surgery and with both NSRRP and NNSRRP. Initial doses were 125 or 250 µg, which were titrated to 500 or 1 000 µg for adequate erectile response. When treatment was administered in the clinic 70% of the participants developed an erection sufficient for intercourse. These subjects were then randomized to a 3-month at-home trial with either PGE-1 or placebo. During this phase 57% of the subjects had successful intercourse at least once at home, compared to an intercourse rate of 6.6% of men treated with placebo. These rates compare

favorably with PDE-5i response rates in younger men with BNSRRP. Adverse events included penile pain and urethral pain/burning. This placebo controlled study supports the use of a less invasive treatment modality in men who would not otherwise respond to PDE-5i.

More recently Raina *et al.* [75] reported the results of a study in 54 post-RP men who used transurethral PGE-1 (250, 500 or 1 000 µg). Subjects experienced ED for at least six months after surgery before initiating treatment. Fifty-five percent of the subjects were able to achieve and maintain erections sufficient for intercourse while on treatment, and 48% continued long-term therapy with a mean use of 2.3 years. There were no significant differences in responses between those men who had a NSRRP surgery (34 patients) and those who had a NNSRRP procedure (20 subjects).

A recent report demonstrated the efficacy of early intervention with transurethral PGE-1 in men with prostatectomy-associated ED [76]. In this nonrandomized study 56 men who had a bilateral nerve-sparing operation began treatment with 125 µg PGE-1 three times a week within 4 weeks of surgery; another 35 men served as an observational control group. Treatment was continued for approximately 6 months, with the dose of PGE-1 increased to 250 µg after six weeks. In the PGE-1 group 38 out of 56 men (68%) continued treatment for the entire six months. At 6 months, 28 out of 38 men (74%) resumed sexual activity; 15 (39%) had natural erections sufficient for vaginal penetration without treatment, and 13 (34%) used PGE-1 as an erectile aid when having intercourse. In the observation group 13 out of 35 men (37%) resumed sexual activity, four (11%) had natural erections sufficient for vaginal penetration, and nine (25%) used adjuvant treatments. This encouraging but nonrandomized small study suggests that post operative transurethral PGE-1 is well tolerated and may be beneficial in penile rehabilitation in the ED that accompanies RP. The ability of PGE-1 to increase SM relaxation and blood supply, even in the presence of local nerve trauma, suggests that this agent may rehabilitate nerves and blood vessels that receive damage during surgery.

One possible mechanism of nerve rehabilitation is through cyclic AMP, which is reported to play a role in

regeneration in both the peripheral and central nervous systems [77, 78]. In an *in vitro* model of axotomy using adult retinal ganglion cell axons, increasing cyclic AMP promoted growth cone regeneration under conditions which normally would result in low regenerative potential [79]. Cai *et al.* [80] demonstrated that endogenous levels of cyclic AMP are higher in young neurons, which are able to regenerate after injury, as compared to older neurons, which lose the ability to regenerate.

Kogawa *et al.* [81] reported on nerve regeneration in dorsal root ganglia (DRG) of diabetic rats. Prior to nerve crush injury there were no apoptosis-positive DRG neurons observed; subsequent to axonal injury, apoptosis-positive neurons were seen in diabetic but not in non-diabetic animals or in rats treated with a PGE-1 analog. The regeneration distance at day 7 after injury was shorter in diabetic rats than in animals in the other groups. The cyclic AMP content of DRG on day 7 was higher than that at day 0 in nondiabetic and PGE-1-treated animals, whereas it was not increased after 7 days in diabetic rats. The results of this investigation suggest that PGE-1 is able to rescue DRG neurons from apoptosis and that it improves axonal regeneration in diabetic rats.

The beneficial effect of PGE-1 on corporal oxygenation has been demonstrated. In 101 patients with ED the administration of PGE-1 intraurethral or intracorporally resulted in a 37–57% increase in corporal oxygen saturation StO₂ [82] (Table 5). The increase in oxygenation occurred in the MUSE patients at a dose of 125 µg and despite marginal tumescence (Table 5) [82]. Hence, PGE-1 may not only rehabilitate penile function after a RP by directly relaxing cavernosal SM, thereby enhancing blood flow, but also may stimulate regeneration of local nerves, thereby increasing NO release. Such a dual mechanism of PGE-1 would shorten recovery time and hasten the return of spontaneous erections and PDE-5 responsiveness. These results indicate that PGE-1 is able to reverse some of the deleterious effects of RP that result in ED. Further, it appears that the earlier after surgery PGE-1 is initiated, the better the recovery of erectile response. The ability of PGE-1 to directly induce SM relaxation and increase blood supply, even in the presence of local nerve trauma, as well as stimulate regen-

Table 5. Corporal oximetry in men after prostaglandin E1 (PGE-1) treatment. MUSE, Medicated Urethral Suppository for Erections.

Site	Mean pre-vasoactive StO ₂ (%)			Mean post-vasoactive StO ₂ (%)			Mean StO ₂ (%) change		
	MUSE	Trimix	P value	MUSE	Trimix	P value	MUSE	Trimix	P value
Right thigh	69.24	58.53	0.31	62.96	54.96	0.10	–6.28	–0.65	0.11
Right corpora	50.86	51.62	0.07	64.27	82.75	0.01	13.57	33.42	0.03
Mid-glans	82.04	74.90	0.03	91.85	91.81	0.98	9.81	17.2	0.10
Left corpora	51.99	56.25	0.61	77.01	84.43	0.12	25.01	28.08	0.74
Left thigh	72.01	63.59	0.26	70.93	68.98	0.25	–1.07	5.41	0.23

eration of damaged nerves, suggests that this drug may be pivotal in rehabilitating nerves and blood vessels that have been traumatized.

10 PDE-5i

The advent of PDE-5i has certainly increased interest in post-RP ED, and PDE-5 responsiveness has been incorporated into the definition of successful ED outcome after RP. The post-RP patient remains one of the most refractory groups of PDE-5i patients [83–85] with intercourse success rates of approximately 40% in placebo controlled studies. An intact cavernous nerve-SM relationship is optimal for maximum PDE-5 efficacy. Any decrease in the number of nerves or SM responsiveness decreases the efficacy of the PDE-5i. In addition, the responsiveness to PDE-5i after RP is clearly dependent on the time from surgery with the maximum recovery taking place at 18–24 months [86], within the time frame expected for nerve recovery [87]. That being the case, what rationale is there for the use of sildenafil in penile rehabilitation? Indeed the early use of chronic PDE-5i post-RP has been questioned [88].

In a randomized placebo controlled study of 76 men after BNSRRP [84] serial NPT (1, 4, 8 and 12 months) and recording of unassisted erectile function satisfactory for vaginal penetration at one year, in men who took 50 or 100 mg of sildenafil nightly for 9 months postoperatively was performed. These researchers found a 7 fold improvement of normalization of erectile function in the treatment group over placebo at one year. NPT was better in the treatment group with most of the benefit demonstrated in the first 4 months with a profound loss of Rigiscan™ detected NPT at one month postoperatively (Table 6) [55].

The purported mechanisms to explain these results were: reduction in post operative corporal hypoxia, enhanced endothelial function and possible neurotropic mechanisms. Montorsi [89] has shown in a placebo controlled study that the use of sildenafil citrate (SC) taken nightly enhances NPT. It is possible that the nightly SC enhances corporal oxygenation to a “sub-erectile” state, much like PGE-1 was shown to enhance corporal StO₂.

The administration of nightly SC decreases penile fibrosis after RP [63]. In patients in whom vascular endothelial function is impaired by conditions such as aging, diabetes, hypertension, or hyperlipidemia, administration of SC improved endothelium-dependent vasodilation [90–92]. As eNOS is important in the maintenance of erections, it is possible that SC is potentiating the pro-erectogenic effect of eNOS. In rats treated within 24 h of stroke, SC increased neurogenesis and reduced neurological deficits [93], suggesting the capacity to promote recovery of nerve function. SC may enhance cavernous nerve regeneration. Comparable studies have not been carried out with the other PDE-5i nor has a larger study been done. It is recognized that there are difficulties to carrying out such a large placebo controlled studies.

11 Post operative steroid administration

In an attempt to improve ED outcomes by modifying the acute post-operative inflammatory response, a 6-day course of methylprednisolone was used in a placebo controlled randomized study of 70 men undergoing BNSRRP [94]. The medication was started 16–22 h after surgery. As can be seen in Tables 7–8, at 3 months there was an statistically significant advantage to the placebo group at 3 months that disappeared by 6 months. At 12 months no differences were seen in SHIM scores or in positive responses to the question “Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory for you?”. Postoperative complication or continence rates were not affected by the steroid administration. According to the authors, it is possible that the timing, short course of administration and low dose may be the reason for the negative findings. A similar study was done with the intra-operative local administration of bethamethasone on the area of the NVB in 60 men [95]. Using similar outcome instruments, no difference in post-operative sexual function was seen and there was no increase in postoperative complications.

12 Neuroimmunophilin ligands

Neuroimmunophilin ligands are orally bioavailable

Table 6. The effect of nightly sildenafil citrate (SC) on the return of nocturnal penile tumescence (NPT).

Mean duration of rigidity > 55% in minutes	Placebo (n = 19)	50 mg SC (n = 17)	100 mg SC (n = 18)
Basal rigidity 55 (preoperative)	82	63	63
Tip rigidity 55 (preoperative)	53	49	49
Basal rigidity (4 weeks)	6	4	2
Tip rigidity 55 (4 weeks)	10	4	2
Tip rigidity 55 responders (48 weeks)	1	16	54
Tip rigidity 55 nonresponders (48 weeks)	8	4	20

small molecules that act like growth factors and provide neuroprotection and neuroregeneration. *In vitro* they promote neurite extension in culture and protect neurons from acute injury. In animal model studies they were found to be neuroprotective during neurotoxic injury and neuroregenerative after nerve crush injury. GPI 1485 (Guilford Pharmaceuticals Inc., MD, USA), a cleavage product from cyclosporine, was used as a neuroprotective agent after efficacy was shown in a rat cavernous nerve crush injury model. It was tested in humans with Parkinson's disease and found to be well tolerated and safe. Between September 2003 and February 2005, a 6-month, phase 3, placebo controlled multiple fixed dose (400 mg and 1 000 mg) trial was undertaken to evaluate the efficacy of GPI 1485. The primary endpoint was the erectile function domain of the IIEF at 6 months. The study group was men undergoing BNSRRP with normal preoperative erectile function at major centers excellence for prostate cancer surgery. There was a primary analysis in the 40–59 year old men ($n = 182$) and a secondary analysis in the 60–69 year old men ($n = 45$). Data captured were IIEF Questionnaire approximately 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 months post-surgery, health related quality of life, Health related quality of life (HRQOL), Questionnaires (Sexual Function-12 [SF-12] and the UCLA Prostate Cancer Index Short Form) approximately 3, 6, 9, and 12 months post-surgery, PDE-5i use and study drug compliance. PDE-5i were the only erectogenic aids permitted throughout the study. Their use has been

shown to impact recovery rates, varied between sites and was therefore recorded as a confounding variable. Eighty-nine percent of men completed the study. The results at 6 months were disappointing. There was a profound decrease from baseline in all domains of the IIEF at three and six months. There was no difference between the treatment groups and placebo in the 40–59 years old group (Table 9) [37]. The treatment arm in the older age group showed a decrease over placebo in EF domain at 6 months though the numbers were small and the difference was not significant (Figure 5). This trial though not demonstrating a short term neuroprotective benefit from the neuroimmunophilin ligand perhaps did not follow the outcome long enough. There are currently ongoing trials with other neuroprotective agents.

13 Conclusion

ED is very common subsequent to surgery for prostate cancer. Factors that affect the development of the ED are varied and include pre-surgery erectile function, age of the patient, stage of the cancer, and the nerve-sparing nature of the surgery. Immediate causes of the dysfunction appear to be related to the status of the local nerve followed by secondary SM injury and corporal fibrosis.

The fact that prostate cancer is being detected earlier and in younger men, and that RP provides for an extended survival time, means that patients will be living

Table 7. Recovery of sexual function in men exposed to short course of methylprednisolone. SHIM, Sexual Health Inventory for Men.

Treatment arm	3 months erectile function/SHIM	6 months erectile function/SHIM	12 months erectile function/SHIM
Placebo	57%/13.4	54%/13.9	71%/15.7
Methylprednisolone	28%/9.36	43%/12.3	74%/17.1

Table 8. Recovery of sexual function in men exposed to intraoperative course of bethamethasone. SHIM, Sexual Health Inventory for Men.

Treatment arm	3 months erectile function/SHIM	6 months erectile function/SHIM	12 months erectile function/SHIM
Placebo	33%/11.5	40%/12.97	60%/15.43
Intra-operation Bethamethasone	27%/9.63	47%/11.73	57%/14.76

Table 9. Effect of neuroimmunophilin ligands on recovery of erectile function in 40–59 years old. IIEF, International Index of Erectile Function.

Outcome	Baseline score	3 months	6 months
Erectile Function Domain	29	10	12
Orgasmic Domain	9.6	4.8	5.13
Sexual Desire	7.9	4.76	4.73
Overall Sexual Satisfaction	9	3.3	4.5
Total IIEF Score	68	29	35
HRQOL Physical Health Component	58	54	56
Prostate Cancer Questionnaire Sexual Function and Bother	95	34	43

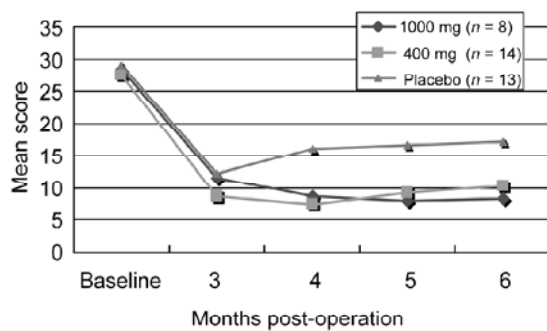


Figure 5. Effect of neuroimmunophilin ligands on erectile function (EF) Domain 60–69 years old cohort. Differences between treatments are not statistically significant, $P < 0.140$.

with the consequences of surgery (and other treatments) such as poor erectile function for a long period of time. It is important to provide these men with therapies that can restore erectile and sexual function as quickly as possible. Contemporary studies suggest that early initiation of local treatments such as PGE-1 or PDE inhibitor (PDE-i), may return the subject to long term spontaneity, or at least to responsiveness to oral therapies. The optimal penile rehabilitation strategy has not yet been devised but may encompass both PGE-1 and vasodilatation with PDE-5i. As the penile atrophy and fibrotic changes penis occur in the first three months after RP early postoperative early intervention is crucial. It is important to present and explain these various options to the patient prior to surgery so that he can make an informed decision as to what type of therapy is most appropriate and desirable for him. More large scale placebo or active control studies are needed to elucidate the best postoperative strategy.

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