
Effect on sexual function of a vacuum erection device post-prostatectomy

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Introduction: Treatment of erectile dysfunction (ED) subsequent to bilateral nerve sparing robotic prostatectomy (BNSRP) with tadalafil plus a vacuum erection device (VED) may improve return of sexual function.

Materials and methods: Men with prostate cancer who had BNSRP were randomized to receive tadalafil, 20 mg three times weekly, or tadalafil plus a VED, 10 minutes unbanded per day for at least 5 days weekly. Treatments started 1 month after surgery; clinic visits were at 1, 3, 6, 9 and 12 months. Patients were requested to attempt intercourse at least twice before each visit. At every visit patients completed the International Index of Erectile Function (IIEF-5) questionnaire and a penile hardness scale (1-4) and were questioned as to their ability to have vaginal penetration and intercourse to orgasm.

Results: Thirteen men started the combination regimen, and there were no dropouts; 10 patients started the tadalafil treatment, and three men dropped out. The mean IIEF-5 at months 6, 9 and 12 were significantly higher for the combination group, while the penile hardness scores were significantly greater for the combination group at 6 and 9 months. After 12 months 92% of combination patients responded yes to the vaginal penetration question versus 57% of the tadalafil group; corresponding figures were 92% and 29%, respectively, for intercourse to orgasm. Compliance to the VED was superior to that of tadalafil.

Conclusion: Men with ED subsequent to BNSRP had a more rapid and complete return of sexual function when treated with tadalafil plus VED versus tadalafil alone.

Key Words: vacuum erection device (VED), phosphodiesterase inhibitor, tadalafil, erectile dysfunction, penile hardness, combination therapy, radical prostatectomy

Introduction

Radical prostatectomy (RP) is one of the primary treatments for prostate cancer.¹ Even with improvements in nerve sparing surgical techniques the incidence of erectile dysfunction (ED) after RP continues to be high,²⁻⁴ particularly in the first year. It has been thought that the primary cause of ED after RP is associated with reduced release of nitric oxide (NO) from penile cavernosal nerves during sexual activity that is related to nerve damage.⁵ Decreased release of NO reduces the

amount of localized cyclic GMP that is produced,⁶ which in turn has a negative effect on penile smooth muscle relaxation⁷ that ultimately reduces blood accumulation in the penis.

Hypoxia in the cavernous tissue that is caused by vascular damage during surgery is also thought to be involved in the etiology of ED in RP patients.⁸ Oxygen deprivation in rats has been shown to increase collagen synthesis and decrease smooth muscle fibers⁹ in penile smooth muscle, adding to the decrease in muscle relaxation.

Treatment of ED subsequent to RP includes phosphodiesterase type 5 (PDE5) inhibitors,¹⁰⁻¹² intracavernosal¹³ as well as transurethral¹⁴ alprostadil (prostaglandin E1). All of these have shown limited success in improving sexual function, either because of poor efficacy and/or lack of compliance to the drug regimen. In a typical office practice most urologists prescribe PDE5 inhibitors, even though the limitations of these drugs are especially evident in the first year

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after surgery. Common practices are to prescribe daily sildenafil or vardenafil, or, alternatively tadalafil every other day or daily in a subtherapeutic dose.

Vacuum erection devices (VED) are another treatment option for post-RP patients experiencing ED; these devices increase the amount of blood flowing into the penis by creating a negative pressure¹⁵ and are therefore not dependent upon functioning nerves or a fully intact vascular supply to enhance blood flow. Recent studies have demonstrated that early initiation of a VED after prostatectomy improves sexual function.¹⁶ The combined use of a VED and a PDE5 inhibitor has been shown to improve sexual function in men with ED in the absence of RP who had failed the inhibitor alone.¹⁷

Materials and methods

Prospective candidates for randomization were men with prostate cancer who were scheduled for a bilateral nerve sparing robotic prostatectomy (BNSRP). Inclusion criteria included age less than 65, no comorbidities, and a subjective high level of motivation for both the patient and his partner. All operations were performed by the same surgeon. One week after surgery the patients were randomized to receive tadalafil (Eli Lilly, Indianapolis, IN, USA), 20 mg per day three times per week, or tadalafil plus a VED (Timm Medical Technologies, Eden Prairie, MN, USA), to be used unbanded at least 5 days per week for 10 minutes daily. Randomization was accomplished using a computer-generated randomization table. Treatment was initiated one month after surgery, and patients returned to the clinic at 3, 6, 9 and 12 months. Prior to each visit (starting with the third month) the subjects were requested to attempt intercourse at least twice. When intercourse was attempted the patients were instructed to use tadalafil, either alone or in combination with the VED (banded) within 1 hour of the sexual attempt.

Compliance to tadalafil was assessed by asking the question "Since your last visit have you taken an average of at least two tablets per week?" Compliance to the VED was assessed by posing the question "Have you used the device an average of four out of seven days per week and have you attempted to use it for intercourse at least once since your last visit?"

At each visit the patient was required to complete the International Index of Erectile Function (IIEF-5), a penile erection hardness scale (1-4), answer a question regarding their ability to have vaginal penetration (yes/no), and answer a question as to whether they were able to have intercourse to orgasm (yes/no). Results were analyzed between treatment groups for each visit using an Analysis of Variance.

The study was formally approved by Ethical Review Committee (Independence, MO, USA). The work was conducted in accordance with the ethical standards of the committee on human experimentation.

Results

Twenty-three men were enrolled in the study, with 10 in the tadalafil group and 13 in the tadalafil plus VED combination group. Three men in the tadalafil group discontinued the study between 3 and 6 months due to lack of efficacy or side effects, whereas all 13 patients in the combination group completed the study.

Compliance to tadalafil was poor in both patients receiving drug alone (40%) and in patients treated with drug plus the VED (38%), whereas compliance to the VED was 100%.

Figure 1 presents the treatment effect on the IIEF-5. The mean pre-surgery IIEF-5 in both groups was 24.7 (range 23-25). There was a precipitous decrease in the IIEF-5 score after surgery; at the randomization visit the mean was 1.8 in the tadalafil group (range of 1-8, with all but one subject in the 1-2 range) and 1.2 in the tadalafil plus VED group (range of 1-3). At the 1 month visit the mean IIEF-5 score in the tadalafil group was 3.3 (range 1-8), compared to 1.9 (range of 1-5) for the combination group. For the remaining visits the mean IIEF-5 was higher for the tadalafil plus VED group, and by the end of the study the score

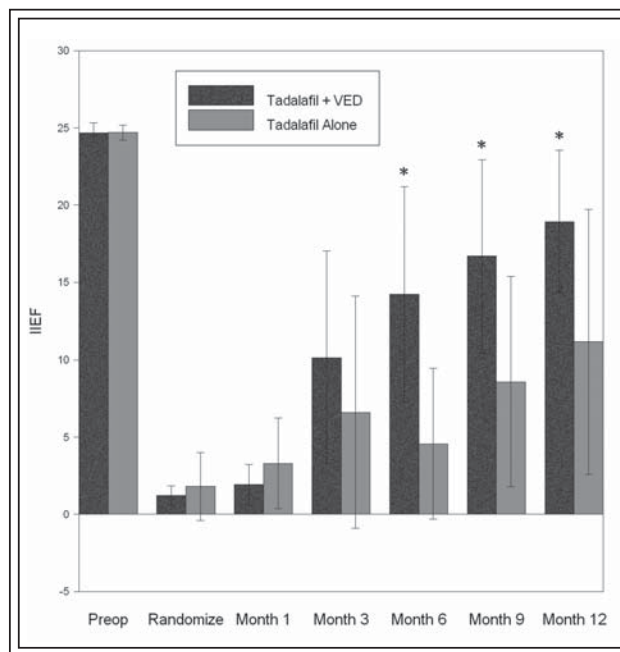


Figure 1. Effect of tadalafil alone and tadalafil + VED on IIEF-5.

TABLE 1. Vaginal insertion: percent yes

	Preop	Random	1 mo	3 mo	6 mo	9 mo	12 mo
Tadalafil	100	0	0	20	14	43	57
Tadalafil + VED	100	0	0	69*	85*	92*	92

*significantly different from tadalafil alone, p < 0.05

TABLE 2. Intercourse to orgasm: percent yes

	Preop	Random	1 mo	3 mo	6 mo	9 mo	12 mo
Tadalafil	100	0	0	20	14	14	29
Tadalafil + VED	100	0	0	54	85*	69	92*

*significantly different from tadalafil alone, p < 0.05

for the combination patients was 18.9 (range 12-25) compared to 11.1 (2-24) for the tadalafil alone group, a 70% difference. The IIEF-5 values were significantly greater for the combination group from 6 months to the end of the study.

The penile hardness scores showed a similar pattern to the IIEF-5, Figure 2. The mean score was 4 in both groups prior to surgery; this decreased to 0.3 (range 0-1) at the randomization visit and was 0.6 (range 0-3) at the 1 month visit. From 6 months to the end of the study there was an increase in the hardness score for both groups, so that at the end of the study the score

was 2.6 (range 1-4) in the tadalafil group and 3.2 (range 2-4) in the tadalafil plus VED group, a 23% difference. The penile hardness scores were significantly higher for the combination patients compared to the tadalafil alone group at the 6 and 9 month visits.

The percentage of patients who responded yes to the vaginal insertion question was 100 before surgery in both groups, and this decreased to 0 after the operation, Table 1. In general this value steadily increased from 3 months to the end of the study, at which time it was 57% for the tadalafil group and 92% for the tadalafil plus VED group.

Similarly, the percentage of patients who responded yes to completion of orgasm was 100 before surgery and 0 immediately after surgery, Table 2. At 12 months the value was 29% in the tadalafil group and 92% in the tadalafil plus VED group.

The main side effects after tadalafil were headache, flushing and muscle ache, while the main side effect after the VED was minor local discomfort.

Discussion

The current pilot study was not a penile rehabilitation study but rather was conducted to determine if the use of a VED, in combination with standard treatment with the PDE5 inhibitor tadalafil, hastened the return of sexual function in men who had a BNSRP when compared to treatment with the PDE5 inhibitor alone. In "real life" practice most patients are prescribed a PDE5 inhibitor after BNSRP, even though the result of monotherapy with these agents is equivocal. The author has historically treated his patients with a PDE5 inhibitor such as tadalafil, typically every other day for 1 year following BNSRP. The primary goal of

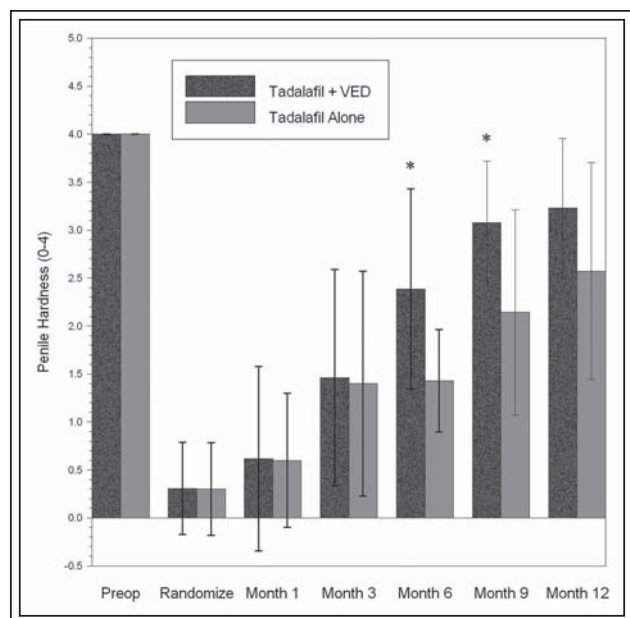


Figure 2. Effect of tadalafil alone and tadalafil + VED on penile hardness.

the present study was to assess whether addition of a VED to his standard practice enhanced the return of sexual function. Admittedly the sample size was small, but by all measures evaluated the addition of a VED to tadalafil improved sexual function compared to the drug alone. Treatment with the VED plus tadalafil for 11 months resulted in a more rapid return of sexual function, greater postoperative penile hardness, increased successful vaginal penetration, and improved ability to have intercourse to orgasm.

The differences between the treatments became evident at 3 months post-surgery, which was 2 months after initiation of treatment. All four parameters that were measured continued to increase throughout the 12 month study in both treatment groups, but the increase was greater for the combination group compared to the tadalafil alone patients. At the end of the study the IIEF-5 and penile hardness scores were 70% and 23% higher, respectively, in the combined treatment group compared to the tadalafil group.

There is a well known, progressive improvement in erectile function after RP,^{18,19} possibly because of the ongoing recovery of penile nerve function and/or the collateralization and repair of altered blood flow after RP. This temporal pattern of recovery after BNSRP has also been demonstrated in this study with not only the PDE5 arm alone but with the combination arm as well. The present study has therefore not only shown the advantage of combining a VED with standard PDE5 inhibitor therapy in enhancing recovery of sexual function after RP, but has also demonstrated that sexual function is relatively low early after BNSRP even with combination therapy. A poor early response, regardless of the post-prostatectomy regiment chosen, along with the temporal nature of the return of sexual function, is an important point to stress to patients when managing sexual function expectations after a prostatectomy.

The addition of a VED to standard PDE5 therapy appears to offer advantages to monotherapy with PDE5 inhibitors when treating post-RP ED. A VED, by drawing blood into the penis through negative external pressure, can overcome neuropraxia as well as increase blood flow and thus provide sexual success even during this recovery period. However, it is clear that the successful patient must recover natural function as well to some degree in order to attain a good response. It is important to note that our findings, although supportive, cannot conclude that a VED is a beneficial penile rehabilitation tool.

However, the author believes that the addition of a VED to a PDE5 inhibitor has a positive or additive effect, not only because of the different mechanisms of action of the two treatments but also because, by

improving sexual function at an earlier stage in the healing process, the VED increases the confidence and enthusiasm of the patient and his partner for a successful sexual encounter. However, since there was no VED alone group in this study, we cannot formally conclude that the addition of tadalafil to the VED did, in fact, have a greater effect than the device alone.

As well as demonstrating that VED success is associated with the length of time after surgery, this study has also confirmed how poor the compliance to PDE5 inhibitors can be, as has been shown previously.²⁰ This poor compliance was documented in both groups in the study. Although a penile rehabilitation program consisting of daily use of oral PDE5 inhibitors appears to be simple, its efficacy has not been firmly established.²¹ The present study demonstrated that when patients are not supplied PDE5 inhibitors free of charge, their relative lack of effectiveness (at least in the first year after surgery) and presence of side effects lead to compliance and efficacy far less than that reported in most penile rehabilitation studies that supply the patient with drug. Similar findings related to the cost of the PDE5 inhibitors have been previously reported.²² The fact that most insurance companies do not reimburse for PDE5 inhibitors, along with the daily cost, which can be as high as 20 dollars per tablet, can result in poor compliance, as was observed in the present study. This study mirrors the situation encountered in daily clinical practice, where patients typically have to pay for all or most of their erectile function medication. Clinicians must be aware that patients are not generally succeeding with PDE5 inhibitors and probably will forego the significant cost of these drugs under these circumstances.

Compliance to the VED, on the other hand was good, which could be accounted for by the return of sexual function as measured by the IIEF and the relatively low cost for the device. This suggests that the use of a VED, as opposed to a PDE5 inhibitor, had a positive effect on the patients and their partners and provided them with more confidence that they would have a successful encounter. Additionally, there were no dropouts in the combination group due to lack of efficacy. The VED, although typically covered by most insurance companies, is still orders of magnitude less costly than a full year's supply of a daily or every other day PDE5 inhibitor after a prostatectomy.

Limitations of this study include its small size and the fact that there was no control, or VED group, alone. The study was intended as a pilot trial only and was largely unfunded with VED patients receiving the device and instruction for its use free of charge. We don't feel this to be a limitation because most patients in the author's practice are able to receive the device predominantly

through insurance companies. However, the patients did not receive the PDE5 inhibitor for free. The lack of a control group does not invalidate the primary purpose of the study, which was to evaluate if addition of a VED to standard practice with a PDE5 inhibitor produced better results than the latter alone. While the number of subjects was small, there was a significant difference in all four treatment parameters between the tadalafil alone group and the tadalafil + VED group.

The current study suggests that addition of a VED to standard PDE5 therapy for ED after RP can improve the chances for more rapid return of sexual function when compared to the PDE5 inhibitor alone. Previous work showed that, in patients with ED in the absence of RP who failed to respond to a PDE5 inhibitor alone, sexual function was improved when a VED was added to the regimen.¹⁷ We believe that not only should a combination approach be considered mandatory for those realistically hoping to achieve sexual success within the first year after RP, but that combination regimens should be the sole focus of future penile rehabilitation research.

Conclusion

The addition of a VED to standard PDE5 inhibitor therapy (tadalafil) in men with ED subsequent to BNSRP resulted in a more rapid and complete return of sexual function compared to men who were taking the PDE5 inhibitor alone. Compliance was far superior for the VED. The use of a VED in conjunction with standard PDE5 inhibitor therapy should be considered for men recovering from ED subsequent to RP. □

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