

SILDENAFIL CITRATE AND VACUUM CONSTRICTION DEVICE COMBINATION ENHANCES SEXUAL SATISFACTION IN ERECTILE DYSFUNCTION AFTER RADICAL PROSTATECTOMY

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ABSTRACT

Objectives. To assess the effectiveness of combining sildenafil citrate with a vacuum constriction device (VCD) in men (after radical prostatectomy) unsatisfied with the results of the VCD alone.

Methods. A total of 31 patients unsatisfied with the early use of VCD alone after radical prostatectomy (mean follow-up of 4.5 months) were instructed to take 100 mg of sildenafil 1 to 2 hours before VCD use for sexual intercourse. Patients used combination therapy for a minimum of five attempts before assessment with the abridged International Index of Erectile Function (IIEF) questionnaire and a visual analogue scale to gauge rigidity. The effect of combination therapy on the total IIEF-5 score and penile rigidity score were assessed.

Results. Of the 31 patients, 7 (22%) had no improvement with the addition of sildenafil with VCD and discontinued the drug, and 24 (77%) reported improved penile rigidity and sexual satisfaction. The IIEF-5 score revealed statistically significant improvement in each domain, and patients reported that sildenafil enhanced their erections 100% of the time. The penile rigidity scores on a scale of 0 to 100 with the VCD alone averaged 55% (range 23% to 85%) for the men and 59% (range 26% to 90%) for their partners. With the addition of sildenafil, it increased to 76% for the men and 82% for their partners. Of the 24 men, 7 (30%) reported a return of natural erections at 18 months using combination therapy, with 5 of 7 reporting erections sufficient for vaginal penetration.

Conclusions. In this study, the addition of sildenafil with VCD improved sexual satisfaction and penile rigidity in patients unsatisfied with VCD alone after radical prostatectomy. *UROLOGY* 65: 360–364, 2005. © 2005 Elsevier Inc.

Although sildenafil citrate has been very successful in treating erectile dysfunction (ED), a vacuum constriction device (VCD) has been an important therapeutic option for patients who do not benefit from oral agents or cannot use them.¹ Although the use of an oral agent (sildenafil citrate) as a first-line agent is optimal, this option for pa-

tients after radical prostatectomy (RP) depends on the presence of one or both neurovascular bundles.^{2,3} Patients who have undergone a non-nerve-sparing procedure and those for whom oral therapy has failed require other options such as intracorporeal (IC) injections, a VCD, or medicated urethral system for erection. In addition, VCDs have been a standard option for ED of neurogenic, psychogenic, arteriogenic, or mixed vasculogenic etiology.

These devices have been used successfully in a variety of patients with organic ED, including those treated for prostate cancer with either RP or radiotherapy. Cookson and Nadig⁴ reported the long-term follow-up results for patients treated with VCDs. They reported long-term efficacy and patient satisfaction rates of more than 80%, with a statistically significant increase in the frequency of

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successful intercourse attempts in 79% of the patients using the device for 1 year that were maintained in 77% beyond the first year. However, despite this excellent satisfaction in this subset of patients, the overall dropout rate was 30% to 40%. The primary reasons for discontinuation were bruising and petechiae (5%), pivoting at the base of the penis (6%), coldness and numbness around the penis (5%), pain related to the VCD or the constriction band (10%), and a decreased ability to achieve orgasm using the device (10%).⁵

Turner and associates⁶ did a prospective comparison of IC of papaverine/phentolamine and external VCD in terms of usage rates, effectiveness, side effects, and impact on sexual and psychological functioning. Both treatments were efficacious and safely used by patients, although the dropout rates were greater for the group using IC injections (60% versus 20%). No statistically significant differences were found between the treatments in sexual or psychological impact.

Although IC injections can reproduce more natural and satisfactory erections, the efficacy is not 100% and the continued use of needles lends itself to a 40% to 60% noncompliance rate after 1 year.⁷ For these patients, a VCD may be a reasonable alternative. Gould and colleagues⁸ reported that 71% of patients who could not achieve satisfactory erections with IC injection subsequently achieved adequate rigidity and satisfactory erections with a VCD.

A recent area of interest is the use of combination therapy for ED after RP when individual therapies are ineffective. Because oral therapy has limited efficacy immediately after surgery, as well as in patients who undergo non-nerve-sparing RP, these subsets of patients must rely on the nonoral treatment options for ED. These treatments have limited compliance and high discontinuation rates, which can lead to a lack of interest in sexual rehabilitation. The management of ED with a combination of available treatment modalities appears to be synergistic in view of their different mechanisms of action. Also, combination therapy may avoid the need for invasive treatment modalities for ED in some patients.⁹

The present study was conducted to determine whether sildenafil can augment the treatment efficacy and response rate when used in combination with VCD for ED following RP.

MATERIAL AND METHODS

PATIENT SELECTION

The institutional review board approved this study, and all patients provided written informed consent. Of 450 sexually active patients undergoing RP (August 1999 to October 2001), 109 (31.7%) were subsequently randomized to use a VCD daily (with or without a constriction ring) to induce intracavernous pressure and tumescence three times weekly for 9

months (group 1, $n = 74$) or observation without any erectogenic treatment (group 2, $n = 35$). The 109 patients had a mean age 58.6 ± 5.8 years, prostate-specific antigen level less than 10 ng/mL, Gleason score of 6 or less, Stage T1-T2 disease, and baseline total International Index of Erectile Function, short form (IIEF-5; also called the Sexual Health Inventory of Men [SHIM]) score of 16 or greater. They were instructed to use the VCD device daily after catheter removal after RP without a constriction ring to induce corporeal engorgement.

Vacuum constriction device use began an average of 3.9 weeks (range 2 to 8) after surgery. These subsets of patients were younger (mean age 58.6 ± 5.8 years), sexually potent preoperatively (mean baseline total IIEF-5 score of 16 or greater), and had no comorbid condition (no coronary artery disease, hypertension, or diabetes mellitus). None of these patients had received preoperative or postoperative hormonal therapy or monotherapy. The VCDs used in this study were either manually or battery operated. The patients were given a training session by an experienced nurse practitioner in selecting and using the VCD. The constriction ring was applied when sexual intercourse was attempted.

In a multidisciplinary Prostate Cancer Clinic, we requested that all patients with prostate cancer complete the IIEF-15 questionnaire before (baseline, pretreatment within 3 months of screening) and after treatment as a part of their initial and routine follow-up evaluations. The 109 patients who agreed and signed the informed consent form to participate in the study were initially evaluated with a comprehensive sexual history, physical examination, and pertinent laboratory tests. All 109 patients had completed the IIEF-15 questionnaire in the office before (preoperative, baseline within 3 months of the screening), after (15 days postoperatively but before ED treatment), and at a mean interval of 9 months (range 6 to 12) after RP during their follow-up visits. All patients were followed up at 2 to 3-month intervals.

The average age of men contacted for follow-up was 58.6 ± 5.25 years. All patients included in the study had used their VCD, with a compliance rate of 80% (60 of 74). Nerve-sparing (unilateral or bilateral) RP had been done in 53 patients and non-nerve-sparing RP in 21 patients. Of the 74 patients, 60 (80%) continued treatment with the device (50 used a manual VCD, 6 used battery-operated devices, and 4 had tried both); 44 had undergone nerve-sparing RP and 16 had undergone non-nerve-sparing RP. Of the 74 patients, 60 (80%) had successfully used the VCD with a constriction band (one or two) for vaginal intercourse at a frequency of twice per week at 2.5 weeks to 7 months (mean 3.5 months) postoperatively, with a spousal satisfaction rate of 55% (33 of 60). The mean frequency of use was three times weekly.

Patients reported improved erectile function after using the VCD, with a statistically significant improvement in the mean IIEF-5 score to 16 ± 7.33 from a baseline pretreatment score of 4.8 ± 3.62 ($P \leq 0.05$). No statistically significant difference was found in the total IIEF-5 score or response to individual questions between the nerve-sparing and non-nerve-sparing groups ($P \geq 0.05$). Of the 60 men who continued treatment, 19 (32%) reported a return of natural erections at a mean interval of 9 months, with 10 patients (52%) having erections sufficient for vaginal penetration without erectile aid.

Of the 74 patients, 14 (18%) discontinued treatment. The reasons given for discontinuation were discomfort (55%), unable to get an airtight seal (8%), social inconvenience (17%), and penile bruising (20%). The mean interval at which the patients discontinued VCD was 2.5 months after starting the therapy. The patients who tried both battery and manual VCD did not seem to prefer one to the other.

Of the 74 patients, 31 (42%) were unsatisfied with their early use of the VCD alone after RP (mean follow-up 4.5 months) and were instructed to take 100 mg of sildenafil 1 to

TABLE I. Comparison of various variables in patients and partners using VCD and combination therapy of VCD plus sildenafil for ED after RP

Variable	VCD Alone	VCD Plus Sildenafil Citrate
Able to penetrate (%)	52	70
Patient rigidity score (0–100)	55	76
Partner rigidity score (0–100)	59	82
Spousal satisfaction (%)	55	64
Total IIEF-5 score	14.5 ± 5.63	18.5 ± 8.20
Return of nocturnal erections (%)	0	29 (7/24)

KEY: VCD = vacuum constriction device; ED = erectile dysfunction; RP = radical prostatectomy; IIEF = International Index of Erectile Function.

2 hours before VCD use for sexual intercourse. Patients used the combination therapy for a minimum of five attempts before assessment with the SHIM (IIEF-5) and a visual analogue scale to gauge penile rigidity. The effect of combination therapy on the total IIEF-5 score and penile rigidity score were assessed.

SURVEY AND DATA ASSESSMENT

The patients' responses were assessed using the IIEF-15 questionnaire.^{10,11} The scores were compared between those after treatment with the VCD alone and those after treatment with VCD plus sildenafil to determine the change in response using the Wilcoxon signed-rank test. Partner and spousal satisfaction were evaluated in parallel.

A second questionnaire (Post Prostatectomy Questionnaire) was used to determine the sexual satisfaction of the patients' spouse or partner.¹² The spouses/partners were specifically asked how often they were satisfied with intercourse and how often the patient was able to achieve and maintain an erection. This questionnaire was scored from 1 to 5 (1, never/occasionally; 2, less than one half the time; 3, sometimes/one half the time; 4, more than one half the time; and 5, almost always). Total spousal satisfaction was calculated from these questions and expressed as a percentage.

The data from the IIEF-15 questionnaire were condensed into the IIEF-5 questionnaire, which is an abridged five-item version of the IIEF-15 questionnaire, also referred to as the SHIM.^{10,11} The SHIM is a validated, multidimensional, self-administered questionnaire that is a sensitive indicator of changes in erectile function. It is scored from 1 to 5 (1, never/occasionally; 2, less than one half the time; 3, sometimes/one half the time; 4, more than one half the time; and 5, almost always). The total IIEF-5 score was calculated by totaling the response to all five questions.

STATISTICAL ANALYSIS

The data are presented as the mean values and percentages as summary statistics. The statistical method consisted of a comparison of scores using Wilcoxon tests. Statistical significance was assessed with a two-tailed test at $P < 0.05$. We used the Statistical Analysis Systems, version 8.1, software (SAS Institute, Cary, NC) for the computations.

RESULTS

Of the 31 patients who tried the combination therapy, 7 (22%) had no improvement with the addition of sildenafil to the VCD and discontinued the drug, and 24 (77%) reported improved penile

rigidity and sexual satisfaction. These 24 patients reported that the VCD and stimulation alone produced an erection that was firm enough for intercourse 80% of time; however, the intercourse was successful only 75% of the time without sildenafil enhancement. When the VCD and sildenafil were used together, all 24 patients reported that the VCD enhanced their erection 100% of the time. Intercourse was also successful 100% of the time with the combination. The rigidity scores on a scale of 0 to 100 with the VCD alone averaged 55% (range 23% to 85%) for the men and 59% (range 26% to 90%) for their partners. With the addition of sildenafil, it increased to 76% for the men and 82% for their partners. Spousal satisfaction increased from 55% with the VCD alone to 64% with use of VCD and sildenafil. Of these 24 patients, 7 (30%) reported the return of natural erections at 18 months using combination therapy, with 5 of 7 reporting erections sufficient for vaginal penetration (Table I). The IIEF-5 score showed statistically significant improvement in each domain (Table II).

COMMENT

In our earlier study, only 43 patients (58.1%) were satisfied with the VCD alone. Because of this considerable rate of unsatisfaction, we decided to consider combination therapy. The successful use of combinations of VCD with IC injections, transurethral prostaglandin E₁, psychotherapy, and even penile prosthesis has been previously reported.^{13–17} Therefore, we tried, in this study, a new combination of VCD and sildenafil to determine whether the latter can augment the treatment efficacy and response rate when used in combination with VCD in a subgroup of patients unsatisfied with the VCD alone.

The sildenafil success rate in RP patients has not been satisfactory with its early use, and its use in

TABLE II. Comparison of IIEF-5 score before and after surgery, after VCD use, and after sildenafil plus VCD use

IIEF-5 Questionnaire	Mean Score Before Surgery (n = 31)	Mean Score After Surgery (n = 31)	Mean Score After VCD Use Alone (n = 31)	Mean Score After Sildenafil Plus VCD Use (n = 31)
Maintenance ability, Q5	4.10 ± 0.65	0.99 ± 0.21	3.61 ± 1.41	3.80 ± 1.65
Erection confidence, Q15	4.33 ± 1.21	0.86 ± 0.21	3.24 ± 1.12	4.21 ± 1.56*
Maintenance frequency, Q4	4.76 ± 1.32	0.91 ± 0.32	2.64 ± 1.23	3.24 ± 1.60*
Erection firmness, Q2	4.81 ± 0.55	0.91 ± 0.22	2.38 ± 1.12	3.80 ± 1.62
Intercourse satisfaction, Q7	4.46 ± 0.65	1.11 ± 0.65	2.65 ± 0.75	3.60 ± 1.77
Total IIEF-5 score	22.5 ± 4.38	4.8 ± 1.61	14.5 ± 5.63	18.5 ± 8.20

Abbreviations as in Table I.
Data presented as mean ±SD.
* P <0.05 between after VCD use alone and VCD plus sildenafil use.

patients who undergo non-nerve-sparing RP is theoretically ineffective.^{2,3} However, some investigators have found it justifiable to use sildenafil in such patients, depending on its effect as mediated through the non-neuronal-nitric oxide pathway to produce tumescence enough to maintain the integrity of the cavernous tissue. They believe this will encourage patients in regaining sexual interest and activity early and thus enhance the chances of spontaneous recovery of erections and/or successful long-term therapy. McAuley and coworkers¹⁸ demonstrated, experimentally, that intracavernosal sildenafil has an erectogenic effect independent of the classic nitric oxide/cyclic guanosine monophosphate pathway. Furthermore, Medina and associates¹⁹ found that the relaxant effect of sildenafil on penile vessels involves, in addition to the nitric oxide-mediated relaxation, an inhibitory effect on noradrenergic contractions and on smooth muscle contractions.

In our study, the addition of sildenafil resulted in improved rigidity and satisfaction in 24 (77%) of 31 patients. This improvement was manifested in an improved IIEF-5 score from a mean of 14.5 ± 5.6 with a VCD alone to 18.5 ± 8.2 with a combination of a VCD and sildenafil. Furthermore, the penile rigidity improvement after adding sildenafil (76 versus 55) resulted in a greater penetration rate (70% versus 52%). Moreover, 7 (30%) of 24 men reported a return of natural erections after 8 months of combined use of VCD and sildenafil, and 5 of them could achieve erections sufficient enough for vaginal penetration.

The theoretical explanation of this successful combination relies on the findings of Kim and associates²⁰ that high oxygen tension is essential for the nitric oxide synthase activation whether neuronal or endothelial and that the low oxygen tension (as in the flaccid state) is associated with in-

hibited nitric oxide synthase. Improving the local cavernous blood oxygen tension by bringing more arterial blood through the VCD in effect allows adequate stimulation of nitric oxide synthase to produce nitric oxide and eventually cyclic guanosine monophosphate such that sildenafil can exert its action in improving the erection.

CONCLUSIONS

The findings of our study have shown that the combined use of a VCD and sildenafil is superior to the use of the VCD alone. This combination could salvage cases of ED not responding to VCD use and may enhance the chances of spontaneous recovery of erections in a subset of patients after RP. Oral therapy (sildenafil citrate) can augment treatment efficacy and compliance when individual therapy is ineffective.

REFERENCES

- Dutta TC, and Eid JF: Vacuum constriction devices for erectile dysfunction: a long-term, prospective study of patients with mild, moderate, and severe dysfunction. *Urology* 54: 891-893, 1999.
- Zippe CD, Raina R, Thukral M, *et al*: Management of erectile dysfunction following radical prostatectomy. *Curr Urol Rep* 2: 495-503, 2001.
- Raina R, Agarwal A, Mascha E, *et al*: Efficacy and factors associated with successful outcome of sildenafil citrate use following radical prostatectomy. *Urology* 63: 960-966, 2004.
- Cookson MS, and Nadig PW: Long term results with vacuum constriction device. *J Urol* 149: 290-294, 1993.
- Derouet H, Caspari D, Rohde V, *et al*: Treatment of erectile dysfunction with external vacuum devices. *Andrologia* 3: 89-94, 1999.
- Turner LA, Althof SE, Levine SB, *et al*: Twelve-month comparison of two treatments for erectile dysfunction: self-injection versus external vacuum devices. *Urology* 39: 139-144, 1992.
- Soderdahl DW, Thrasher JB, and Hansberry KL: Intracavernosal drug-induced erection therapy versus external vac-

uum devices in the treatment of erectile dysfunction. *Br J Urol* 79: 952–957, 1997.

8. Gould JE, Switters DM, Broberick GA, *et al*: External vacuum devices: a clinical comparison with pharmacologic erections. *World J Urol* 10: 68–70, 1992.

9. Chen J, Sofer M, Kaver I, *et al*: Concomitant use of sildenafil and a vacuum entrapment device for the treatment of erectile dysfunction. *J Urol* 171: 292–295, 2004.

10. Rosen RC, Cappelleri JC, Smith MD, *et al*: Development and evaluation of an abridged 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 11: 319–326, 1999.

11. Rosen RC, Riley A, Wagner G, *et al*: The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile function. *Urology* 49: 822–830, 1997.

12. Raina R, Lakin MM, Ausmundson S, *et al*: Long-term intracavernous (IC) therapy responders can potentially switch to sildenafil citrate after radical prostatectomy (RP). *Urology* 63: 532–538, 2004.

13. Chen J, Godschalk MF, Katz PG, *et al*: Combining intracavernous injection and external vacuum as treatment for erectile dysfunction. *J Urol* 153: 1476–1477, 1995.

14. Marmar JL, DeBenedictis TJ, and Prais DE: The use of a vacuum constrictor device to augment a partial erection following an intracavernous injection. *J Urol* 140: 975–979, 1988.

15. John H, Lehmann K, and Hauri D: Intraurethral prostaglandin improves quality of vacuum erection therapy. *Eur Urol* 29: 224–226, 1996.

16. Segenreich E, Israilov SR, Shmueli J, *et al*: Vacuum therapy combined with psychotherapy for management of severe erectile dysfunction. *Eur Urol* 28: 47–50, 1995.

17. Soderdahl DW, Petroski RA, Mode D, *et al*: The use of an external vacuum device to augment a penile prosthesis. *Tech Urol* 3: 100–102, 1997.

18. McAuley IW, Kim NN, Min K, *et al*: Intracavernosal sildenafil facilitates penile erection independent of the nitric oxide pathway. *J Androl* 22: 623–628, 2001.

19. Medina P, Segarra G, Vila JM, *et al*: Effects of sildenafil on human penile blood vessels. *Urology* 56: 539–543, 2000.

20. Kim N, Vardi Y, Padma-Nathan H, *et al*: Oxygen tension regulates the nitric oxide pathway: physiological role in penile erection. *J Clin Invest* 91: 437–442, 1993.