

Combination Therapy: Medicated Urethral System for Erection Enhances Sexual Satisfaction in Sildenafil Citrate Failure Following Nerve-Sparing Radical Prostatectomy

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ABSTRACT: The objective of our study was to assess the effectiveness of combining medicated urethral system for erection (MUSE) with sildenafil citrate in men unsatisfied with the sildenafil alone. Baseline and follow-up data from 23 patients (mean age, 62.5 ± 5.23 years) unsatisfied with the use of the sildenafil citrate alone for the treatment of erectile dysfunction following nerve-sparing radical prostatectomy (mean use, 4 attempts/100-mg dose) was obtained. All patients started oral sildenafil citrate more than 6 months after radical prostatectomy. Combination therapy was initiated using 100 mg sildenafil citrate orally 1 hour prior to intercourse. Patients used combination therapy for a minimum of 4 attempts prior to assessment with the Sexual Health Inventory of Men (International Index for Erectile Function-5) and visual analog scale to gauge rigidity (0–100). The effect of therapy on the total International Index for Erectile Function (IIEF) score and penile rigidity score was as-

essed. Of the 23 patients, 4 (17%) had no improvement with the addition of medicated urethral system for erection and discontinued the drug, while 19 (83%) reported improvement with the penile rigidity and sexual satisfaction. The IIEF scores of these 19 patients showed significant improvements in each sexual domain, and the patients reported that erection was sufficient for vaginal penetration 80% of the time. Rigidity scores on a scale of 0–100 with sildenafil alone averaged 38% (23–53) for men and 46% (26–67) for their partners. With the addition of MUSE, scores increased to 76% for men and 62% for their partners. We conclude that the addition of MUSE to sildenafil improved sexual satisfaction and penile rigidity in patients unsatisfied with sildenafil alone.

Key words: Erectile dysfunction, MUSE, intraurethral alprostadil.
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The advent of oral sildenafil has opened a new wave of enthusiasm in patients seeking noninvasive treatment for male erectile dysfunction (ED) following radical prostatectomy (RP). Unfortunately, the efficacy and outcomes determined in the general urology practice may not compare with the clinical trials conducted both with the healthy group and, subsequently, with patients with minimal and moderate ED. Sildenafil has been proven to be effective in patients with ED following RP; however, a certain subset of this population does not respond to sildenafil alone, even following nerve-sparing RP (NSRP). The precise reasons for this nonresponsiveness are not understood (Zippe et al, 2001), but these patients may benefit from combination treatments.

Although sildenafil citrate has been very successful in treating dysfunction, medicated urethral system for erection (MUSE) using alprostadil (prostaglandin PGE1) con-

tinues to be an important therapeutic option for patients with ED who do not benefit from oral agents or cannot use them. Because oral therapy has limited efficacy following surgery, as well as in patients who undergo a non-NSRP, many patients must rely on nonoral-treatment options for ED (Raina et al, 2004). A recent area of interest is the use of combination therapy for ED following RP when individual therapies are ineffective.

A combination treatment that acts through different pathways of erection (cyclic adenosine monophosphate [cAMP] mediated and cyclic guanosine monophosphate [cGMP] mediated) will have a synergistic effect and produce maximal response. Corpus cavernosum smooth muscle relaxation and penile erection are regulated, in part, by an increase in the smooth muscle synthesis of the second messenger cGMP. Phosphodiesterase-5 inhibitors, such as sildenafil, act indirectly and require sexual stimulation and endogenous nitric oxide production for efficacy, activating the cGMP pathway (Burnett, 1997). In contrast, agents such as PGE1 act directly on the trabecular smooth muscle, binding to specific receptors and increasing cAMP synthesis. Thus, combination therapy using both cAMP- and cGMP-mediated vasodilatation may

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be more efficacious in the salvage of patients who desire noninvasive therapy, but have not responded to single treatment modality alone (Montorsi et al, 2003).

In this study we have evaluated the effectiveness of MUSE-sildenafil combination therapy in patients who are unsatisfied with sildenafil citrate alone for ED following RP.

Materials and Methods

We obtained and reviewed the records of 470 preoperatively sexually active patients with localized prostate cancer who underwent RP (320 bilateral NSRP, 30 unilateral NSRP, and 120 non-NSRP) between July 1998 and January 2000. After a minimal follow up of 3 months, only 151 patients (32%) were able to have erections sufficient for vaginal penetration, and 319 (68%) had experienced severe ED. These 319 patients were not able to have erections sufficient for successful penetration, and their mean International Index for Erectile Function (IIEF-5; Sexual Health Inventory of Men [SHIM]) score had decreased from 19.65 (preoperative baseline) to 4.27 (3 months after RP). Of the 319 patients, 227 (71%) sought treatment for ED and were initially evaluated with a comprehensive sexual history, physical examination, and pertinent laboratory testing. The remaining 92 patients did not seek any treatment despite sexual counseling. Of the 227 patients, 174 (76%) preferred treatment with sildenafil citrate. None of the 227 patients had received pre- or postoperative hormonal therapy or radiotherapy. All patients started on oral sildenafil citrate >6 months after RP. Out of 174 patients, 100 responded to sildenafil and 74 were nonresponders (determined by IIEF-5 scores). Out of these 74 patients, 23 (who underwent bilateral NSRP) agreed to use a combination of sildenafil with MUSE. Baseline and follow-up data from these 23 (mean age, 62.5 ± 5.23 years) sildenafil citrate nonresponders (mean use, 4 attempts/100-mg dose) were obtained. Of the 23 sildenafil users, 10 were found to have comorbid diseases like hypertension ($n = 4$), diabetes ($n = 4$), and hyperlipidemias ($n = 2$).

Combination therapy was initiated using 100 mg sildenafil citrate orally 1 hour prior to intercourse and 500 μ g of MUSE intraurethral immediately before intercourse. A nurse practitioner trained all patients to self-administer transurethral alprostadil (PGE1; Vivus, Menlo Park, Calif) via a plastic applicator into the distal urethra using a sterile technique and, when possible, provided partner education. Each patient used combination therapy for a minimum of 4 attempts prior to assessment with the IIEF-15 (Rosen et al, 1997) and a visual analog scale to gauge rigidity (0–100). The effect of combination therapy on total IIEF-15 score and penile rigidity were assessed. If no response was noted following 500 μ g, MUSE was titrated to 1000 μ g.

The data from the IIEF-15 questionnaire were condensed into the IIEF-5 questionnaire. The IIEF-5 is a validated, multidimensional, self-administered questionnaire that is a sensitive indicator of changes in erectile function and treatment outcomes (Rosen et al, 1999). It is scored from 1 to 5 with 1 indicating never/occasionally; 2, less than one half of the time; 3, sometimes/one half of the time; 4, more than one half of the time;

and 5, almost always. The total IIEF-5 score was calculated by totaling the responses to all 5 questions.

In the questionnaire, all partners were directly asked about their sexual satisfaction, their partner's ability to achieve and maintain an erection, and their satisfaction with intercourse. This questionnaire was scored from 1 to 5, with 1 indicating never/occasionally and 5 indicating almost always. Total spousal satisfaction was calculated from these questions and expressed as a percentage.

Statistical Analysis

The data are presented as means and the percentages are presented as summary statistics. The methods consist of comparison of scores of the patients before and after treatment using mean values. The number of patients discontinuing treatment for multiple reasons was calculated as a percentage of the total. In addition to the Wilcoxon tests, χ^2 tests were used to compare categories. Four patients who did not respond to combination therapy were excluded from the final analysis. A 2-tailed significance level of $P < .05$ was used for statistical tests, and all tests were performed with SAS version 8.0 software (SAS Institute, Cary, NC).

Results

Of the 23 NSRP patients, 4 (17%) had no improvement with the addition of MUSE (even after increasing the dose to 1000 μ g) with sildenafil and discontinued the drug, while 19 (83%) reported improvement in penile rigidity and sexual satisfaction. In these 19 patients, the IIEF-5 score showed significant improvement in each domain, and patients reported that erections were sufficient for vaginal penetration 80% of the time. The baseline IIEF-5 score was 5.67 ± 1.61 . The IIEF-5 score increased to 18.6 ± 5.20 in patients with combination therapy compared with sildenafil alone (13.2 ± 5.78 ; Table 1). Rigidity scores on a scale of 0–100 with the addition of MUSE increased to 76% for men and 62% for their partners. Spousal satisfaction with sildenafil alone was 52%, which increased to 69% with combination therapy (Table 2).

The most common side effects reported with MUSE were urethral burning ($n = 3$) and urethral bleeding ($n = 1$). However, they were transient and none of the patients discontinued the treatment due to side effects.

Discussion

In this study, we evaluated the efficacy of transurethral alprostadil combination with sildenafil in salvaging sildenafil-alone nonresponders. A total of 23 patients who were unsatisfied with sildenafil alone following NSRP were started on combination therapy with MUSE and sildenafil. Our analysis revealed that combination treatment

Table 1. Comparison IIEF-5 before RP, after nerve-sparing RP, after sildenafil citrate use, and the combination of MUSE and sildenafil citrate*

IIEF-5 Questionnaire	Mean Score Before Surgery (n = 23)	Mean Score After Surgery (n = 23)	Mean Score After Sildenafil Citrate Use Alone (n = 19)	Mean Score After MUSE + Sildenafil Use (n = 19/23)	P
Maintenance ability, Q5	4.10 ± 0.65	0.99 ± 0.21	2.72 ± 1.30	3.80 ± 1.65	.067
Erection confidence, Q15	4.33 ± 1.21	0.86 ± 0.21	2.30 ± 1.29	4.21 ± 0.56†	.032
Maintenance frequency, Q4	4.76 ± 1.32	1.91 ± 0.32	2.67 ± 1.21	3.24 ± 1.60	.093
Erectile firmness, Q2	4.81 ± 0.55	0.91 ± 0.22	2.40 ± 1.30	3.97 ± 1.62†	.048
Intercourse satisfaction, Q7	4.46 ± 0.65	1.11 ± 0.65	2.47 ± 1.01	3.60 ± 1.77†	.041
Total IIEF-5 score	22.5 ± 4.38	5.67 ± 1.61	13.2 ± 5.78	18.6 ± 5.20	.057

* Data are means ± SD unless specified. IIEF-5 indicates International Index for Erectile Function; RP, radical prostatectomy; and MUSE, medicated urethral system for erection.

† P < .05 sildenafil alone vs MUSE + sildenafil citrate.

using MUSE and sildenafil was effective in 83% (19/23) of post-NSRP patients who did not respond to sildenafil alone. This improvement might be due to sildenafil and alprostadil, which promote erection by stimulating different pathways within the corporal smooth muscle. Our results were consistent with the response rate reported in the literature (Mydlo et al, 2000; Nehra et al, 2002). Nehra et al (2002) reported that in a study population of 28 patients (17 NSRP, 11 vascular), combination therapy with sildenafil and MUSE improved patient satisfaction and erections sufficient for intercourse after a follow up of 18 months. A preliminary study by Mydlo et al (2000) reported that 60 of 65 patients who failed with monotherapy responded to combination therapy, as shown by improvement in total IIEF scores (19.2 ± 1.8 vs 23.1 ± 2.0). A follow-up study conducted by the same authors reported that combination therapy showed an improved IIEF score (24.1) compared with sildenafil (19.8; baseline, 10.8 ± 1.1). Our study also showed a similar improvement in the IIEF-5 scores in patients receiving combination therapy compared with sildenafil alone. However, our

study population was exclusively limited to post-RP patients compared with the previously mentioned studies, which also included vascular and other systemic causes of ED. McMahon et al (1999) reported that in patients with vasculogenic ED, 47% of patients who did not initially respond to monotherapy with sildenafil or intracavernous PGE1 responded to the combination of both (McMahon et al, 1999). So, our study may be the first in which the role of MUSE in sildenafil nonresponders was evaluated in a post-NSRP population.

Of 23 patients, 19 (83%) reported an improvement in penile rigidity and sexual satisfaction. With the addition of MUSE, the rigidity score (on a scale of 0–100) increased to 76% from 38%, and the rate of successful vaginal penetration increased to 70% from 50%.

Sildenafil is a selective PDE5 inhibitor that produces smooth muscle relaxation by increasing cGMP (Goldstein et al, 1998). Efficacy of sildenafil ranges between 56%–89%, depending on the severity of ED. Our previous experience showed that the response to sildenafil depends on the nerve-sparing status, preoperative IIEF-5 score greater than/equal to 15, age of 65 years or younger, and interval from RP to drug use of more than 6 months ($P < .001$; Raina et al, 2004). Even in NSRP patients, a certain subset of patients have suboptimal responses to sildenafil. The reasons for suboptimal responses were still unclear. Combination therapy may be useful to salvage the sildenafil nonresponders. Commonly used agents are intracavernosal injections, vacuum erection device, and MUSE.

Alprostadil is a synthetic compound similar to PGE1 that produces relaxation of smooth muscle by stimulating cAMP synthesis directly in the cavernosal muscle. The overall efficacy rate of reported intraurethral alprostadil was 44% (Padma-Nathan et al, 1997), but subsequent studies could not confirm this finding (Zippe et al, 2001). Paolone reported that MUSE was effective in only 15%

Table 2. Comparison of various variables in patient and partner using sildenafil citrate and combination therapy of MUSE + sildenafil for ED following nerve-sparing RP*

Variables	Sildenafil Alone	MUSE + Sildenafil Citrate
Able to penetrate (%)	52	70
Patient rigidity score (0–100)	38	76
Partner rigidity score (0–100)	46	62
Total mean IIEF-5 score	12.17	18.67
Erection firmness	2.40 ± 1.30	3.97 ± 1.62†
Ability to maintain erection	2.72 ± 1.30	3.80 ± 1.65
Satisfactory intercourse	2.47 ± 1.01	3.60 ± 1.77†
Spousal satisfaction (%)	52	69

* ED indicates erectile dysfunction.

† P < .05 sildenafil alone vs MUSE + sildenafil citrate was considered significant (Student's t test was used).

of patients who underwent pelvic surgery (Zippe et al, 2001). MUSE alone has only moderate efficacy in treating ED, and repeated applications are necessary to achieve the desired effect, which contributes to high drop-out rates (Khan et al, 2002). MUSE was reported to be less successful when used alone in patients with ED. Khan et al (2002) reported that intracavernous alprostadil is more effective than MUSE, but intracavernous therapy was associated with high discontinuation rates (Porst et al, 1997).

Porst et al (1997) observed that cAMP can inhibit PDE-5 activity in vitro. Kim et al (2000) reported that treatments that increase cAMP enhance cGMP synthesis in human cavernosal smooth muscle cells (Kim et al, 2000). Repeated intracavernous PGE1 injections have been reported to up-regulate NO synthase expression in animal models (Escrig et al, 1999). An increase in cAMP is also shown to dampen the adrenergic receptors, which may be useful as these patients are more anxious with the failure of initial therapy (Traish et al, 2000). This mechanism may be the possible reason for MUSE combination being effective in salvaging the sildenafil failure cases in our study. A study by Chen et al (2004) showed that the combination of sildenafil and a vacuum device was effective in nonresponders. However, vacuum compression devices are found to be cumbersome to use, which causes high discontinuation rates. Recently, Mydlo et al (2005) reported that the use of combination treatment with intracavernosal injections led to improved erectile function in 68% of patients (22/32) who had suboptimal responses to sildenafil-vasodenafil monotherapy. This study showed that intracavernosal injections are also useful options to salvage patients who failed on oral treatments alone (Mydlo et al, 2005). However, high discontinuation rates are always a major concern with IC injection treatment.

So, MUSE combined with the sildenafil combination can be useful in sildenafil-alone nonresponders because they act through different mechanisms and augment each other, which produces a higher success rate in the management of ED. Our results need to be confirmed by further randomized studies including 3 parallel groups (ie, sildenafil alone, MUSE alone, and combination treatment). However, our study can provide an important option for physicians to salvage sildenafil nonresponders following RP.

Conclusion

In our study, patients unsatisfied with oral sildenafil alone responded to combination treatment with MUSE and sildenafil, with significant improvement in IIEF-5 scores and spousal satisfaction. Although oral therapy is the first option for ED following RP, the combination therapy of

MUSE and sildenafil is more effective in the salvaging of patients who are unsatisfied with sildenafil alone. The MUSE-sildenafil combination is well tolerated, with good patient and partner satisfaction following RP.

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