

The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity

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Accepted for publication 17 May 2007

Study Type – Therapy (case series)
Level of Evidence 4

OBJECTIVE

To assess whether early introduction of the Medicated Urethral System for Erection (MUSE™, Vivus Inc., Mountain View, CA, USA) after radical prostatectomy (RP) results in a shorter recovery time for the return to functional erections and successful sexual activity.

PATIENTS AND METHODS

In a prospective study of 91 sexually active men who had a nerve-sparing RP for prostate cancer, 56 were treated with MUSE (125 or 250 µg three times per week for 6 months) while the remaining 35 had no erectogenic aids, except as necessary when attempting

sexual activity. Self-administration of MUSE was initiated ≈3 weeks after RP. Treatment efficacy was analysed by the patient's response to the Sexual Health Inventory for Men (SHIM) questionnaire.

RESULTS

The mean patient age was ≈59 years and the median follow-up 6 months; the compliance rate was 68%. Patients reported a significant improvement in all domains of the SHIM questionnaire after using MUSE. At the end of 6 months 74% of the patients who remained on MUSE were able to have successful vaginal intercourse. Of patients who completed the 6-month course of MUSE, half were able to have successful vaginal intercourse by the end of treatment. Most of these patients reported the recovery of spontaneous erections and required no additional erectogenic aids for successful intercourse. They had a mean SHIM

score of 18.9. All 56 patients who received MUSE reported mild penile aching or urethral burning, and of these, 32% discontinued treatment. In the untreated control group, 37% regained erections sufficient for vaginal intercourse at the 6-month follow-up, with a mean SHIM score of 15.8. Of the control patients who recovered penile function, 71% were dissatisfied with the quality of their erections and sought adjuvant therapy.

CONCLUSIONS

Initiating MUSE shortly after RP is safe and tolerable, and appears to shorten the recovery time to regain erectile function.

KEYWORDS

alprostadil, radical prostatectomy, early rehabilitation, erectile function, MUSE

INTRODUCTION

Oral phosphodiesterase type 5 inhibitors such as sildenafil citrate has become standard treatment option for erectile dysfunction (ED). However, they are contraindicated in some patients and are ineffective in others; patients who have had a radical prostatectomy (RP) generally belong to the second category [1]. In these patients standard treatment options like vacuum constriction devices (VCDs), intracavernosal injections (ICIs) and transurethral alprostadil (prostaglandin E1) remain the mainstay of treatment. Intraurethral alprostadil (Medicated Urethral System for Erection; MUSE™, VIVUS, Inc., Mountain View, CA, USA) is a prostaglandin E1 derivative reported to be effective for treating ED. Costabile *et al.* [2] reported that the

response to MUSE was 70% in the office setting, compared to a 57% success rate when used at home.

Bilateral nerve-sparing RP is common for organ-confined localized prostate cancer. Even after nerve-sparing surgery a temporary period of neuropraxia is inevitable, during which patients will have no spontaneous erections and that might predispose them to penile hypoxia. This period of neuropraxia is variable, at 9–24 months [1]. Theoretically, early pharmacological intervention after RP can maintain vascular perfusion of the corpus cavernous and subsequently inhibit corporeal hypoxia and fibrosis. Recently, Montorsi *et al.* [3] reported that early ICIs of alprostadil soon after a RP led to an earlier recovery of spontaneous erections.

These studies opened a new era of interest for the role of local treatment with alprostadil for restoring erectile function after RP. As oral therapy has limited efficacy soon after RP alprostadil might be useful as a treatment for men after RP during the recovery from temporary ED. Therefore, we conducted the present study to determine whether early pharmacological intervention with MUSE after RP can restore nocturnal erections and facilitate early sexual activity.

PATIENTS AND METHODS

The Cleveland Clinic Institutional Review Board approved this study, and written informed consent was obtained from all patients. We obtained and reviewed the records of 165 men with localized prostate cancer who were sexually active before RP

and who had a nerve-sparing RP between August 2002 and October 2004. The baseline evaluation comprised an assessment of sexual function using a comprehensive sexual history, and patients completed the Sexual Health Inventory for Men (SHIM, an adaptation of the International Index of Erectile Function). None of the patients were able to have erections sufficient for vaginal penetration and had severe ED; their mean SHIM score had decreased from 19.65 (baseline before RP) to 4.27 (2 months after RP). All these men had nerve-sparing RP (PSA level <10 ng/mL, Gleason score ≤6, tumour stage T1-T3) by the same surgeon (C.Z.). The mean (SD) age of the patients was 55.6 (3.78) years; they were sexually potent before RP, with a mean baseline SHIM score 22 (4.27). Of the 165 patients, 121 (71%) sought treatment for ED and were initially evaluated with a comprehensive sexual history and physical examination and pertinent laboratory testing. The remaining 44 patients sought no treatment despite sexual counselling. At that time the patients were offered standard ED treatments, including a VCD, ICIs, MUSE and oral therapy with sildenafil citrate. Of the 121 patients, none of the 121 had received hormonal therapy or radiotherapy before or after RP; 12 preferred treatment with sildenafil citrate; 32 (14%) chose ICIs and 21 (10%) agreed to try a VCD. The patients who tried standard treatment with a VCD and ICIs had not tried sildenafil citrate for ED after RP. The 21 patients who tried a VCD had enrolled in our earlier VCD trial in an attempt to encourage early sexual activity and prevent veno-occlusive dysfunction after RP. Of the 32 patients who chose ICIs, 10 did so because they were receiving oral nitrate treatment for cardiovascular disease and sildenafil treatment was contraindicated. Fifty-six patients agreed to try early treatment with MUSE three times per week at a mean of 12–15 days after catheter removal.

Patients who participated in the early penile rehabilitation study were initially evaluated by physical examination, laboratory evaluation and a comprehensive sexual history questionnaire. Patients were trained by an experienced nurse practitioner (S.A.) in using MUSE, and all partners were educated. All patients who agreed to participate in the early penile rehabilitation program were encouraged to use MUSE at least twice before RP to familiarise themselves with the application technique.

All 56 patients who agreed to early treatment after RP were asked to use 125 µg of MUSE three times per week for 9 months; the treatment began 3 weeks after RP. The baseline SHIM score was obtained before surgery and then 3 weeks after RP, before starting MUSE. After 4 weeks of treatment patients returned to the clinic to complete the SHIM again and to titrate to a dose of 250 µg of MUSE. If the patients tolerated the higher dose they were instructed to remain on 250 µg of MUSE at least three times weekly; if there was significant local discomfort with the 250 µg dose, the patient remained on the 125 µg dose for the duration of the study. At the end of 0, 3, 6 and 9 months of treatment patients again returned to the clinic and completed the SHIM questionnaire.

For comparison with the untreated group, 35 of 44 patients who sought no early treatment to facilitate their recovery were matched in age, cancer staging and pre-morbid condition, and served as controls. Of the remaining nine patients, after subsequent counselling, five tried early VCD, two early ICIs and two agreed to use sildenafil citrate for early penile rehabilitation; there was no randomization. The remaining 35 patients agreed to follow the natural progression of return of sexual function and preferred to use no erectile aid. A further survey assessing the reasons why these 35 patients did not try other erectogenic agents showed that 20 were more concerned about a complete biochemical recovery and cancer-free survival than ED, which they thought could be assessed later; five were reluctant to use early treatments, as they were not sure about the risks and benefits, and declined, there were no significant reports available at the time; 10 had other comorbid factors (diabetes mellitus, coronary artery disease and hypertension) and were concerned about cancer survival, wishing to use an erectile aid only 'on-demand' rather than daily as a prophylactic measure.

All 35 patients were concerned about their prostate cancer survival rate and thought that the quality-of-life issues like ED and incontinence were not their main concerns. Interestingly, this subset of patients preferred on-demand treatment for ED rather than prophylactic treatment for 9 months. Almost all were reluctant to use any early prophylactic treatment because there were no reports available; the men were also followed in the clinic at 0, 3, 6 and 9 months.

The patients' response to MUSE was assessed using the SHIM questionnaire, assessed before and after RP at regular intervals (0, 3, 6 and 9 months). The control group also completed the questionnaire at same intervals. The SHIM is a validated, multidimensional, self-administered questionnaire that is a sensitive indicator of changes in erectile function [4,5]. The SHIM is scored from 1 to 5, with the scores indicating: 1, never or occasionally; 2, less than half the time; 3, sometimes/half of the time; 4, more than half of the time; and 5, almost always. Baseline SHIM scores were compared to those obtained after treatment with MUSE to determine the change in response. The return of natural erections and erections sufficient for vaginal intercourse, and the reasons for drug discontinuation, were also assessed.

A second questionnaire, The Cleveland Clinic Post Prostatectomy Questionnaire, was used to determine the sexual satisfaction of the partners. The partners were 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, with the scores indicating: 1, never or occasionally; 2, less than half the time; 3, sometimes/half of the time; 4, more than half of the time; and 5, almost always. Total partner satisfaction was calculated from these questions and expressed as a percentage. At the sample times, data on the number of attempts at intercourse, and the number of successful attempts of vaginal penetration, were also collected. Natural erections sufficient for intercourse were considered an endpoint of the study.

An algorithm for determining potency was devised to assess the patients' status before treatment; data are presented as the mean (SD) or percentage, as summary statistics. Scores were compared before and after MUSE treatment (or no treatment) using the Wilcoxon signed-rank test; partner/satisfaction was evaluated in parallel. The numbers of patients discontinuing treatment for several reasons were calculated as a percentage of the total. In addition to the Wilcoxon test, chi-square tests were used to compare categories. Statistical significance was assessed with a two-tailed test at $P < 0.05$.

RESULTS

The mean follow-up for all 91 patients (mean age 59 years) was 9 months; all had ED after

TABLE 1 Early MUSE treatment after RP; SHIM scores for the 38 of 56 men who completed early prophylactic treatment for 9 months

Mean (SD) score for:	Before RP	After RP	After MUSE
No. of men	21	21	21
SHIM Questionnaire			
Q5, Maintenance ability	4.06 (1.1)	1.42 (0.51)	3.42 (0.50)*
Q15, Erection confidence	4.60 (0.60)	1.42 (0.64)	3.67 (0.49)
Q4, Maintenance frequency	4.33 (1.05)	1.35 (0.74)	3.83 (0.72)
Q2, Erection firmness	4.20 (0.94)	1.28 (0.72)	3.92 (0.79)*
Q7, Intercourse satisfaction	4.26 (0.884)	1.28 (0.72)	4.08 (0.66)*
Total mean score	21.46 (3.22)	6.78 (2.72)	18.92 (2.27)*

*P < 0.05 before vs after MUSE, considered significant, Wilcoxon signed-rank test.

RP. Overall, 68% (38/56) of patients using MUSE completed the 9-month treatment schedule, with the median frequency of drug use being 2–3 times a week. In this compliant group there were no differences in response between those who used 125 µg or 250 µg of MUSE.

At the end of 9 months, 28/38 (74%) men using MUSE who finished the study were capable of having successful vaginal intercourse, with a corresponding partner satisfaction rate of 67%. Of these 28 men, 21 (75%) reported the recovery of spontaneous erections sufficient for satisfactory intercourse (mean SHIM score ≥ 18 'almost always'). Of those who reported spontaneous nocturnal erections, 15 (71%) require no adjuvant therapy (MUSE) for intercourse in more than half of their attempts at intercourse, with a mean SHIM score of 18.9 (Table 1). These patients used MUSE for sexual activity only once in every 3.8 (3–6) attempts, while the remaining six (29%) required MUSE for sexual activity in more than half of their attempts at intercourse. The duration of erections after using MUSE was 5–12 min. Overall, in the MUSE group, half (28/56) of the men had successful vaginal intercourse with or without erectile aids. In patients who continued to use MUSE, 15 or 38 (40%) reported having natural erections sufficient for vaginal intercourse.

Patients under observation only were followed for 9 months after RP, with no treatment except for adjuvant therapy, if necessary, when they were planning sexual activity. Of the 35 men in this group, 13 (37%) reported some return of erectile function, with four of the 13 requiring no adjuvant

treatment, and the remaining nine needing some type of adjuvant therapy for successful intercourse. In the 13 patients who were able to have intercourse, the mean SHIM score was 15.8 and the partner satisfaction rate was 54%. Overall, in the control group, 13 of 35 (37%) had successful vaginal intercourse with or without erectile aids, and four (11%) had natural erections sufficient for vaginal intercourse.

In the 56 men treated with MUSE, 18 (32%) discontinued therapy before the end of the 9-month treatment period (mean use 4 months). Reasons stated for discontinuing included lack of efficacy or insufficient erections in nine, reduced sexual interest in five and urethral pain and/or burning in four.

DISCUSSION

RP is considered the standard treatment for organ/specimen-confined prostate cancer. While improved surgical techniques have reduced the incidence of RP-associated urinary incontinence to <10% most patients still have ED [6,7]. The rate of erectile function after RP by experienced surgeons at centres of excellence is reported to be 40–85% [8,9], but for men treated by most other urologists the rate of return to erectile function is 9–40% [7,9–11].

The cause of ED after RP is hypothesized to be hypoxia of the cavernosal bodies as a result of the vascular and/or nerve damage [3,12]. While a temporary period of hypoxia is inevitable even in nerve-sparing surgery, because the period required for the recovery is 6–24 months [9,13,14], the spontaneous

recovery of erectile function is much less common in men who have had a non-nerve-sparing technique [15].

Currently sildenafil is the commonest pharmacological treatment prescribed to provide erections sufficient for intercourse in men who have had RP. Sildenafil appears to work in men with intact neurovascular bundles [16,17], but is much less effective in men who have had a non-nerve-sparing RP [18]. Even so, an interval of ≥ 12 months after RP appears to be required for patients to respond to sildenafil [19,20].

The treatment of patients with MUSE after RP was reported to improve penile function. Costabile *et al.* [2] reported a 70% response rate in men with ED after RP when treatment was administered in an office setting, and a 57% success rate when used at home. In the present study MUSE was well tolerated, with a compliance rate of 68%, compared to previously reported series which had compliance rates of only 44%. Interestingly the major reasons for discontinuation were insufficient erections, with urethral pain/burning in a minority of patients.

The hypoxia associated with RP is hypothesized to result from reduced blood flow in the corpus cavernosum, producing local fibrosis [3,21,22]. Fibrosis will further reduce blood flow as a result of decreased smooth muscle relaxation. It is possible that procedures that increase blood flow, and therefore decrease hypoxia, in the period soon after RP could decrease or prevent fibrosis, allowing for a more rapid return to spontaneous or at least erections induced with erectogenic aids. Prostaglandin E₁ or alprostadil, the active ingredient in MUSE, is a potent vasodilator and a potential candidate for improving blood flow after RP.

Such penile rehabilitation has been advocated by several authors; Montorsi *et al.* [3] reported a more rapid recovery of spontaneous erections in men who used early ICIs three times weekly, starting 1 month after a nerve-sparing RP. At 3 months 67% of men reported full recovery, compared to only 20% of patients who were untreated. Gontero *et al.* [12] reported that IC alprostadil, initiated within the first 3 months after a nerve-sparing RP, was associated with a more rapid return of penile tumescence. In the present study, compared to no treatment, patients treated with 125 or 250 µg of MUSE three

times weekly had a faster recovery, as shown by a quicker return of spontaneous erections. In men who completed the 6-month course of therapy, half were able to have successful vaginal intercourse by the end of treatment. Most of these patients reported the recovery of spontaneous erections and required no additional erectogenic aids for successful intercourse. These men had a SHIM score of ≈ 19 at the end of the study. The 40% recovery of spontaneous erections after RP is comparable to the results of the small series by Montorsi *et al.*

In men who had no treatment during the 6-month study period, except as needed for intercourse, about a third reported some return of erectile function, a lower rate than in the group treated with MUSE. Further, the percentage of men in this group who required erectogenic aids for intercourse was much higher, at 69% vs 29% for men treated with MUSE. The SHIM score in the untreated men was 15.8, also lower than in men treated with MUSE. These results show that early pharmacological treatment not only improves the early return of natural erections, but also an earlier return of sexual activity, that will have a positive effect on patient satisfaction and quality of life.

While initial clinical results reported in early 1997 showed an advantage for early ICIs [3], no confirmatory studies followed, due to the lack of patient compliance (pain and fear of needles). Similarly, poor patient compliance using early penile injections led us to consider other early options such as the VCD and MUSE. Our clinical data using a VCD were promising, with all patients returning to sexual activity and 32% having some return of natural erections, but disappointing in that only 17% had a return of natural erections [23] sufficient for vaginal intercourse. Our clinical data using early MUSE were promising, in that 74% of patients resumed sexual activity, 55% had some return of natural erections and 40% had return of erections sufficient for vaginal intercourse [23]. However, this response was still suboptimal as at 6 months, 60% of patients were still dependent on erectile aids to achieve sexual intercourse [3,23]. While early daily sildenafil appears to improve natural erections, it does not promote early sexual activity [24]. Recent data using early daily sildenafil showed a significant advantage, with a return of natural erections at 11 months (27% vs 4%), but again 73% of

men were still unable to have sexual intercourse at 1 year [24]. When entered into a rehabilitation programme, many uncontrolled factors, including personal relationships, other health issues and simply variations in commitment and motivation for the rehabilitation, all promote patients to continue the involvement in treatment arms.

In conclusion, we showed that starting MUSE treatment soon after RP speeds the recovery of penile function. Whether this is due to alprostadil-induced improved blood flow to the corpus cavernosum is unknown. However, the data suggest that early intervention with MUSE might significantly improve erectile function sooner after RP than orally available agents.

ACKNOWLEDGEMENT

The authors thank Ms. Amy Moore for scientific editing and Mrs. Robin Verdi for secretarial assistance.

CONFLICT OF INTEREST

None declared.

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Abbreviations: ED, erectile dysfunction; RP, radical prostatectomy; VCD, vacuum constriction device; ICI, intracavernosal injection; MUSE, Medicated Urethral System for Erection; SHIM, Sexual Health Inventory for Men.