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

Rupesh Raina*, Geetu Pahlajani, Ashok Agarwal and Craig D. Zippe

Glickman Urological Institute, Cleveland Clinic, and *Department of Internal Medicine and Paediatrics, Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio, USA

Accepted for publication 17 May 2007

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 have 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.
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, stage (T1-T3) by the same surgeon (C.Z.). All 56 patients who agreed to early treatment and were initially evaluated with a comprehensive sexual history and physical examination and pertinent laboratory testing. The remaining 44 patients sought treatment for ED and were initially evaluated with a comprehensive sexual history using a 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...
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 E, 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

| 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.
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 \( \approx 19 \) 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.

REFERENCES


Correspondence: Craig D. Zippe, Glickman Urological Institute at Marymount, Cleveland Clinic, 12000 McCracken Road., Suite 451, Garfield Hts., OH 44125, USA. e-mail: zippec@ccf.org

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.