

Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis

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Baseline and follow-up data of 54 patients from a single surgical series (1998–2001), who used medicated urethral system for erection (MUSE) for the erectile dysfunction (ED) associated with radical prostatectomy (RP), were obtained. Patients were surveyed using the abridged five-item version of the International Index of Erectile Function (IIEF) questionnaire, commonly referred to as the Sexual Health Inventory of Men (SHIM), to determine presence and severity of ED and efficacy of ED treatment modalities. The mean patient age was 63.7 ± 5.6 y and the mean follow-up period was 2.3 ± 1.2 y. All patients experienced ED for at least 6 months after their surgery before starting MUSE therapy. Overall, 55% of the patients achieved and maintained erections sufficient for sexual intercourse while on MUSE and 48% continued long-term therapy with a mean use of 2.32 ± 1.2 y. The mean presurgery SHIM score in these patients was 19.2 ± 1.3 , which decreased to 5.2 ± 0.5 after surgery and increased to 16.3 ± 1.3 after MUSE treatment. A total of 28 patients (52%) discontinued treatment after a mean use of 8 ± 1.4 months. The reasons for discontinuation were insufficient erections ($n = 16$, mean SHIM score of 10.5 ± 4.4), switch to other ED therapies ($n = 4$), natural return of erections ($n = 4$) and urethral pain and burning ($n = 4$). Excluding the patients ($n = 8$) who preferred other therapies and return of natural erections, the compliance to MUSE was 63%. There were no significant differences in the IIEF-5 responses between the patients who had a nerve-sparing technique ($n = 34$) and those who did not ($n = 20$) or among patients who used different doses (250, 500 or 1000 µg) of MUSE. The results of the current trial indicate that MUSE is a successful treatment option in RP patients with established ED. It appears that a post-treatment SHIM score of ≥ 16 defines a successful outcome with MUSE therapy.

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Introduction

Although sildenafil citrate has been very successful in treating erectile dysfunction (ED), medicated urethral system for erection (MUSE) using alprostadil (prostaglandin-PGE1) continue to be an important therapeutic option for patients who do not

benefit from oral agents.¹ While the use of an oral agent (sildenafil citrate) as a first-line agent is optimal, this option in postprostatectomy patients depends on the presence of one or two neurovascular bundles.² Patients who have had non-nerve-sparing procedures and those who have failed oral therapy will require other options such as intracorporeal (IC) injections, vacuum constriction device (VCD) or MUSE (transurethral insertion of alprostadil (PGE1)).^{1,3} In addition, MUSE is also an option for treatment of ED of neurogenic, psychogenic, arteriogenic or mixed vasculogenic causes.^{3,4}

A number of studies have documented the successful treatment of ED with MUSE. Padmanathan *et al*⁵ reported that 65.9% of men achieved erections sufficient for intercourse after transurethral alprostadil was administered in a clinical

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setting. Fulgham *et al*,⁶ however, reported only a 30% response rate to transurethral alprostadil and the reason for this discrepancy is not known.

Costabile and associates were among the first to examine the effects of transurethral alprostadil in men with ED after radical prostatectomy (RP). The response in the office setting was 70%, compared to a 57% success rate at home.⁷ Subsequent investigations could not confirm these initially favorable results and reported significant urethral pain and burning.

Recent work by Montorsi *et al* in RP subjects demonstrated that early postoperative IC alprostadil injections may limit the development of hypoxia-induced tissue damage and produced an overall improvement in the recovery of spontaneous erections. This study opened a new area of interest regarding the role of local treatment with alprostadil in restoration of erectile function subsequent to RP.⁸ Since IC alprostadil injections are often painful in the early postoperative period and oral therapy has a limited role in the postoperative period, intraurethral alprostadil may have a role as an early treatment option in postprostatectomy patients.^{1,2}

The existing literature contains no reports on the long-term effects and sustainability of MUSE for ED following RP. We conducted the current study to evaluate the long-term efficacy of and compliance to MUSE in a post-RP population and to document the reasons for its discontinuation. We also sought to determine whether the efficacy of MUSE in postprostatectomy patients is affected by preservation of the neurovascular bundles during surgery or by the dose used.

Materials and methods

Patients

The Cleveland Clinic Institutional Review Board approved this study, and written informed consent was obtained from all patients. We obtained and reviewed the surgical records of a single surgeon (CZ) (April 1997 to October 2000) who performed radical prostatectomies on 450 sexually active patients with localized prostate cancer. With a mean follow-up of 9 months (6–12 months), 68% (306/450) patients experienced severe ED defined as inability to achieve vaginal penetration. All 306 patients who sought treatment for ED were initially evaluated by a comprehensive sexual history and physical examination and further evaluated by laboratory investigations like blood glucose and testosterone levels, etc., as guided by clinical findings. Patients were encouraged to use one of standard ED treatments, which included VCD, intracavernous (IC) or MUSE and oral therapy with

sildenafil citrate. Of the 306 patients, 54 (18%) chose MUSE therapy.

We retrospectively stratified these 54 patients according to the type of nerve-sparing (NS) RP procedure they had undergone. The surgeon recorded the anatomic status of the neurovascular bundle at the time of surgery; no intraoperative function tests were performed. The type of NS procedure was confirmed by reviewing operative records.

Drug therapy

In monitored clinical setting, patients received 250, 500 or 1000 µg of the drug. The patients started with a 250 µg dosage and were retested with 500 or 1000 µg dose, if they did not achieve the desired level of rigidity. Patient training was conducted by an experienced nurse practitioner during two to three office visits and consisted of selection of an appropriate vasoactive transurethral alprostadil (PGE1) (MUSE; Vivus, Menlo Park, CA, USA) agent, dose titration, patient education regarding sterile technique and partner education. In some cases, the spouse or sexual partner performed the MUSE if the patient was unable or unwilling to do so. Patients were routinely instructed to titrate their drug dosage to ensure effectiveness. All patients were followed at 6- to 9-month intervals.

Survey and data assessment

The patients' response to MUSE was assessed using the International Index of Erectile Function (IIEF-15) questionnaire.^{9,10} To be included in the study, participants must have completed the office training and IIEF-15 questionnaire, and reported satisfactory home use. Men were excluded if they received preoperative or postoperative hormonal therapy, radiation therapy or any concurrent form of therapy for ED.

A second questionnaire (The Cleveland Clinic Post Prostatectomy Questionnaire (CCPPQ)) was used to determine the sexual satisfaction of the patients' spouses/partners. 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. The median scores for each group from 1 to 5 (1 = never/occasionally; 2 = less than half of the time; 3 = sometimes/half of the time; 4 = more than half of the time; and 5 = almost always) have been reported. Overall percentage of the spouses/partners responded ≥ 3 (more than half of the time) on a Likert scale of 1–5 were considered positive and results were converted to a continuous variable

scale using percentage. Thus, the total spousal satisfaction was calculated as a percentage of spouses/partners responded positively to the CCPQ (1&2) questionnaire.^{1,2}

Patients completed the IIEF-15 questionnaire⁹ in office before (preoperative, baseline) and at a mean interval of 9 months (6–12 months) after RP surgery during their follow-up visit. Both surveys were mailed to the 54 patients and their respective spouses/partners. At this time, we also performed a retrospective chart review to collect data on treatment effect, frequency of use, duration of erection following MUSE application and side effects. All 54 patients answered IIEF-15 questionnaire⁹ and their spouses/partners completed the corresponding spousal questionnaires.²

Data from the IIEF-15 questionnaire⁹ were condensed into the IIEF-5 questionnaire,¹⁰ which is an abridged five-item version of the IIEF-15 questionnaire, referred to as the Sexual Health Inventory of Men (SHIM). 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 half of the time; 3=sometimes/half of the time; 4=more than half of the time; and 5=almost always. The total IIEF-5 score was calculated by totaling the response to all five questions.^{9,10}

Statistical analysis

The patients were retrospectively stratified according to the type of NS procedure they had undergone: bilateral NS, unilateral NS or non-NS. The type of surgical procedure was determined by a chart review and confirmed by the questionnaire. Skewness and kurtosis were used as statistical tests to evaluate the distribution of the results. The Wilcoxon's signed-rank test was used to compare baseline IIEF-5 (SHIM) scores before surgery, before treatment and after treatment to determine changes in response. The χ^2 test was used to compare categories (NS vs non-NS). The number of patients discontinuing treatment for multiple reasons was calculated as a percentage of the total. The data are presented using mean, standard deviation and percentages. A two-tailed significance level of $P \leq 0.05$ was used for all statistical tests, and all tests were performed with SAS version 8.0 software.

Results

The mean follow-up period of all the patients was 2.3 ± 1.2 y and mean patient age was 63.7 ± 5.6 y. NS (unilateral or bilateral) RP was performed in 34

patients (62.5%) and non-NS procedures were performed in 20 (37.5%) patients. All of the patients experienced ED for at least 6 months after their surgery before starting MUSE therapy. The mean presurgery SHIM score in these patients was 19.2 ± 1.3 , which decreased to 5.2 ± 0.5 after surgery and increased to 16.3 ± 1.3 post-MUSE treatment (Table 1). Furthermore, the total mean SHIM score after MUSE use was similar to the total presurgery mean score $P \geq 0.05$. There were no statistically significant differences in the SHIM (IIEF-5) responses between the type of RP surgery (NS (bilateral NS, unilateral NS) ($n=34$) and non-NS ($n=20$)) groups (Table 2) and the type of dosage (250 μg 25.9% (14/54); 500 μg 59.2% (32/54); 1000 μg 14.8% (8/54)) used.

Overall, 55% (30/54) of patients achieved and maintained erections sufficient for sexual intercourse with spousal satisfaction of 61% (33/54). Out of 54 patients, 26 (48.2%) continued long-term therapy with a mean use of 2.3 ± 1.2 y. The frequency of use in this compliant subgroup (median, 25 and 75% interquartile range) was 4 (2, 8) times a month. In the compliant group, no significant differences

Table 1 Response of MUSE after RP ($n=54$): SHIM (IIEF-5) analysis

Variables	Before surgery ($n=54$)	After surgery ($n=54$)	After MUSE use ($n=54$)
<i>IIEF-5 questionnaire</i>			
Q5—maintenance ability	4.4 ± 0.2	1.3 ± 0.1	$3.0 \pm 0.4^*$
Q15—erection confidence	3.4 ± 0.3	1.1 ± 0.1	3.1 ± 0.3
Q4—maintenance frequency	4.2 ± 0.2	1.2 ± 0.1	3.3 ± 0.1
Q2—erection firmness	3.4 ± 0.3	1.2 ± 0.1	$3.2 \pm 0.1^*$
Q7—intercourse satisfaction	3.8 ± 0.3	0.4 ± 0.1	$3.7 \pm 0.4^*$
Total mean IIEF-5 score	19.2 ± 1.3	5.2 ± 0.5	16.3 ± 1.3

Data are presented as mean \pm s.d. unless otherwise noted. * $P < 0.05$ before vs after MUSE use was considered as significant. Wilcoxon's signed-rank test was used.

Table 2 Response to MUSE in patients following bilateral NS, unilateral NS and non-NS RP

Variable	Bilateral NS (24/54)	Unilateral NS (10/54)	Non-NS (20/54)
Age (mean, y)	62.8 ± 4.8	63.5 ± 5.4	64.7 ± 5.8
<i>IIEF-5 questionnaire</i>			
Q5—Maintenance ability	3.4 ± 0.2	3.4 ± 0.6	3.38 ± 0.7
Q15—Erection confidence	3.3 ± 0.1	3.3 ± 0.5	2.96 ± 0.2
Q4—Maintenance frequency	3.4 ± 0.2	3.3 ± 1.5	2.85 ± 0.4
Q2—Erection firmness	3.2 ± 0.3	3.1 ± 0.6	3.14 ± 0.5
Q7—Intercourse satisfaction	3.4 ± 0.3	2.7 ± 0.3	2.73 ± 0.2
Total mean IIEF-5 score	16.7 ± 1.0	15.9 ± 1.1	15.1 ± 1.3

Data are presented as mean \pm s.d. unless otherwise noted. $P < 0.05$ NS vs non-NS was considered as significant. χ^2 test was used.

were found when responses were stratified by the drug dosage.

Out of 54 patients, 28 (52%) discontinued treatment after a mean use of 8 ± 1.4 months. The reasons given for discontinuation were insufficient erections (16 patients), switched to other therapy (IC injections $n = 2$, sildenafil citrate $n = 2$), natural return of erections ($n = 4$), urethral pain and burning ($n = 4$). However, excluding the patients who preferred the other therapy ($n = 4$) and return of natural erections ($n = 4$), the compliance to MUSE was 63% (34/54). The mean SHIM score for the 16 patients who stopped using MUSE because of a lack of efficacy (insufficient erections) was 10.5 ± 4.4 . These 16 patients did not differ from the compliant patients in the type of dosage used. The SHIM (IIEF-5) scores and treatment discontinuation rates showed a distinct pattern. Patients with an IIEF-5 score < 10 while on MUSE therapy were much more likely to discontinue treatment (10 of 12 or 87% of patients discontinued) than were patients with post-therapy IIEF-5 scores > 16 (four of 15 patients or 27% discontinued).

Discussion

In this study, we found that 30 (55%) of our 54 postprostatectomy patients were satisfied with MUSE therapy and 26 out of 54 (48.2%) chose to continue therapy for a long period (mean use of 2.3 ± 1.2 y). However, excluding patients who prefer other therapy ($n = 4$) and who had return of natural erections ($n = 4$), the compliance to MUSE was 63% (34/54). The type of RP surgery (bilateral NS, unilateral NS and non-NS) and dosage (250 μ g 25.9% (14/54); 500 μ g 59.2% (32/54); 1000 μ g 14.8% (8/54)) did not affect the efficacy of this therapy.

Our findings that MUSE is effective in 55% of postprostatectomy patients with a long-term drug compliance rate of 63% are consistent with reports by Padma-Nathan *et al*⁵ and Costabile *et al*.⁷ Padma-Nathan *et al*⁵ reported that 60–70% of men regardless of age and underlying etiology had successful intercourse at home using MUSE therapy.⁵ In analysis of an NS radical postprostatectomy group, Costabile *et al*⁷ have shown a 70% MUSE response in the office and 50% response at home. Our 55% response rate was comparable with Costabile *et al* with similar efficacy at the home use. We have found no significant difference in SHIM (IIEF-5) scores between office and home use. In this study, the compliant patients (who had a mean follow-up of 2.3 ± 1.2 y) continued to use MUSE at a frequency of 4 (2–8) times a month with an efficacy equivocal to presurgery SHIM (IIEF-5) scores (19.2 ± 1.3 vs 16.3 ± 1.3). Our high compliance rate of 63% at a

mean time of 2.25 y is attributed to regular follow-up and comprehensive training to the patients.

Cost, urethral burning, penile pain, lack of penile rigidity and patient–partner problems are the major reasons for discontinuation.^{4–7,11} The primary reasons for discontinuation were inadequate erections and a preference for other treatment. We found adverse side effects to be an infrequent (4/28 (14%)) reason for discontinuing treatment. Although MUSE was frequently associated with local adverse events such as urethral burning and penile discomfort, it did not cause fibrosis or plaque formation seen with some other ED treatments.^{1,6,11}

When the responses of MUSE are stratified according to NS status, we found MUSE equally as effective in non-NS patients as NS patients. Thus, MUSE therapy can be used as a first option in patients with non-NS procedures and also in patients who do not respond to oral therapy.

In patients who failed oral therapy, there have been reports that combination therapy, sildenafil with MUSE, improves efficacy. A study conducted by Nehra and colleagues (Rochester, MN, USA) demonstrated that a combination of sildenafil (100 mg) and intraurethral prostaglandin E1 (1000 μ g) salvaged a refractory population of men with ED. The proposed use of combination therapy will provide an alternative option for many patients who do not accept more invasive treatments such as VCD and intracavernosal injections.¹²

Conclusions

MUSE can provide good efficacy and compliance in up to 63% of patients. A mean SHIM score of ≥ 16 stratified for a successful and long-term outcome with MUSE therapy. Comprehensive patients and partner's education may contribute to high compliance rates. MUSE is just as effective in patients who underwent non-NS prostatectomy as those who had NS procedures. MUSE is a very useful treatment modality in selected patients and will continue to have an important role following RP until the results from NS procedures improve.

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