Comparing Transurethral Alprostadil with Intracavernosal Injections in a VA Impotence Clinic

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Despite offering the advantage of needle free medication delivery, transurethral treatment produced disappointing results in these veterans with erectile dysfunction.

Erectile dysfunction (ED), the inability to maintain an erection adequate for sexual intercourse, is a common and underreported condition. It is estimated to affect approximately 15 to 20 million men in the United States alone. Reports suggest the prevalence approaches 50% of men between the ages of 50 and 70 years.[1,2]

Oral phosphodiesterase (PDE)-5 inhibitors are considered the first-line therapy for ED and constitute the gold standard to which all other modalities must be compared with. Currently, insufficient evidence exists to suggest superiority of one oral agent over another. At the time of the writing of this paper, however, only one oral agent, sildenafil, was available to patients in the VA health care system. Sildenafil has been FDA approved since 1998 and has shown efficacy across many parameters, including patient age, race, body mass index, ED severity, ED etiology, ED duration, and the presence of various comorbidities.[3] It also has shown to be effective in patients after spinal cord injury and radical prostatectomy.[4,5]

Despite the successes described with sildenafil to treat ED, significant adverse effects can result, including headache, dizziness, and blurred vision. In addition, sildenafil is contraindicated in patients taking nitrates, those who have a hypersensitivity to the medication, and those with certain hereditary visual disturbances. Thus, for these patients, an alternative treatment for ED is recommended.

Other treatment options include penile prosthesis, revascularization surgery, and vacuum pumps. Penile prosthesis has been proven to be an effective treatment but runs the risk of infection, erosion, and fibrosis. Revascularization surgery is effective in men with discrete lesions of the larger penile arteries, but is reserved for only a small subset of young patients with ED. Vacuum pumps are relatively awkward to use and may cause trauma if not used properly.[6–8]

ED treatment also includes therapies that deliver vasoactive substances directly to the corpora by injection through the urethra.[9] Intracavernosal injection (ICI) has been reported to be effective in 30% to 90% of men with at least a three-month history of impotence.[8] In an investigation of three separate prospective studies, Linet and Ogrinc reported that all 683 men with ED in one of the studies developed erections sufficiently adequate for sexual activity after 94% of the injections they received during a six-month period.[9] The most common adverse effects of treatment in all three of the studies were penile pain, ecchymosis, fibrotic complications, and priapism, experienced in 11%, 8%, 2%, and 1% of patients, respectively. This led to drop-out rates that approached 75% in two of the investigations.[9]

In 1996, medicated urethral system for erection (MUSE), which delivers prostaglandin E1 into the urethra to be absorbed into the erectile bodies, was introduced as a less invasive alternative to ICI for ED treatment. The original investigations reported that MUSE was highly effective, that it had a favorable safety profile, and that patients adhered to its medication administration requirements.[9,10] In addition, since it is safe for patients who are taking nitrates or who have a history of visual disturbances, MUSE represents a realistic alternative for patients with contraindications to oral ED therapies.

In order to investigate the efficacy and safety of MUSE in patients who were currently using ICI at the impotence clinic of the James J. Peters VA Medical Center, Bronx, NY, we offered MUSE to patients who had experienced ED treatment failure

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with ICI or refused injections completely. Here we report the results of our investigation, including patients' response rates and their satisfaction with MUSE. We also look specifically at how MUSE compared with ICI for those patients who had been treated previously with injections.

OUR STUDY

The men included in the study were all treated at the impotence clinic between January 1998 and December 2000. (During this period, no oral ED therapies were available on the VA formulary.) This population is predominantly older and generally has concurrent medical conditions. At the initial visit to the clinic, all patients completed a baseline questionnaire that was created by the section of urology and included questions regarding medical history, current medications, and duration of ED. Clinicians also completed a thorough history and physical examination, on which they based the etiology of ED.

All patients were offered ICI initially for treatment of their ED, regardless of the etiology. The ICI used was a combination of alprostadil and papaverine. If patients chose treatment with ICI, they were formally instructed by the clinic nurse regarding proper self-injection techniques and subsequently were titrated up to a dose that was adequate to achieve an erection.

If patients chose treatment with MUSE, they were instructed on how to insert the suppository properly and the most effective techniques to achieve a satisfactory erection. This instruction also was given to those patients who elected to switch to MUSE after using ICI. During successive visits, patients were evaluated and the MUSE dose was titrated up until a satisfactory erection was achieved. If the patient did not achieve an erection sufficiently adequate for penetration at a dose of 1,000 µg, the treatment was considered a failure. Patients returned every three months for routine follow-up (up to 12 months) and were asked to complete a questionnaire regarding frequency of MUSE use, quality of their erections, frequency of successful intercourse, and their overall satisfaction with their MUSE treatment at each appointment. For this study, we compared patients' responses on the last questionnaire completed with their responses at baseline.

Table 1. Characteristics of study participants who had and had not previously used ICI[a] to treat ED[b]

Characteristic	Prior use of ICI (n = 124)	No prior use of ICI (n = 89)
Age (years)		
Mean (SD)	64 (9)	63 (7)
Range	27–82	29–84
Duration of ED (months)		
Mean	50	46
Range	6–360	6–360
Duration of MUSE[c] use (months)		
Mean (SD)	8 (4)	8 (4)
Range	1–20	1–20

[a]ICI = intracavernosal injection. [b]ED = erectile dysfunction. [c]MUSE = medicated urethral system for erection.

Table 2. Etiology of ED[a] among the study participants

Etiology[b]	No. (%) of patients (n = 213)
Diabetes	70 (33)
Hypertension	69 (32)
Hypercholesterolemia	31 (15)
Prior radical prostatectomy	22 (10)
Psychogenic	12 (6)
Cancer	12 (6)
Spinal cord injury	8 (4)
Low testosterone levels	4 (2)

[a]ED = erectile dysfunction. [b]The etiology of ED was attributed to more than one cause for some patients. In such cases, they were assigned more than one cause, which accounts for the sum of percentages being greater than 100.

RESULTS

At the clinic, 246 patients underwent the initial evaluation and the supervised instructional MUSE insertion. Our study sample consisted of the 213 patients from this group who had completed at least one three-month follow-up visit. Of these 213 patients, 124 had used ICI previously as a treatment for their ED.

The average age of the study patients was 64 years (range, 27 to 84 years) (Table 1). They reported having ED for an average of four years (range,

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Table 3. Reasons reported by the study participants for switching to MUSE[a] after previous ICI[b] use

Indication[c]	No. (%) of patients (n = 124)
Fear of needles	98 (79)
Pain	72 (58)
Poor coordination	27 (22)
Bleeding	6 (5)
ICI failure[d]	3 (2)

[a]MUSE = medicated urethral system for erection. [b]ICI = intracavernosal injection. [c]Several men stated more than one reason for stopping treatment with ICI, which accounts for the sum of percentages being greater than 100. [d]ICI failure was defined as the inability to achieve an erection after titration up to an injection dose of 1.0 mL of the alprostadil and papaverine mixture.

Table 4. Frequency of MUSE[a] and ICI[b] use among the study participants

Frequency of use[c]	% of patients using MUSE (n = 213)	% of patients using ICI (n = 124)
Greater than once per week	14	19
Once per week	48	34
Twice per month	11	23
Once per month	20	16
Less than once per month	7	8

[a]MUSE = medicated urethral system for erection. [b]ICI = intracavernosal injection. [c]Patients were asked to note how often each treatment modality was used, regardless of whether it resulted in an adequate erection or successful intercourse.

six months to 30 years) before treatment. The patients used MUSE for an average duration of eight months.

The etiology of the patients' ED, as determined by history and physical examination, was sometimes attributed to more than one cause (Table 2). Diabetes was the number one underlying cause of impotence (33% of patients). Complications secondary to hypertension followed closely behind (32% of patients).

Among the 124 patients who had previous experience with ICI, 98 (79%) listed their fear of needles as one of the reasons they opted to switch to MUSE (Table 3). The pain associated with self-injection was reported as a reason for switching by 72 patients (58%). The inability to self-inject secondary to poor coordination, bleeding at the site of injection, and failure to achieve an erection also were noted as reasons for switching.

For those patients who had never used ICI, fear of needles was the universal indication as to why this treatment was never tried. In fact, when MUSE became available on the VA formulary, it was nearly impossible to convince patients to try injections first.

The frequency of use of both treatments for ED was determined (Table 4). Our data showed no significant difference in how often the patients used MUSE compared with ICI.

Quality of erections

Of the 213 patients using MUSE, none subjectively rated the erections they developed as excellent, though 21 (10%) of patients rated their erections as either very good or good, and 42 (20%) of patients rated their erections as fair. The overwhelming majority of the patients—150 (70%)—rated their erections as poor and inadequate for penetration.

The ratings of erection quality for the 124 patients who had initially tried ICI were markedly higher for treatment with ICI than with MUSE (Figure 1). Six (5%) of the ICI patients rated their erections as excellent, 29 (23%) rated them as very good, 25 (20%) rated them as good, and 50 (40%) rated them as fair. Only 14 (12%) of the patients in the ICI group rated their erections as poor.

Only three (2%) of the patients in the ICI group rated the quality of erection they developed with MUSE as being superior to the quality experienced with ICI. Twenty-six (21%) stated that the quality remained the same, including 14 who rated their ICI erection quality as poor. The majority, 95 (77%), rated their MUSE erections of lesser quality than the ones they achieved with ICI.

Frequency of successful intercourse

Only 11% of patients in the MUSE group said they were able to have intercourse at least half or most of the time after insertion of the alprostadil suppository, including the three patients (1%) who said they were always successful (Figure 2). Twenty percent responded that they had successful intercourse after MUSE some, but less than half, of the time they used it. More than two thirds (69%) said they were never able to have intercourse after treatment with MUSE.

More patients in the ICI group than in the MUSE group reported successful intercourse—10 (8%) reported the ability to have successful intercourse every time they used the injections. Nearly half said they were

able to have intercourse at least half of the time. Forty-six (37%) said they were able to have successful intercourse some of the time, whereas 12 (10%) said they were never able to have intercourse after ICIs. Five (4%) of patients in the ICI group said they were able to have successful intercourse more frequently with MUSE than with ICI, whereas 95 (77%) said they were successful with ICI more often than with MUSE.

Overall patient satisfaction

A total of 30% of MUSE patients were satisfied with therapy, with two patients (1%) indicating extreme satisfaction (Figure 3). The overwhelming majority of patients—149 (70%)—said they were not satisfied at all with the result of their treatment with MUSE. At the end of the study, 92% of the patients had decided not to renew their prescriptions for MUSE.

The 124 patients who used ICI were more pleased with their ED treatment results. One third of these patients were extremely or moderately satisfied with ICI treatment and half said they were somewhat satisfied. Twenty-four patients (19%) said they were not satisfied at all with ICI. Only 11 (9%) of the patients who used ICI said they were more satisfied with the results they obtained with MUSE. Sixty-eight percent said they were less satisfied with the results of their treatment with MUSE as compared to their results with ICI.

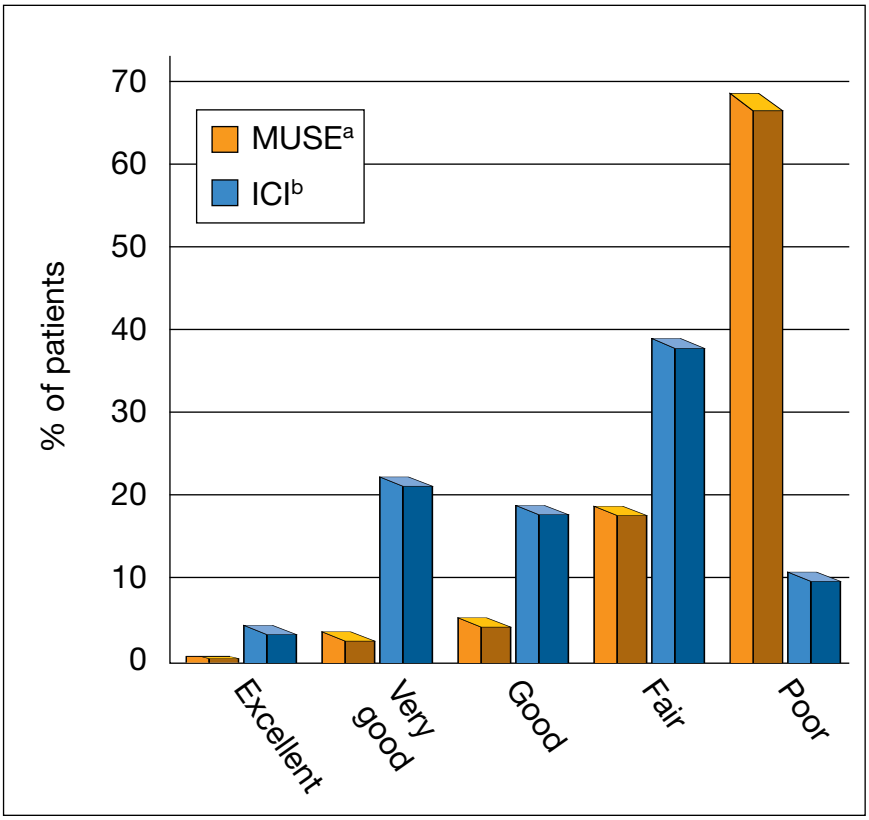

Figure 1. Self-reported erection quality for study participants using MUSE (n = 213) versus ICI (n = 124) to treat erectile dysfunction. [a]MUSE = medicated urethral system for erection. [b]ICI = intracavernosal injection.

THE EVIDENCE ON MUSE

The original study report on MUSE by Padma-Nathan and colleagues—a double-blind, placebo-controlled study of 1,500 men—found that 66% of patients achieved an erection in the clinic sufficient for intercourse and 65% who administered a treatment at home had intercourse successfully, compared with only 19% with placebo.[10] The report showed that the efficacy of MUSE was independent of either the cause of ED or age of the patient.

A great disparity exists between our experience with MUSE in our clinic and the original published results on this treatment. The baseline characteristics of our population were similar in age and duration of dysfunction (50 months in our study compared with 51 months in the original study), but the causes of their ED were different. For example, whereas 33% of our patients listed diabetes as the cause of their impotence, only 20% of the original MUSE patients listed it as the underlying cause. Surprisingly, for 39% of the original MUSE patients, surgery or trauma was the cause of their dysfunction, compared with only 10% of our population. The only other major difference was that, to be included in the original MUSE study, patients had to discontinue any other treatment for their ED at least 30 days before starting MUSE treatment, which was not a requirement for inclusion with our study population.

Kim and colleagues, who conducted a multicenter study of MUSE in Korea, reported similarly disappointing results as those found in our study. In their study, 334 subjects used transurethral alprostadil titrated in a stepwise fashion from 250 to 1,000 µg based on erectile response and tolerability[11]—a protocol similar to that

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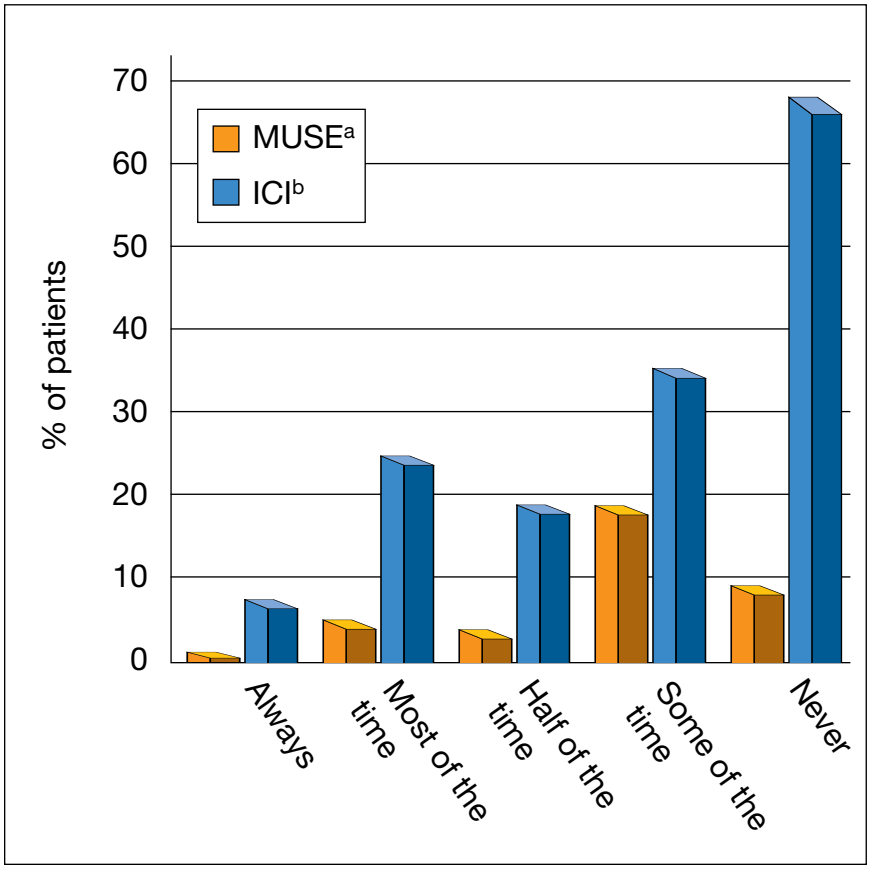

Figure 2. Self-reported frequency of successful intercourse for study participants using MUSE (n = 213) versus ICI (n = 124) to treat erectile dysfunction. [a]MUSE = medicated urethral system for erection. [b]ICI = intracavernosal injection.

used in our study. The authors found that 53% of patients had successful intercourse at least once during the study period. They noted, however, that 27 (15%) of the 178 study participants who went on to home treatment with MUSE dropped out of the study because of insufficient erectile quality for penetration.[11]

Guay and colleagues described their experience with MUSE in 229 patients with ED.[12] The initial titration dose in their study was 125 or 250 µg. In-office testing was performed, similar to our present study. The overall success rate in their study was 56%. Of the 44% of study participants in whom treatment failed, 61% believed that there was lack of efficacy with MUSE, while 39% reported that genital pain or urethral bleeding motivated the patients to stop using the treatment. Patients who were successful with MUSE stated that hands-on education, as well as education of their partner, were important to their success.[12] Similarly, in our present study, we found, through answers on the questionnaires, that those patients who were successful with MUSE had a strong commitment to the therapy and a partner who understood the purpose and procedure for using the therapy.

In a clinical investigation similar to Guay and colleagues, Fulgham and colleagues reported that, of 115 men using MUSE, only 27% achieved an erection sufficient for penetration.[13] At follow-up, only 19% of patients continued to use MUSE, and many cited disappointment with the therapy's results and cost of treatment as the most important reasons they discontinued MUSE.

MUSE versus ICI

In a comparative study of MUSE and ICI in 103 men, Porst reported overall response rates of 43% with MUSE and 70% with ICI.[14] Complete rigid erections were achieved 10% of the time in patients using MUSE and 48% of the time in those using ICI. Porst also noted that clinically relevant systemic adverse effects (such as dizziness, hypotension, or syncope) occurred in 6.8% of patients after treatment with MUSE.[14] No such adverse events were reported with ICI use.

Werthman and Rajfer found similar results when comparing MUSE with ICI. They reported that only seven of 100 consecutive patients who had all used ICI previously to treat ED had rigid erections with MUSE and 63 did not respond at all to MUSE.[15] The proportion of patients who had rigid erections, full erections with partial rigidity adequate for intercourse, and inadequate response with ICI were 49%, 40%, and 11%, respectively.

Engel and McVary investigated the response to MUSE in patients who failed or withdrew from treatment with ICI.[16] Of the subset of patients who reported that ICI treatments were ineffective, 58% achieved an erection sufficient for intercourse with MUSE. For the patients who reported effective or sometimes effective treatment with ICI, 67% had an adequate erection after administration of MUSE in the clinic setting. Interestingly, only two thirds of the men who had adequate erections with MUSE in

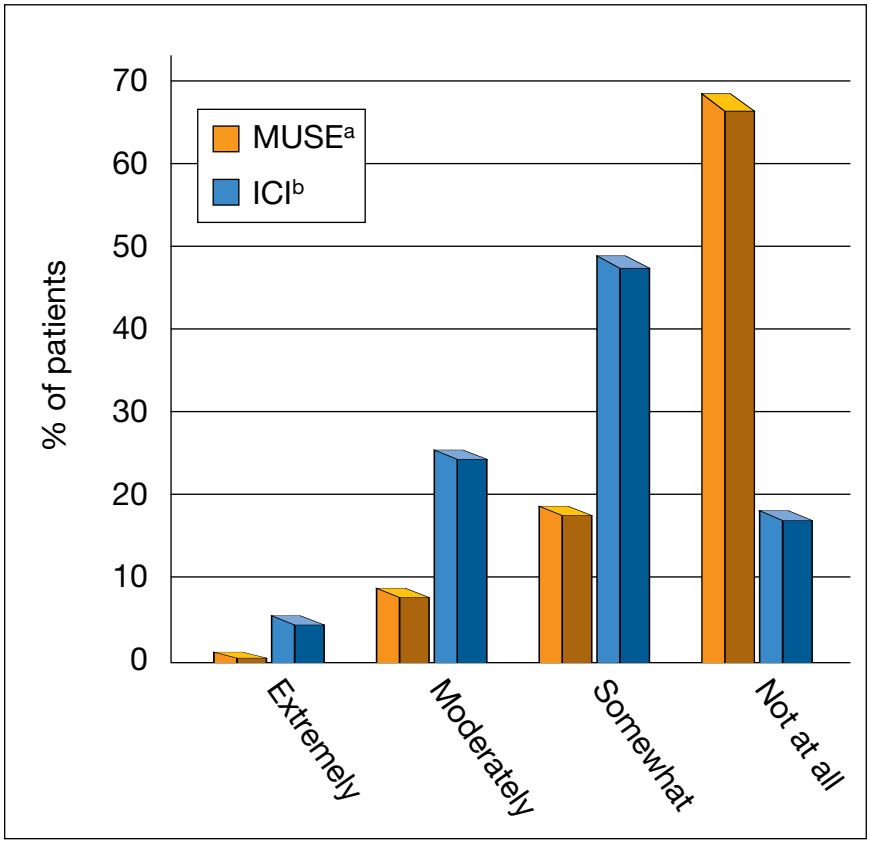

Figure 3. Self-reported overall satisfaction for study participants using MUSE (n = 213) versus ICI (n = 124) to treat erectile dysfunction. [a]MUSE = medicated urethral system for erection. [b]ICI = intracavernosal injection.

the clinic were able to have successful intercourse after MUSE therapy while at home—which suggested that the observed decrease in efficacy may be secondary to improper administration by the patients at home.[16]

One of the possible reasons for the observed difference in efficacy between ICI and MUSE is that the transurethral route is simply a less effective mode of delivery of the vasoactive alprostadil to the erectile bodies. The ICI dosages needed to elicit an erection range from 10 to 20 µg because it is delivered directly into the corpora. The dosages for MUSE range from 125 to 1,000 µg, with many patients not able to achieve an erection after being titrated up to the highest dose.

A ROLE FOR MUSE IN ED TREATMENT?

In a patient population that is predominantly older and has multiple comorbidities, the results of MUSE have been disappointing. The vast majority of patients in our study responded poorly to the treatment and were unable to achieve erections suitable for penetration. These patients should be counseled realistically and be offered alternative therapies. According to the 2005 consensus paper of the American Urological Association Practice Guidelines Committee on the treatment of ED, prior to counseling on ED therapy, clinicians should comprehensively review a patient's medical conditions, risk factors, and psychosocial status and perform a thorough physical examination.[7] Once the relevant clinical information has been collected and the diagnosis of ED is confirmed, appropriate therapies (in the order of least invasive to most invasive) include PDE-5 inhibitors, a vacuum pump erection device, MUSE, ICI with alprostadil, and penile prosthesis implantation. In general, discussion of therapeutic considerations proceeds in this given order. Optimally, such discussion includes the patient and his partner.[7] Given patients' aversions to using ICI to treat their ED, and the fact that MUSE is effective with proper administration in some patients, we believe that MUSE still represents a viable treatment option for men with ED who have contraindications to the use of PDE-5 inhibitors. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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