

# Transurethral Alprostadil for the Treatment of Erectile Dysfunction: Results of a Multicentre Trial

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## Abstract

**Introduction:** The incidence of erectile dysfunction (ED) has been shown to increase significantly in Singaporean male population. Thus, this prospective study (no controls) assessed the clinical efficacy and safety of a medicated urethral system for erection (MUSE) in Singaporean male patients with a known history of ED. **Subjects and Method:** Eighty-six men with a mean age of 55.7 years with differential causes of ED were administered with MUSE in the clinic with a titration adjustment of 4 possible dose regimes (125, 250, 500 and 1000 mcg) till efficacy is achieved. Subsequently, patients were subjected to home treatment for a duration of 3 months. **Results:** Sixty per cent of in-clinic patients exhibited good responses and were given MUSE for home treatment. The efficacy rate for home treatment was 86%. Overall, the patients (n = 86) had a 51.2% success rate in achieving satisfactory sexual intercourse. Diabetic and psychogenic patients were noted to respond well to MUSE. No severe adverse events were found in this study. **Conclusion:** MUSE showed to be a safe, less invasive, well-tolerated and efficient alternative treatment for ED in Singaporean men.

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**Key words:** Penile erection, Prostaglandin E<sub>1</sub>, Urethral suppository

## Introduction

As the population is growing older and the society getting more affluent, people are aiming for a better quality of life. This has resulted in greater awareness of erectile dysfunction (ED), thus increasing the number of patients approaching the doctor for consultation. Sexual activity is an important part of life and for men it depends on erectile function,<sup>1</sup> sex hormone levels and its regulation.<sup>2</sup> Organic causes of ED are mainly vascular, neurogenic or hormonal

in nature. On the other hand, smoking and alcoholism, depression, stress, smoking and lack of exercise can be important contributory factors for ED. However, ageing, diabetes and hypertension constitute the largest share of organic factors for EDs.<sup>3,4</sup> Kaiser<sup>1</sup> has found that the incidence of ED rose sharply after the age of 50. Recently, NIH<sup>5</sup> has reported that in the United States, nearly 20 to 30 millions are suffering from ED and this figure may increase to 47 million by the year 2020. Presently in Singapore, the

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percentage of population affected by ED is quite significant. Although the Chinese population in Singapore has a higher prevalence of ED, there were no significant differences in ED between the different races.<sup>6</sup> Despite the high prevalence of ED, many men in Singapore are reluctant to seek proper treatment and would rather resort to taking herbal or traditional medicine with no proven clinical value.

At present, several treatments are available for ED. These include oral medications, vacuum pumps, intracavernous injections (ICIs), vascular surgery and penile prostheses. Sildenafil has been proven to be very effective;<sup>7</sup> however, the adverse effects and contraindications can be serious. On the other hand, penile implant is expensive and requires invasive surgery. In contrast, intracavernous injection with prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) alone or in combination with other vasodilators is very effective but with disadvantages of pain, haematoma formation and variable degree of discomfort.<sup>8,9</sup> On long-term follow-up, ICIs are expected to result in a wide range of shortcomings like loss of interest, needle phobia, pain, priapism, penile haematomas and fibrosis,<sup>10</sup> which limit the efficacy of ICIs as a long-term therapy for ED.

In this context, transurethral alprostadil [medicated urethral system for erection (MUSE) from Vivus, California] was introduced in 1997 as an alternative mode of treatment for ED that eliminates the need for the needle with no systemic adverse reactions. Since then, it has been widely studied<sup>11,12</sup> and accepted by health care professionals, patients and their partners as an alternative therapy with good efficacy and fewer adverse effects. This study is based on a prospective multicentre trial done in Singapore in 1998 on the clinical safety and efficacy of MUSE and also to determine whether Asian patients have similar response profile to the west.<sup>11,12</sup>

## Subjects and Method

Men over 21 years with known history of ED for at least 3 months (due to organic and psychogenic causes, and having a stable heterosexual relationship) were included in this study after obtaining written consent. The causes of ED were identified by history, physical examination and laboratory evaluation. Exclusion criteria of the trial included known hypersensitivity to alprostadil, sickle cell disease, multiple myeloma, thrombocytopenia, polycythemia, ischaemic heart disease within the previous 6 months, abnormal penile anatomy, urethral stricture, balanitis, urethritis, urinary tract infection and sexually transmitted disease. The design of the study had the approval of all the ethical committees of the respective hospitals. Out of 108 patients screened, 22 patients dropped out from the study due to pain, difficulty in learning how to use the medication and other personal reasons. Patients with and without

previous PGE treatment were chosen from the clinics for the study.

Thus, we had 86 patients from the National University Hospital (n = 31), Singapore General Hospital (n = 24), Tan Tock Seng Hospital (n = 16) and Changi General Hospital (n = 15) enrolled into the titration study using an increasing dosage of alprostadil, of which 34 patients were found to be unsuitable because the erection was not strong enough despite using the highest dose. The remaining 52 patients who had sufficient erection were assigned to home prescription. At the initial screening visit, prostate specific antigen, full blood count, urinalysis and renal function, liver function, calcium, glucose, iron levels and prothrombin time were estimated in all patients. The same parameters were also analysed again at the end of the trial. During screening visit, the patients were taught and shown a video on how to apply MUSE.

## Study Design

The study was conducted at 4 public hospitals in Singapore viz., Changi General Hospital, National University Hospital, Singapore General Hospital and Tan Tock Seng Hospital. Patients who were eligible to be included in the study were tested in the clinic to determine the appropriate dose of transurethral alprostadil. Initially, step-wise titration with doses of 125, 250, 500 and 1000 mcg alprostadil were evaluated. Based on the in-clinic response, the appropriate doses were given to the patients to take home for definitive treatment. The duration of the study period was 3 months.

## Drug Application

Alprostadil was administered into the urethra by a drug delivery system as described by Padma-Nathan et al,<sup>11</sup> which consisted of a polypropylene applicator with a hollow stem of 3.2 cm in length and 3.5 mm in diameter and the tip of the applicator contained a semi solid pellet of the medication. The stem of the applicator was fully inserted into the urethra; following this, a gentle push of a button on top of the applicator released the medication into the urethra and the applicator was then removed. For easy application and effective diffusion of the drug, patients were asked to pass urine before the application of study drug, as residual urine in the urethra facilitate easy application and absorption. Otherwise, the stem of the applicator was moistened with few drops of water.

## Erectile Assessment and Safety Measurements

The penile erectile responses were measured using the Erection Assessment Score (EAS).<sup>11</sup> A score of 1 = no response, 2 = some enlargement, 3 = full enlargement, 4 = erection sufficient for intercourse and 5 = full rigidity. The EAS was determined at 15, 30, 45 and 60 min after application. Patients with an EAS of 4 or 5 were considered

adequate for home treatment with similar doses. In addition to the EAS, the following safety measurements were also done. Levels of discomfort, blood pressure and pulse rates were also measured at 15, 30, 45 and 60 min. Patients experiencing significant giddiness, tachycardia or a drop of 30% blood pressure were considered unsuitable for the study. Levels of discomfort were estimated based on a scale, in which A = no discomfort, B = minimal discomfort, C = some discomfort, D = moderate discomfort and E = severe discomfort.

## Results

Demographic and baseline characteristics of men with ED are shown in Table I. The mean age of the study population was 55.7 years and 64% subjects had an earlier diagnosis of partial erections insufficient for penetration, out of which nearly 51% had undergone other therapeutic methods for the problem of ED, which included intracavernous injections, oral medications, vacuum pump and surgery. The main organic causes for the ED in this study were diabetes, hypertension, ageing and psychogenic.

### In-clinic Response

Patient responses and results are shown in Table II. During in-clinic study, 60% of patients were found to be successful with EAS of 4 or 5 while 40% of patients had EAS less than 3. The efficacy of alprostadil measured as penile erection assessment was also found to increase with

increasing doses of alprostadil. Nearly 58% of patients exhibited an EAS of 4 or 5 at 1000 mcg of alprostadil; whereas 29% and 13% of in-patients had EAS of 4 or 5 at doses of 500 and 250 mcg, respectively. Patients who did not respond to a lower dosage were given a higher dosage at another visit. We found that dosage of 125 mcg not effective at all.

### Response at Home

The percentage of patients having successful intercourse with home treatment is shown in Table II. During a 3-month period of home treatment, the success rate of patients having successful intercourse was found to increase with the duration of home treatment. The success rates were 79%, 83% and 92% at 1, 2 and 3 months, respectively. Similar to the success rate of sexual intercourse, the number of patients having successful sexual attempts was also found to increase with the duration of treatment. The success rate for patients was noted to increase from 86% to 100% at the end of the 3-month period as a result of improvement in the application of the medication and technique. However, the efficacy rate was 51.2% out of the total cohort of 86 patients.

### Adverse Events

After initial screening, 3% of 108 patients dropped out due to severe urethral pain. The cumulative (in-clinic as well as home treatment) discomfort levels are shown in Table II. About 87% of patients did not complain of any major discomfort. Some and moderate discomfort were

TABLE I: DEMOGRAPHIC AND PRE-TREATMENT CHARACTERISTICS OF MEN WITH ERECTILE DYSFUNCTION IN SINGAPORE

|                                       |        |
|---------------------------------------|--------|
| Number of patients                    | 86     |
| Age (y)                               |        |
| Mean                                  | 55.7   |
| Range                                 | 33-82  |
| Duration of erectile dysfunction (y)  |        |
| Mean                                  | 4.2    |
| Range                                 | 0.3-12 |
| Previous therapy for ED (%)           | 51     |
| Types of therapy (%)                  |        |
| Intracavernous injections             | 77     |
| Other medications                     | 48     |
| Surgery                               | 2      |
| Vacuum pump                           | 12     |
| Aetiology of erectile dysfunction (%) |        |
| Diabetes                              | 50     |
| Hypertension                          | 45     |
| Ageing                                | 23     |
| Psychogenic                           | 15     |
| General arteriosclerosis              | 12     |
| Tobacco                               | 10     |
| Alcohol                               | 7      |

TABLE II: RESPONSES OF PATIENTS TO ALPROSTADIL WITH IN-CLINIC AND HOME TREATMENT

| Variable                         | Response level (%) |
|----------------------------------|--------------------|
| In-clinic titration efficacy     | 60                 |
| Erection Assessment Score 4 or 5 |                    |
| 250 mcg                          | 13                 |
| 500 mcg                          | 29                 |
| 1000 mcg                         | 58                 |
| Patients successful at home      |                    |
| One month                        | 86                 |
| Two months                       | 88                 |
| Three months                     | 100                |
| Success rate of attempts         |                    |
| One month                        | 79                 |
| Two months                       | 83                 |
| Three months                     | 92                 |
| Discomfort level                 |                    |
| No discomfort                    | 37                 |
| Minimal                          | 50                 |
| Some                             | 12                 |
| Moderate                         | 1                  |
| Severe                           | 0                  |

reported by 12% and 1% of patients, respectively. One patient had hypotension during in-clinic titration and 4 partners (5%) complained of vaginal discomfort or mild discharge and 1 patient developed urinary tract infection during home treatment. Among the trial patient's (86), there was no patient with severe discomfort when using alprostadil for the treatment of ED (Table II). We could not establish the rate of compliance after the 3-month study period.

### *Blood Results*

The results of the blood and urine tests, prostatic specific antigen, full blood count, urinalysis, liver function, renal function, calcium, glucose, iron levels and prothrombin time did not show any change after the trial.

### **Discussion**

Erectile function involves the interaction of vascular, neurological and hormonal systems of the body.<sup>13</sup> Primarily, any hindrance to the mechanism that relaxes corporal smooth muscle, penile blood vessels and sinusoids would result in varying degrees of ED. Recently, treatment modalities such as oral medications, surgical methods and IC injections are available. Among this, sildenafil has been widely accepted as an effective oral therapeutic agent.<sup>7</sup> However, contraindications are mainly due to its systemic side effects. Further to the first report of its relaxation of the corpus cavernosum by Karim and Hiller in 1975<sup>14</sup> and elucidation of its mechanism of erection,<sup>15</sup> intracavernosal PGE<sub>1</sub> has been clinically acclaimed to be efficacious in ED of differential aetiology.<sup>16</sup> As a result, IC injection-containing prostaglandin E<sub>1</sub> has been routinely used as another therapeutic method.<sup>17</sup> However, IC injection responses were estimated to be widely different.<sup>10</sup> Alprostadil has been shown to increase the intracellular levels of cyclic AMP; in addition, it has short half-life compared to other vasodilators<sup>18-20</sup> as it reverts ED with minimal effect on prolonged erection. In the present study, all patients given alprostadil had responded with an erection of a certain degree irrespective of the aetiology, mainly due to the fact that alprostadil works locally and has no systemic effects.

The mean age of patients having ED was 55.7 years, which is below the mean age of patients having ED in the United States,<sup>11</sup> viz., 61 years. The capacity for partial erection in Singaporean males was almost similar to the western population. In the present study, the prime cause for ED has been identified as diabetes mellitus (50%), this is in sharp contrast to the observations made by Padma-Nathan et al<sup>11</sup> and Williams et al<sup>12</sup> in the United States and Europe where only 21% and 17% respectively of the study population had diabetes mellitus.

Alprostadil application elicited an EAS of 4 to 5 in 60% of patients with ED. This concurs with previous findings<sup>11,12</sup> which reported 65% and 64% success rates. Alprostadil relaxes the smooth muscle leading to engorgement of the sinusoids within the cavernosa and subsequently veno occlusion occurs. This suggests that the application of transurethral alprostadil could be a complementary therapeutic technique for ED. However, in the present study, 40% of the in-clinic patients were estimated to have EAS of 3 and below. This can be attributed either to an ineffective transfer of alprostadil into the corpora cavernosa, unfamiliarity with the clinic setup or problems with application of the medication or patients were too nervous at the clinical situation.

During a 3-month home treatment, our study showed a mean success rate of 84.6% in attempts at sexual intercourse. The obtained clinical efficacy is relatively higher than the 69% success rate achieved by European patients for the same dosage.<sup>12</sup>

A good percentage of patients (87%) found this method of therapy clinically effective with no discomfort or minimal discomfort. Engel and McVary<sup>10</sup> observed that urogenital mucosa may be traumatised with the application of alprostadil. Similarly, Padma-Nathan et al<sup>11</sup> have reported penile pain as the commonest adverse effect. However, in this study the adverse effect was minimal. The limitations of this study such as 1) patients with previous PGE treatment showed less response, 2) learning and application of the study drug and 3) non-prospective and non-comparative nature of the study warrant due consideration.

In summary, the obtained data on multiracial Singaporean men with ED of broad-spectrum aetiology suggest that the application of transurethral alprostadil is a safe, less invasive, well-tolerated alternative therapy for EDs with minimal adverse events.

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