Blackwell Publishing

Asian J Androl 2006; 8 (2): 219–224
DOI: 10.1111/j.1745-7262.2006.00095.x

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·Clinical Experience·

Long-term treatment with intracavernosal injections in diabetic men with erectile dysfunction

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Abstract

Aim: To assess the behavior of patients with diabetes mellitus (DM) and erectile dysfunction (ED) during 10 consecutive years of treatment with self-injection of vasoactive drugs. **Methods:** Thirty-eight diabetic men, including 12 with type I and 26 with type II diabetes, were followed up regularly for 10 years after they began self-injecting for severe ED. Real time rigidity assessment was used for the objective determination of the initial dosage and then doses were regulated in order to introduce an erection suitable for penetration and maintenance of erection for approximately 30 min. Patients were followed up every two months, and doses were increased only when the treatment response was not satisfactory. **Results:** The number of injections used per year by the patients was reduced each year (mean numbers: 50 in the first year and 22.5 in the 10th) and treatment shifted towards stronger therapeutic modalities (mixtures of vasoactive drugs instead of prostaglandin E1 alone). Type I diabetic men were standardized to a level of treatment as early as 5 years after the initiation of treatment. That level was finally reached by type II patients after another 4-5 years. **Conclusion:** Treatment with self-injections of vasoactive drugs in diabetic men with severe ED is a safe and effective alternative in the long term. Diabetic men of both types show the same preferences in quality and quantity of treatment after 10 years. The key point for maintenance in treatment is the adjustment of the therapeutic method and dosage to optimal levels for satisfactory erections. *(Asian J Androl 2006 Mar; 8: 219–224)*

Keywords: diabetes mellitus; erectile dysfunction; impotence; intracavernosal injections; prostaglandin E1; papaverine

1 Introduction

The incidence of sexual dysfunction in men with diabetes mellitus (DM) is approaching 50% and, as diabetes is a problem that is increasing at an alarming rate, diabetic men already made up one-quarter of those seeking advice for erectile dysfunction (ED) [1]. Although a successful impotence assessment and treatment service may be offered to diabetic men, sexual problems, despite their relevance, are still seldom investigated by general practitioners and specialists [2]. However, the etiology of diabetic ED has been thoroughly investigated [3, 4] and the therapeutic management became satisfactory with the use of a wide spectrum of treatments [4–6].

The natural history of ED indicates the importance of age. In diabetic individuals, ED is more progressive and usually irreversible. Its etiology is multifactorial, including neuropathy, vascular disease, metabolic control, nutrition, endocrine disorders, psychogenic factors, and drugs coadministered for comorbidities, such as antihypertensives. The role of autonomic neuropathy has been emphasized, and is considered the major factor.

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Received 2005-02-03 Accepted 2005-06-23

Zhu *et al*. [7] reported a 50% rate of abnormal pudental evoked potentials, and recently, Xu *et al*. [8] reported on the decrease of nitric oxide (NO) synthase content in corpus cavernosum of diabetic rats. NO synthase is the only enzyme for the synthesis of NO, the neurotransmitter mediating smooth muscle relaxation and introducing erection. Although ED is a marker for the development of generalized vascular disease, diabetic arteriopathy may affect blood supply, contributing to the neurogenic factor [4], but does not appear to result often in entire penile artery occlusion. The psychological component has also been emphasized. The results of the largest study evaluating quality of life in diabetic patients with ED provide clear evidence that ED is associated with higher levels of diabetes-specific health distress and worse psychological adaptation to diabetes, which are, in turn, related to worse metabolic control. Erectile problems are also associated with a dramatic increase in the prevalence of severe depressive symptoms and lower scores in mental components [2].

Diabetic men are more likely to achieve a satisfactory response to intracavernosal injections than those with other types of ED [9]. Moreover, diabetic patients accept self-injecting more easily and comply better with treatment for ED compared to non-diabetics [10]. However, in general, the frequency of non-compliance with self-injecting is high, approaching 50%, and is probably the most common event in clinical practice [11]. In this study we assessed the main characteristics of long-term treatment with self-injection of vasoactive drugs in diabetic men with ED.

2 Materials and methods

2.1 Study recruitment

Only diabetic patients with ED who had completed 10 years of treatment with self-injection of vasoactive drugs were included in this study. In 1993 and 1994, 78 men with DM and ED were referred or presented to our sexual dysfunction clinic. A detailed history was obtained from all patients, who filled out a questionnaire about their sexual activities. Most of them underwent laboratory tests and all had a simple test of intracavernosal injection with 10 mg prostaglandin E1 (PGE1). Of them, 25 men achieved satisfactory erections responding to conservative treatment and psychosexual counselling during the assessment period and were not managed further. The remaining 53 patients underwent a detailed investigation with Doppler ultrasonography and tests of vasoactive drugs. They were all proposed to start on self-injections but six refused treatment. Of the 47 men who started on self-injections, nine stopped therapy gradually for several reasons, and 38 completed 10 years of treatment. Twelve (31.6%) of them had type I diabetes and 26 (68.4%) had type II diabetes. The process of enrolment for the studied patients is depicted in detail in Figure 1. The patients had acceptable metabolic control. Glycosylated hemoglobin levels ranged between 6% and 8%.

2.2 Treatment for ED and follow-up

Each patient was initially examined in privacy under discrete conditions. The response to intracavernosal injections was evaluated in real time by Rigiscan (Dacomed, Minneapolis, MN, USA). The device was applied for 30 min after the injection with simultaneous audiovisual stimulation. The aims of this test were to assess tumescence and rigidity and to determine the proper drug and dosage for the achievement of an erection for up to 30 min. A response was considered objectively satisfactory if there was a 30-mm or more increase in circumference and a rigidity of 70% or more, both for at least 10 min. To determine the response to vasoactive drugs and the therapeutic dose, all patients were initially injected with 5–10 μg PGE1 and the non-responders were given 15–20 μg PGE1 after 1 week. A few patients, who did not respond to the higher dose of PGE1 (20 μg), needed a further mixture of PGE1 and papaverine (PAP).

The drugs were prepared and given in the clinic at follow-up, and dosages were regulated to provide an erec-

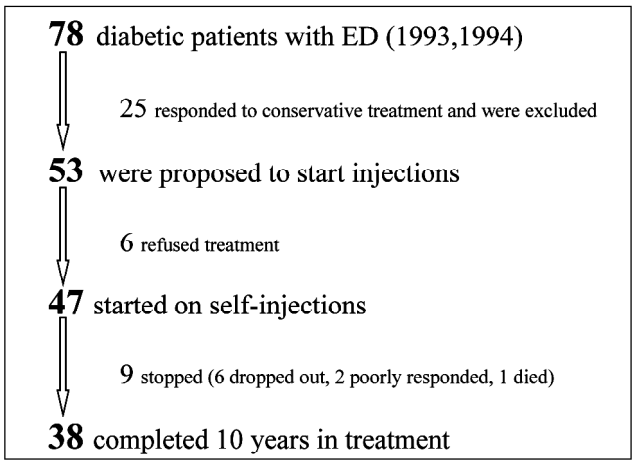

Figure 1. Enrolment process of patients in our study of diabetic men with erectile dysfunction (ED).

tion suitable for penetration and maintenance of approximately 30 min. The patients were asked to complete a consent form because the drugs used were not licensed for intracavernosal treatment, and approval was required for possible scientific publication of the data. The patients were taught how to self-inject and were advised to use injections not more than once per week, alternating between the two sides of the penis. They were also asked to record the results of their attempts for intercourse, to bring back the unused injections (in order to record the frequency of sexual activity and to verify the number of recorded attempts), and to report any complications immediately. All data of the patients' follow-up were prospectively entered into the departmental database.

Drug doses were increased only when the treatment response was not satisfactory. The doses of PGE1 were increased by 5–10 μg, and PAP by 8–16 mg. The use of 20 μg PGE1 without satisfactory response was the criterion for switching to a drug mixture. The mixtures were combinations of PGE1 20 μg and various doses of PAP. For practical reasons, treatment with self-injections was classified as low PGE1, high PGE1, low MIX and high MIX. This classification is shown in detail in Table 1. Patients were followed up every 2 months to reassess their erectile function.

2.3 Statistics

The McNemar test[a], Pearson's χ^2-test[b], the Wilcoxon signed-ranks test for paired observations[c], and the Mann–Whitney *U*-test[d] were applied for statistical evaluation of the data where appropriate, using a designated statistical package (SPSS 12.0 for Windows, SPSS Inc., Chicago, Illinois, USA). Statistical significance was set at $P < 0.05$.

3 Results

Patients' demographic characteristics at baseline are shown in Table 2. According to age and dysfunction duration, this group represents a typical sample of men with ED [12]. Seventeen men (32%) had abnormal penile Doppler assessments (maximum penile systolic velocity < 25 cm/s). Overall, during initial real-time Rigiscan evaluation, 19 men responded to low and 12 to high PGE1 doses, whereas four men responded to low and three to high MIX doses. Treatment with self-injections was safe and well tolerated. Five patients noticed fibrosis in the corpora without bend. Episodes of prolonged erections or priapism were not recorded during the treatment period.

The majority of patients responded initially to PGE1, especially to low doses, but with time they needed increasing doses of PGE1, and later, increasing doses of mixtures of PGE1 and PAP to achieve a satisfactory erection. After 7 years of treatment, none was treated with low doses of PGE1. After 5 years the majority needed a mixture of the vasoactive drugs, and particularly after 7 years the majority needed high doses of MIX. During the first year of treatment, 31 patients used prostaglandins only and seven used mixture treatments. In the 10th year, however, only two patients used prostaglandins and the majority, 36, used mixtures.

Without taking into consideration the type of DM, there was a statistically significant ($^aP < 0.001$) turn in the patients towards stronger treatments (mixtures) after 10 years. The changes in treatment in the long term are depicted analytically in Figure 2. In the 10th year of treatment, the type of diabetes was not related to the treatment used, as there was no statistically significant relation between the two variables ($^bP = 0.324$). All DM type I patients (12/12) used mixtures, as did almost all DM type II patients (24/26). But in the first year, the type of diabetes was significantly related to the kind of treatment: patients with DM type II used only prostaglandin and patients with DM type I used prostaglandin and mixtures almost equally, 5 of 12 and 7 of 12, respectively ($^bP < 0.001$). This relationship between the type of diabetes and treatment began to weaken as early as the sixth year and lost its significance in the ninth year ($^bP = 0.151$). By definition, ^bP values estimate the statistical significance of the difference between the ob-

Table 1. Classification of treatment with self-injections of vasoactive drugs in diabetic men with erectile dysfunction (ED). PAP, papaverine; PGE1, prostaglandin E1; MIX, combinations of 20 μg PGE1 and various doses of papaverine.

Treatment	Drugs and doses
PGE1 low	5–10 μg PGE1
PGE1 high	15–20 μg PGE1
MIX low	20 μg PGE1 + 8–16 mg PAP
MIX high	20 μg PGE1 + > 16 mg PAP

Table 2. Patient demographics at the beginning of our study of men with diabetes mellitus (DM) and erectile dysfunction (ED).

	Mean ± SD	Range
Age (year)	56.4 ± 3.9	42–62
DM duration (year)	5.8 ± 2.7	2–12
ED duration (year)	3.1 ± 1.9	1–8

Table 3. Relationship between patients' type of diabetes mellitus (DM) and the treatment used for erectile dysfunction. *$^{b}P < 0.001$; **$^{b}P = 0.151$. PGE1, prostaglandin E1; MIX, combinations of 20 μg PGE1 and various doses of papaverine; Count, number of patients; Expected count, number of patients according to the null hypothesis.

			First year* (ninth year**)		
			PGE 1	MIX	Total
DM type	I	Count	5 (0)	7 (12)	12
		Expected count	9.8 (1.3)	2.2 (10.7)	12
	II	Count	26.0 (4)	0 (22)	26
		Expected count	21.2 (2.7)	4.8 (23.3)	26
Total		Count	31 (4)	7 (34)	38
		Expected count	31 (4)	7 (34)	38

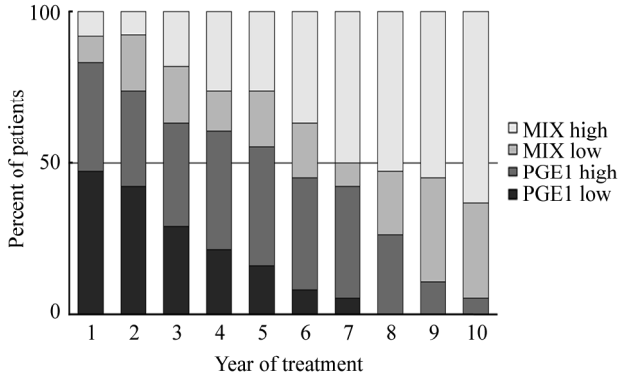

Figure 2. Treatment methods over 10 years applied to the whole study group of 38 diabetic men with erectile dysfunction (ED). prostaglandin E1 (PGE1) low, 5–10 μg PGE1; PGE1 high, 15–20 μg PGE1; MIX low, 20 μg PGE1 + 8–16 mg papaverine (PAP); MIX high, 20 μg PGE1 + > 16 mg PAP.

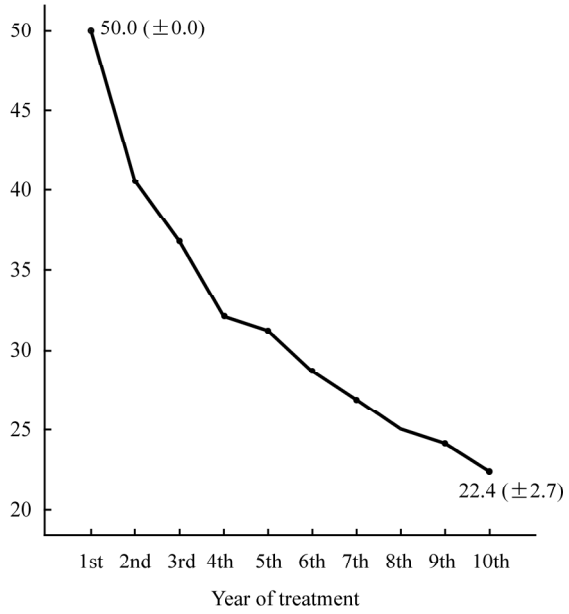

Figure 3. Mean number (±SD) of self-injections of vasoactive drugs in the whole study group of 38 diabetic patients over 10 years.

served and the expected counts of patients in each treatment method (Table 3).

The mean number of injections required by the patients as a whole was 50 in the first year and 22.5 in the 10th year. The number of injections, regardless of the type of diabetes, was significantly reduced year by year ($^{c}P < 0.001$), with a temporary weakening of significance between the fourth and fifth years ($^{c}P = 0.035$). The number of injections per year is depicted in Figure 3. Both groups of diabetic patients significantly reduced the number of injections ($^{c}P = 0.001$ for each of the groups). Between the second and fourth years, type I diabetic men used fewer injections than the type II patients ($^{d}P < 0.05$), but after the fifth year the type II patients began to close the gap, standardizing to 22.42 ± 2.67 (mean ± SD) injections at the 10th year. The mean number of injections used per year by both groups is depicted in Figure 4.

4 Discussion

The treatment of severe ED with self-injection of vasoactive drugs in diabetic patients has been a very common alternative. The mixtures of vasoactive drugs in particular, which use different mechanisms of action and exert pharmacological synergism, are an effective and safe treatment for severe diabetic ED. Self-injection is also a safe treatment, especially in terms of concerns about the perceived risk of priapism. It has been reported that priapism never occurred during the long-term treatment phase of experienced patients [13]. Although the majority of pa-

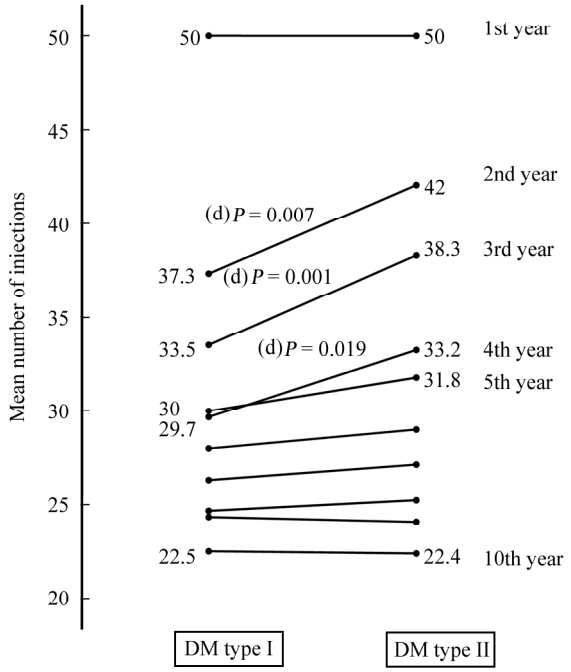

Figure 4. Mean number of self-injections of vasoactive drugs per year for each type of diabetes mellitus (DM).

tients with ED strongly prefer oral therapeutic compounds, which represent the first-line treatment because of the potential benefits and lack of invasiveness [14], diabetic men who have started self-injecting are not likely to switch successfully to oral treatment [15]. Therefore self-injection should be considered at this time a long-term therapeutic option and these patients should be advised accordingly.

In this study of men who started therapy before, but continued within, the Phosphodiesterase 5 inhibitors era, we attempted to assess the behaviour of patients with either type I or type II DM, towards continuing treatment with intracavernosal self-injections of vasoactive drugs. The group presented here are the non-responders to oral treatment after the launch of PDE5 inhibitors. Thus continuing injections, they complied with treatment because of satisfaction with the response, the quality of erections and the care undertaken for the treatment success.

To keep a patient satisfied in the long term with a semi-invasive treatment, such as the penile injection, is not easy. This issue may be mainly responsible for the high rate of non-compliance with self-injecting in the general population of men with ED. Thus, we conclude that it is very important for the physician to have a constant, personal, face-to-face communication with the patient, to solve practical problems regarding the injections and to encourage patients and their partners to continue and comply with the treatment. The adjustment of dosage to appropriate levels is also very important, particularly for the patient treated with injections. The patient must be reassured that the treatment works, and to be confident that when an increase in the dose is needed, it is necessary to go along with his physician's advice. Men with type I (insulin-dependent) DM are more familiar with self-injecting on a daily basis. On the other hand, men with type II DM, who end up using injections, are generally patients who have used oral treatment in the past unsuccessfully and injections seem the last option left before penile implantation.

The erectile tissue and penile musculature is not modified negatively or positively by intracavernosal injections [16], but the biochemical and ultrastructural changes by DM, as well as aging, affect it in a negative way [17, 18]. These factors could play a major role in the observed increased need for stronger remedies (higher doses of PGE1 or more effective mixtures of PGE1 and PAP). It is well established that the combination of low or reasonable doses of vasoactive drugs are more effective than high doses of PGE1 to achieve an erection suitable for penetration, with a lower incidence of pain [19].

In our study, in the 10th year of treatment, there was no difference between the two groups of diabetic patients in the number of injections or the kind of treatment they used. Insulin-treated men proceeded earlier than the others towards the final standardization of their treatment. Because they were more familiar with the possibility of ED, they may compromise quickly with lower expectations for sexual life, so they find their quantitave and qualitative balance earlier. DM type II patients continued for longer to make more effort for successful intercourse, which actually meant more injections per year, but ended up reaching the same levels of effort as the DM type I group. The obvious decrease of injection frequency per year for both groups may also show tiredness by time of having to self-inject and an attempt to minimize side-effects.

In conclusion, the self-injection of vasoactive drugs continues to be, in the long term, a highly effective and safe treatment for ED in men with DM. The key point for maintaining the treatment is the adjustment of the therapeutic method and dosage to optimal levels for satisfactory erections. For this reason, systematic follow-up of these cases is of the utmost importance. Diabetic men de-

crease the number of self-injections over time, set realistic expectations and create a baseline of satisfactory sexual life with aging.

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