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Intracavernous injections for erectile dysfunction in patients with cardiovascular diseases and failure or contraindications for sildenafil citrate

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The aim of this study was to evaluate the effectiveness of a progressive program for the treatment of erectile dysfunction in patients with cardiovascular disease in whom sildenafil citrate (Viagra) was not an option. The study population included 106 patients selected from 267 with cardiovascular disease. The intracavernous injection program consisted of three protocols of increasingly complex combinations of vasoactive drugs, papaverine, phentolamine, prostaglandin E1 and atropine sulfate. Patients who failed the first protocol were switched to the second, and those who failed the second were switched to the third. A positive response was defined as an erection sufficient for vaginal penetration. A positive response was achieved on protocol I in 61 of the 106 patients (57.5%); protocol II in 32 of the remaining 45 patients (71.1%); and protocol III in seven of the remaining 13 patients (53.8%); the total success rate was 94.3%. These 100 patients were included in the 1-year follow-up, and 90 reported successful coitus at the end of that period: 79 patients (87.8%) with intracavernous injection and 11 (12.2%) without injection. The remaining 10 patients (10%) dropped out of the program, seven (7.0%) for health or marital reasons and three (3.0%) because of treatment failure. We conclude that a progressive program of intracavernous injections of vasoactive drugs may be a good alternative for the treatment of erectile dysfunction in patients with cardiovascular disease.
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Introduction

Men with cardiovascular disease often also have erectile dysfunction (ED), probably because of shared factors that impair hemodynamic mechanisms in the penile and ischemic vasculature.[1] Sildenafil citrate (Viagra) has been used extensively and successfully for the last 5 y for the treatment of ED.[2–4] Though it has proven effective in most patients with underlying cardiovascular disease,[5,6] patients after ischemic heart disease,[1] and patients with severe coronary artery disease without adverse cardiovascular effects,[7] there remains a substantial proportion who either do not respond (35.1%)[8] or have severe adverse effects (31.6–50%).[3–9] In addition, sildenafil is contraindicated in patients receiving nitrate therapy.[10,11]

The aim of the present study was to investigate the effectiveness of a progressive program of injection with various combinations of vasoactive agents in patients with cardiovascular disease and ED who failed or were ineligible for treatment with sildenafil citrate.

Methods

Patients

The study group of 106 patients was selected from among 267 men aged 41–80 y (mean 64.9 ± 3.4 y) with known cardiovascular disease who were referred between 1997 and 2000 to the Institute of Urology from the Institute of Cardiology of our Center for treatment of suspected ED. The diagnosis of ED was based on the International Index of

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Erectile Function (IIEF) score,[12,13] the medical social and psychosexual history of the patient and his female partner, physical examination, nocturnal penile tumescence (NPT) testing (RigiScan®), glucose loading, and blood testosterone and prolactin levels.

Procedure

Patient selection. In 28 of the 167 patients with cardiovascular disease (10.4%), sildenafil citrate was contraindicated because of long-term nitrate therapy. The remaining patients were instructed to take one tablet of sildenafil citrate 1 h before coitus or sexual activity, 2–3 h after a meal.[3] Sildenafil was prescribed at a starting dose of 25 mg, increasing to 50 and 100 mg, depending on age, general state of health, and response. Of the 239 patients 161 (67.4%) had a positive response. Forty-nine patients (20.5%) failed to respond to the maximum dose in two consecutive trials, 3–4 days apart, and 29 (12.1%) had serious adverse effects, two (6.9%) after 25 mg, five (17.2%) after 50 mg, and 22 (75.9%) after 100 mg. The adverse effects included facial flushing in 10 (34.5%), headache in nine (31%), dizziness in three (10.3%), tachycardia in four (13.8%), abnormal vision in two (6.9%) and dyspepsia in one (3.4%). The 37 patients with adverse effects, the 28 with contraindications, and 49 failed patients, to sildenafil were enrolled in the study.

Cardiovascular status. All patients were referred to our Institute of Urology by the Institute of Cardiology at our Center. Their records were checked to determine that before starting treatment for ED, they were in stable condition, with an interval of at least 1.5 months after catheterization for angina pectoris, 2 months after catheterization with angioplasty, 2.5 months after coronary artery bypass grafting, and 3.5–4 months after myocardial infarct. There were no patients with labile or difficult-to-control blood pressure or low blood pressure. Of the 106 patients, 28 (26.4%) had hypertension, 27 (25.5%) had cardiac disease, and 51 (48.1%) had both. The duration of the cardiovascular disease after the incident or procedure ranged from 1.5 months to 20 y. The patients were receiving two to five different medications, including beta blockers, calcium channel blockers, anticoagulants, alpha blockers, aspirin, antiarrhythmic drugs, ACE inhibitors, and antilipid and diuretic drugs, two to three times a day depending on the severity of the disease. All continued to take their medications during the treatment for ED in the same manner as before the program. All patients who participated in the program were kept under ongoing surveillance by the treating cardiologist.

Patient preparation and protocols. On inclusion in the study, the patients were given a written explanation of the 18-y history of treatment with intracorporeal injection; the high effectiveness of this method for various forms of ED; the long-term use of natural vasodilators for intracorporeal injection; the lack of contraindications for this method; and its long-term effect, even after the injections are stopped, because of spontaneous action. The patients were also informed of the possible side effects: priapism, subcutaneous hemorrhage, decreased blood pressure, and plaques (nodules).

Once the appropriate dosage was selected (on an individual basis), the physician performed the first injection, with a simultaneous explanation of the technique. To ensure complete understanding, the second injection was performed at the clinic by the patient or his spouse, under supervision of the team. Thereafter, patients were instructed to perform the next injections at home 10–30 min before coitus at intervals of 4 to 8 days or according to their desire, age, and health status.

All injections were performed with a 28 gauge × 1/2 inch, 0.36 mm × 13 mm needle.

Treatment was divided into three protocols.

Protocol I: All patients initially received protocol I, which consisted of three injections at intervals of 4–6 days of papaverine 6–25 mg and phentolamine 0.05–2.0 mg. The initial dose was determined individually by age, physical condition, and anamnestic data. After injection, the patient was asked to wait for 5–20 min, and his erection was then evaluated. A positive response was defined as an erection sufficient for vaginal penetration. Patients with a positive response were given 6–10 doses to use at home.

Protocol II: Patients who failed protocol I with the maximal dose of papaverine and phentolamine were switched to protocol II, which consisted of three injections at intervals of 4 to 6 days of a combination of papaverine 18–25 mg, phentolamine 1.0–2.0 mg, and prostaglandin E1 10–25 mcg (trimix). Those who achieved a positive response after three sessions received 6 to 10 doses for self-injection at home. Patients who reported pain after the first injection of prostaglandin E1 were given a lower dose of 5–8 mcg.

Protocol III: If the maximal dose of the trimix was ineffective, the patients were given a combination of four drugs: papaverine 20–25 mg, phentolamine 1.5–2.0 mg, prostaglandin E1 20–25 mcg, and atropine sulfate 0.02–0.08 mg. Patients who failed protocol III were recommended for intracavernous injection plus a vacuum erection device.

The compatible protocol was determined after 8–22 days depending on the protocol and the receptiveness of the patient and his spouse.

Follow-up

On completion of the program, all patients who had achieved an erection under any of the protocols were re-evaluated for quality of erection. The evaluations were repeated every 2.5–3 months for one year. At each visit a physical examination was performed to identify fibrotic nodules or areas of scarring. Thereafter, the patients were given an additional 12–15 doses for self-injection until the next visit. The recommended interval between self-injections during follow-up was 3–8 days, according to patient desire, age, and health status. NPT (RigiScan) was performed after one year. The need for an increase or decrease in drug dosage or a switch to a higher-level protocol was determined by consensus by our team. Patients who failed protocol III were recommended for intracavernous injection plus a vacuum erection device or a penile prosthesis.

Statistical analysis

The results were analyzed according to Bland.[14] To determine the statistical significance of differences, we calculated the average arithmetic value and error or the average value. The significance of the difference between compared indicators was determined according to Student's *t*-test; a *P*-value of < 0.05 was considered significant.

Results

Outcome

Protocol I: All 106 patients received protocol 1, with a positive response in 61 (57.5) after three injections. Specifically, 15 of the 61 patients (24.6%) responded to the first injection, 35 (57.4%) to the second, and 11 (18%) to the third. The average duration of the positive response was 56.4 ± 4.5 min. The average dose of papaverine was 18.5 ± 1.5 mg, and of phentolamine, 1.4 ± 0.2 mg.

Protocol II: The remaining 45 patients who did not achieve an erection sufficient for vaginal penetration with protocol I received protocol II. Thirty-two (71.7%) responded, six (18.7%) to the first injection, 19 (59.4%) to the second, and seven (21.8%) to the third. The mean duration of the positive response was 50.4 ± 4.2 minutes. The average dose of papaverine was 19.4 ± 2.5 mg, of phentolamine, 1.6 ± 0.4 mg, and of prostaglandin E_1, 16.4 ± 2.5 mcg. After the first dose of 10 mcg, mild pain was reported by 11 patients (24.4%) and moderate pain by eight (17.7%).

Protocol III: Of the 13 patients who failed protocol II, seven (53.8%) responded to protocol III, four (57.2%) to the first dose and three (42.8%) to the second. The mean duration of the positive response was 42.4 ± 2.5 minutes. The average dose of papaverine was 19.8 ± 2.8 mg, of phentolamine, 1.9 ± 0.5 mg, of prostaglandin E_1, 17.5 ± 2.6 mcg, and of atropine sulfate, 0.05 ± 0.01 mg.

The remaining six patients were recommended for intracavernous injection plus the vacuum erectile device.

Comparative evaluation of the effectiveness of the progressive program by type of cardiovascular disease (Table 1) showed that 78.6% of the patients with hypertension responded to protocol I. Protocol II proved more effective in the patients with coronary artery and hypertension, and protocol III in the patients after cardiac catheterization for angina pectoris and hypertension.

Evaluation of the effectiveness of the progressive protocol program in the 29 patients who manifested adverse effects of Viagra showed that of the four

Table 1 Effectiveness of the protocols by type of cardiovascular disease

		Positive response to protocols							
		I		*II*		*III*		*Negative response*	
Cardiovascular disease	*Total no.*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Angina pectoris	2	1	50	1	50				
Myocardial infarction	3	1	33.3	2	66.7				
Myocardial infarction, angina pectoris and hypertension	4			1	25	2	50	1	25
Congestive heart failure and hypertension	3	2	66.7	1	33.3				
Valvular heart disease, myocardial infarction, and hypertension	3			1	33.3	1	33.4	1	33.3
Arrhythmia (atrial fibrillation)	7	6	85.6	1	14.3				
Arrhythmia and hypertension	6	3	50	3	50				
Hypertension only	28	22	78.6	6	21.4				
Cardiac catheterization for diagnostic angina pectoris	11	6	54.5			3	27.3	2	17.2
Cardiac catheterization with angioplasty	7	7	100						
Coronary artery bypass grafting	6	5	73.4	1	16.6				
Coronary artery bypass grafting and hypertension	24	8	33.3	14	58.3	1	4.2	1	4.2
Valvular replacement	2			1	50			1	50
Total	106	61	57.5	32	30.2	7	6.6	6	5.7

patients who had tachycardia after receiving Viagra, three had a positive response to protocol I (papaverine 18.6 mg, phentolamine 0.9 mg) and one had a positive response to protocol II (papaverine 20 mg, phentolamine 1.2 mg + prostaglandin E_1 10 mcg). Of the 10 with facial flushing after receiving 50 or 100 mg of Viagra, six (60%) had a positive response to protocol I, three (30%) to protocol II, one to protocol III. Of the nine patients with headache, six (66.7%) responded to protocol I, and three (33.3%) to protocol II. No patient had adverse effects to intracavernous injections.

Of the 49 patients who failed Viagra treatment, 37 (75.5%) responded to protocol I, 10 (20.4%) to protocol II, and two (4.1%) to protocol III.

Follow-up

The duration of follow-up was one year. Of the 61 patients receiving protocol I, 10 (16.4%) were eventually able to achieve coitus without injection, and 40 (65.6%) continued the intracavernous injections. Two patients (3.3%) discontinued protocol I for health or family reasons. The remaining nine patients (14.7%) failed to respond during follow-up and were switched to protocol II.

Of the 32 patients receiving protocol II before follow-up, 1 (3.1%) eventually achieved coitus without injection and 26 (81.2%) continued the injections. Two patients (6.3%) discontinued protocol II for health reasons. The remaining three (9.4%) failed to respond and were switched to protocol III.

Of the seven patients receiving protocol III before follow-up, four (57.1%) continued the intracavernous injections. One (14.3%) discontinued treatment for health reasons and two (28.6%) failed to respond.

Overall, after one year of follow-up, 90 of the 100 patients continued to achieve coitus: 79 (87.8%) with intracavernous injection and 11 (12.2%) without (all 11 patients had hypertension). A total of 10 patients (10%) dropped out of the program, seven (7%) because of marital problems and three (3%) because of treatment failure.

We compared the results of the NPT test before the progressive treatment and after 1 y of follow-up. A severe NPT test was defined as no episodes of tumescence or rigidity or one or two episodes of 15–20% rigidity, and changes in tumescence of less than 2–1.5 cm in the base and tip of the penis. Of the 61 patients on protocol I, NPT was severe in $75.4 \pm 4.5\%$ before treatment and in $65.5 \pm 3.6\%$ after ($P < 0.05$). NPT was severe both before and after treatment in all 32 patients receiving protocol II and all seven on protocol III.

Scores on the IIEF before and after one year of treatment were compared for erection and orgasm frequency, sexual desire, and overall and relationship satisfaction in the 90 patients with successful coitus (Table 2). According to the IIEF score at the onset of the study before the treatment program, 11 of the 106 patients (10.4%) had mild ED (score 17–21), 30 (28.3%) had moderate ED (score 11–16), and 65 (61.3%) had severe ED (score 1–10). The results after 1 y revealed a significant difference, especially in intercourse satisfaction, for which the score before treatment was 4.21 ± 1.16 and after, 12.42 ± 1.61 ($P < 0.001$). A comparison of the change in IIEF score by change in NPT results showed that all 11 patients who had successful coitus without injection after follow-up had mild ED before treatment (score 22–25). At follow-up, four (36.4%) had normal erectile function (score 22–30) and seven showed no change. NPT test results (2, 3 episodes) before treatment were as follows: rigidity $42.6 \pm 3.2\%$, tumescence 2.1 ± 0.6 cm; at follow-up: rigidity $69 \pm 3.9\%$ ($P < 0.001$), tumescence 3.2 ± 0.7 cm ($P < 0.05$).

Side effects

Two of the 106 patients who received protocol I (1.8%) had a prolonged erection (3–4 h) without pain. Of the 61 responders to protocol I, two (3.2%) had subcutaneous hemorrhage during the program and two (3.2%) had small nodules during follow-up. Of the 32 responders to protocol II, two (6.2%) had subcutaneous hemorrhage during the program, and three (9.3%) had small nodules during follow-up. In addition, 11 patients (34.4%) had mild pain after the first dose and eight (25%) had moderate pain. Of the seven responders to protocol III, one (14.3%) had small nodules and two (28.6%) had subcutaneous hemorrhage during follow-up.

Prolonged erection, which occurred only with protocol I, was treated by reducing the dosage of

Table 2 Mean response to five questions on the International Index of Erectile Function—($n = 90$)

	Score	*Before treatment (mean ± s.d.)*	*After treatment (mean ± s.d.)*	P-*value*
Erection frequence	1–30	7.15 ± 2.15	15.15 ± 3.16	< 0.001
Orgasm frequence	0–10	4.12 ± 1.05	8.91 ± 1.18	< 0.001
Sexual desire	2–10	3.46 ± 1.66	8.01 ± 1.19	< 0.001
Intercourse satisfaction	0–15	4.21 ± 1.16	12.42 ± 1.61	< 0.001
Overall satisfaction	2–10	4.81 ± 1.12	9.15 ± 1.12	< 0.001
Total IIEF	5–75	23.75 ± 7.14	53.64 ± 8.25	< 0.001

both drugs for the next injection. Thereafter, the erection lasted 1–2 h. In patients with subcutaneous hemorrhage ($n=6$), ED treatment was stopped for 6–10 days. Thereafter, the patients reported only slight, nonsignificant pain which did not interfere with their continuing the program.

Cardiovascular status

Follow-up of the patients by the attending cardiologist revealed no changes in brachial blood pressure or deterioration in general health state. In no patient was there a change in medications received for cardiovascular diseases during the progressive treatment program or follow-up.

Discussion

Many authors have used sildenafil citrate to treat ED in patients with cardiovascular disease,[1,5,6] with improvement in erections (up to 70%) and in IIEF scores. However, they did not note the mode of treatment for patients with contraindications to sildenafil, adverse effects of the drug, or failure to respond. In other studies of noncardiovascular patients with different forms of ED, those who failed sildenafil treatment were referred for intracorporeal injections.[15–17] For example, McMahon *et al*[15] used sildenafil citrate in 93 patients, starting with 50 mg and going up to 100 mg. When it was not effective (in 61, 65.6%), the patients were given intracorporeal injections of alprostadil, papaverine and phentolamine 1 h after taking sildenafil citrate, 10 min before coitus. Twenty-nine of them (31.2%) had adverse effects. Shabsigh *et al*[16] followed sildenafil failure with intracavernous alprostadil and noted improved scores for questions 3 and 4 on the IIEF in 60 of them (89.6%) and side effects (penile pain) in 25 (29.4%). These results, and those of Hatzichristou *et al*[17] were similar to the positive response rate to intracavernous injections achieved in our study (67.4%) in patients who had side effects of sildenafil or failed to respond to it. The rate reported by McMahon *et al*[15] was lower (34%). We explain this difference by the use of sildenafil in the latter study in patients with mixed vasculogenic ED. The specific side effects of sildenafil citrate noted in our patients were similar to those reported earlier,[15–17] except for facial flushing and headache. In four of our patients with sildenafil-induced tachycardia, the effect occurred 30–45 min after intake of 100 mg. The tachycardia lasted for 3–5 min. Thus, sildenafil citrate in high doses in patients with underlying cardiovascular disease should be prescribed with caution. As of 1998, the FDA reported 69 deaths apparently due to sildenafil citrate.[5]

Comparison of our findings with studies of analogous agents showed that using our protocol I, Gasser *et al*[18] reported a much higher success rate of 87.5% and Bechara *et al*[19] reported a rate closer to ours, of 54%. However, the dosages in the latter study differed: maximum 30 mg papaverine versus 25 mg in our study, and only 0.5 mg phentolamine versus 2 mg in our study. Other researchers have reported side effects with protocol I. Levine *et al*[20] noted painless nodules in 8% of patients in the first month, in 17% after 3 months, and in 57% after 12 months. Our rates were much lower: 3.2% painful nodules, in addition to 3.2% subcutaneous hemorrhage and 1.8% prolonged erection; all the nodules appeared during follow-up. This discrepancy may be explained by the relatively long interval between injections in the present study (4–8 days) and the use of a very small, disposable syringe and needle.

Our protocol II (trimix) was found to have high success rates of 72.5 to 78% in studies of analogous compositions.[21–22] Nevertheless, despite its effectiveness, we chose not to start the program with the trimix because prostaglandin E_1 often causes pain (11.7–80% of patients)[23] and it is costly (20–25 US$) compared to papaverine + phentolamine (0.5–0.8 US$ for the maximum dose). Furthermore, in combination, the three agents require special storage conditions. Age was also a consideration: nine of our 11 patients aged 40–50 y (91.8%) responded to protocol I and were spared the side effects of the trimix. Of the patients who received protocol II, 71.1% responded.

Protocol III was a quadmix of papaverine, phentolamine, prostaglandin E_1, and atropine sulfate. Montorsi *et al*[24] emphasized the effectiveness of this combination, whereas Sogari *et al*[25] reported no difference in patient response between the trimix and the quadmix. Our results agree with the former study: the addition of atropine sulfate raised the success rate of the protocol to 53.8%. The discrepancy between our study and that of Sogari *et al*[25] may be attributable to the difference in dosages. These authors administered papaverine 50 mg, phentolamine 0.2 mg, prostaglandin E_1 10 mcg, and atropine sulfate 0.07 mg, whereas our doses were 20–25 mg, 1.5–2.0 mg, 20–25 mcg, and 0.02–0.08 mg, respectively. We believe the addition of atropine sulfate increased the synergism of the pharmacological combination, leading to a relaxation of the smooth muscles of the cavernous sinusoids and helicine arteries and thereby improving the hemodynamics of arterial dilation, venous compression and sinusoidal relaxation during erection. None of the patients on protocol III had decreased brachial blood pressure after the injection, and only two (28.6%) had subcutaneous penile hemorrhage. In the latter, the intracavernous injection was stopped for 6–10 days and the hemorrhage disappeared.

Overall, localized treatment with intracavernous injection was effective, acceptable and generally well-tolerated in men with cardiovascular disease. At the 1-year follow-up, penile circulation was improved, and 11 men (11%) achieved coitus without injection, despite their continued intake of antihypertensive drugs. All 11 also had improved NPT parameters: increased episodes and increased rigidity and tumescence at the base and tip.

A spontaneous erection after intracorporeal injection with alprostadil was also observed by Brock *et al.*[26] Maniam *et al*[27] using analogous vasoactive drugs in 19 patients, noted a spontaneous erection in six, but not changes in NPT parameters. We explain our findings as follows: penile erection depends on the activity of a variety of erector systems: vascular, autonomic efferent, endocrine and central nervous systems. Our 11 patients had no damage to any of their systems other than the hemodynamic mechanisms in the penile and vasculatory ones (Conti *et al*[1]). Vasoactive drugs affect corporeal smooth muscle relaxation. The arteries dilate, permiting blood to enter into the penis, and the cavernous tissue trabeculae become engorged, contributing to the veno-occlusive mechanism that restricts egress of blood from the penis. Therefore, it was improvement in the hemodynamic mechanism that enabled these 11 patients to achieve coitus without injection even in the presence of hypertensive medication.

Conclusions

Progressive treatment with intracavernous injection of increasingly complex combinations of vasoactive drugs in patients with cardiovascular diseases who failed or had contraindications for sildenafil treatment was found to be immediately effective in 94.3% and effective after 1 y in 96%. By starting with the most available, inexpensive and extensively used drug combination, we were able to spare early responders the more complex, painful and costly drugs.

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