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ANDROLOGY

A study of the possible effects of repeated intracorporeal self-injection of vasoactive drugs in patients with elevated end diastolic velocity during pharmacopenile duplex ultrasonography

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Introduction. The aim of the work is to evaluate the effect of repeated intracavernosal self-injection of vasoactive drugs in patients with elevated End Diastolic Velocity (>5 cm/sec) during pharmacopenile duplex ultrasonography (PPDU).
Methods. Duplex evaluation was performed to the patients on self-injection therapy for comparison of end diastolic velocity and resistive index before and after completing the eight doses of IC self-injection.
Results. After the 8 trials of home therapy, 21 (52.5%) patients showed improvement in the duplex parameters regarding the end diastolic velocity, ten of them showed improvement in the EDV to the level of <5 cm/sec. The effect of different factors that may contribute to the improvement in EDV to <5 cm/sec are shown in the table 2. Age was the only predictive factor for successful response to home therapy intracavernous injection (ICI).Improvement in erectile response was assessed before and after the course of the therapy. Erection response to ICI during penile duplex improved in only six patients (E4 & E4-5)) to the point that it was sufficient for satisfactory sexual performance, 3 of them (7.5%) regained spontaneous erection and stopped using ICI (Table 3). The IIEF score was 10.6 ±2.8 before the home therapy and it became 14 ±3.9 one month after completing the treatment course (P value <0.001).
Conclusions. Early rehabilitation of the patients with venous leakage ED using ICI may help to regain normal erection and avoid unnecessary penile prosthesis surgeries.

Key Words: erectile dysfunction ‹› venous leakage ‹› intracavernosal injection

INTRODUCTION

Erectile dysfunction can be defined as the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In the face of an aging population, decreasing social stigma associated with erectile dysfunction, and an increasing availability of effective oral therapy for its treatment, the number of patients presenting with this complaint has increased dramatically [1].
Etiology of venogenic erectile dysfunction is not exactly known. Various pathologic processes have been accused as being the cause, but none proved entirely satisfactory. These include: presence of large venous channels draining corpora cavernosa, Peyronie's disease, diabetes, and structural alterations in fibroblastic components of trabeculae and cavernous smooth muscles.
The aim of therapy is to restore rigid erections in order to improve the quality of erection, the frequency of penetration, and the overall sexual experience. Current pharmacologic approaches include oral therapies (phosphodiesterase-5 [PDE-5] inhibitors), intracavernosal injections, and intraurethral applications. The selection of an agent, however, depends

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on the underlying etiology, disease severity, treatment success, and modality tolerance.

Intracavernosal-injection therapy is an important therapeutic option for men with erectile dysfunction of various causes [1]. The combinations were logically based on the differing mechanisms of action of these drugs. PGE1 activated cAMP, phentolamine inhibited the alpha-adrenoceptors, and papaverine promoted the action of the generated cAMP/cGMP by nonspecifically inhibiting phosphodiesterases [2].

Duplex Doppler penile ultrasound (DDPU) is a useful, minimally invasive method for evaluating penile hemodynamics in patients with erectile dysfunction. The measurement of peak flow velocity, end-diastolic flow, and resistance index is helpful in assessment of the penile vascular status, especially in patients who do not respond to oral therapy.

Patients who continue to have high end diastolic velocity (EDV) over 5 cm/sec throughout the examination despite normal arterial inflow may have venogenic erectile dysfunction [3]. The value of end diastolic velocity is of no importance if arterial insufficiency is present [4]. This study aimed at evaluating the effect of repeated home therapy ICI on men with erectile dysfunction and high EDV (>5 cm/sec) as diagnosed by DDPU.

MATERIAL AND METHODS

Patients are selected from those attending Andrology outpatient clinic in Kasr El-Ainy hospital Cairo University, with the following inclusion criteria:

- The patient must be suffering from erectile dysfunction for more than 6 months.
- The patient showed poor response to oral sildenafil 100 mg (6-8 trial times).
- The patient showed unsatisfactory response when he underwent ICI trials in the clinic with a maximum dose of 1 cc Quadmix .
- Penile duplex showed elevated EDV (>5 cm/sec).

Exclusion criteria:

- Any patient suffered from neurological manifestations or motor deficit.
- Any patient with penile fibrosis or Peyronie's disease.
- Any patient showed satisfactory response to ICI.

Each patient was subjected to the following:

1. Proper history taking with emphasis on IIEF-5; as valid and reliable instrument in determining efficacy of treatment [5].
2. General and local examinations were done with inspection of secondary sexual characters and exclusion of all neurological or endocrinal manifestations, vascular abnormality, penile fibrosis or Peyronie's disease.
3. Estimation of blood sugar level, TTE, and PRL.
4. Patients underwent intracavernous injections (ICI) test using Quadmix, which is a combination of four drugs: Papaverine (15 mg/ml Quad), phentolamine (0.5 mg/ml Quad), PGE (5 µg/ml Quad), and atropine (0.2 mg/ml Quad); this was done by examination of the penis for the degree and duration of penile rigidity after the intracavernosal injection starting with 0.25 cc Quadmix using a 29-gauge needle. The grade of erection was evaluated throughout the study, according to Vanahlen and Hertle [6]. If the patient did not show satisfactory response, the dose was increased to 0.5 cc Quadmix and if still no response a maximum dose of 1 cc Quadmix was injected and erection quality was evaluated.
5. Penile duplex study was done using 1 cc Quadmix for non-responders to ICI test, measuring peak systolic and end diastolic velocities as well as resistive index on both right and left cavernosal arteries 5, 10, and 20 minutes after the injection, According to duplex findings, patients with elevated EDV (>5 cm/sec) were given home therapy ICI.
6. Therapeutic trial. Each patient was given home therapy ICI of 1 cc Quadmix for eight trials. The patient was instructed to inject himself twice weekly irrespective to the coitus after teaching him how to use ICI home therapy .
7. Penile duplex was redone to each patient one month after the end of the eight trials to compare between the pre and post treatment values.
8. IIEF was evaluated one month after stoppage of the therapy and scores were compared before and after the therapy to detect whether there is any improvement after the course therapy.

Informed consent was obtained from all patients prior to the study together with approval of our local institutional ethics research committee.

Statistical method

Data were statistically described in terms of range, mean ± standard deviation (±SD), frequencies (number of cases), and percentages when appropriate. Comparison of numerical variables between pre and post treatment was done using paired t test. For comparing categorical data, chi square, and Cramer's V test for symmetric measures were performed. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

This study included forty patients who were complaining of erectile dysfunction attending the An-

drology outpatient clinic, Kasr El-Aini hospital, Cairo University. The results showed elevated EDV (>5 cm/sec) by CDDU. Their mean age was 39.6 ±8.9. Duration of erectile dysfunction was 3.8 ±3.8 years with absent morning erection in 92.5% of cases. Twenty-one of them were smokers (52.5%), 10 diabetics (25%), two hypertensive (5%), four hypogonadal (10%), and two hyperprolactinemic (5%). The following table shows the pharmacopenile duplex parameters before and after the ICI therapy. Duplex parameters before and after the home therapy ICI showed statistically significant improvement in EDV & RI of right and left cavernosal artries. There was no significant change in MSV (Table 1).

After the eight trials of home therapy, 21 (52.5%) patients showed improvement in the duplex parameters regarding the end diastolic velocity, ten of them showed improvement in the EDV to the level of <5 cm/sec. The effect of different factors that may contribute to the improvement in EDV to <5 cm/sec are shown in the table 2. Age was the only predictive factor for successful response to home therapy ICI.

Improvement in erectile response was assessed before and after the course of the therapy. Erection response to ICI during penile duplex improved in only six patients (E4 & E4-5) to the point that it was sufficient for satisfactory sexual performance, three of them (7.5%) regained spontaneous erection and stopped using ICI (Table 3). The IIEF score was 10.6 ±2.8 before the home therapy and it became 14 ±3.9 one month after completing the treatment course (P value <0.001). Apart from minor discomfort with injection, no serious side-effects (penile pain, priapism, faulty injection or penile fibrosis) occasionally associated with the injections were reported.

Table 1. *Pharmacopenile duplex parameters before and after the ICI therapy*

	Before ICI	After ICI	P value
Rt PSV	36.6 ±8.5	39.2 ±10.5	0.094
Lt PSV	37.7 ±7.3	38.8 ±7.2	0.353
Rt EDV	7.6 ±2.2	5.9 ±3.6	0.003
Lt EDV	7.6 ±2.3	5.5 ±3.8	0.001
Rt RI	0.78 ±0.06	0.83 ±0.1	<0.001
Lt RI	0.78 ±0.07	0.84 ±0.1	<0.001

Table 2. *Factors that may contribute to normalization of EDV after home therapy*

	Post ICI normal EDV <5 cm/sec (N = 10)	Post ICI abnormal EDV >5 cm/sec (N = 30)	P value
Age (Mean ±SD)	34.5 ±7.4	41.27 ±8.8	0.003
Smoking	6 (60%)	15 (50%)	0.583
Duration (Mean ±SD)	3.23 ±2.7	3.93 ±4.1	0.718
Diabetes	1 (10%)	9 (30%)	0.474
Low TTE	1 (10%)	3 (10%)	1.000
Elevated PRL	1 (10%)	1 (3.3%)	0.583

DISCUSSION

This study was carried out on forty patients complaining of erectile dysfunction who were diagnosed as venous leakage using Duplex Doppler penile ultrasound (DDPU), all of them used 1 cc Quadmix twice weekly as intracorporeal injection for eight consecutive doses 15 minutes precoital as home therapy.

Our study showed improvement of EDV bilaterally (<5 cm/sec) in ten patients (25%), six of them (15%) could achieve erection sufficient for satisfactory sexual performance after completing the whole eight doses of the ICI (three aided and three unaided), and it was found that improvement among E2 patients happened in 88.9%, while in E2-3 patients it happened in 63.6%, and among the E3 patients it occurred in 42.1% after finishing the treatment course. The results of IIEF showed a highly significant difference before and one month after the therapy (p value = <0.001).

It has long been recognized that some patients will recover spontaneous erections with many non-surgical treatment techniques, including intracavernosal injection therapy. Studies have reported return of

Table 3. *The response of the patients to ICI during penile duplex before and after the treatment course*

Erection grade	No. of Pts. before ICI	Post ICI							
		E2	E2-3	E3	E3-4	E4	E4-5	E5	% improved
E2	9	1 11.1%	2 22.2%	3 33.3%	2 22.2%	1 11.1%	0 0%	0 0%	88.9%
E2-3	11	0 0%	4 36.4%	5 45.5%	2 18.2%	0 0%	0 0%	0 0%	63.6%
E3	19	0 0%	0 0%	11 57.9%	3 15.8%	4 21%	1 5%	0 0%	42.1%
E3-4	1	0 0%	0 0%	0 0%	1 100%	0 0%	0 0%	0 0%	0%

erectile ability in two of 29 (7%) patients [7], three of 35 (9%) [8] and three of 30 (10%) [9], after a course of intracorporal injection therapy. This study gave similar result with return of natural function in three out of 40 patients (7.5%).

The proposed mechanisms of improvement are resolved psychogenic issues, improved cavernous blood flow, improved cavernous oxygen tension, and/or normal episodic fluctuation in erectile function [10]. Other factors that might contribute to the improvement include improved cavernous hemodynamic responses resulting from mechanical dilatation of cavernous arteries and/or mechanical stretching of cavernous and tunical tissues. This, in turn, may produce improvement in tissue compliance and corporo-venous occlusive efficacy. Angiogenesis and neovascularization of cavernous tissue induced by prostaglandin injection and hypertrophy of cavernous smooth muscle, resulting in enhanced efficiency of cavernous physiology.

The large study of the long-term effects of intracavernous injection therapy is that of Virag et al. [11]. They reported on 533 patients followed while on intracavernous injection therapy with papaverine alone and a combination of papaverine with alpha blockers. Of the total group, 27.5% were classified etiologically before treatment as psychogenic, 25.2% as organic, and 47.3% as mixed psychogenic and organic impotence. Of the entire group of patients followed while on therapy, 7.8% stopped using ICI and were considered cured and 7.2% maintained good natural erectile function by monthly maintenance ICI.

Another 49% of the patients were partially dependent on self-injection therapy, requiring only occasional injections to maintain adequate sexual function. It is notable that the percentage of psychogenic etiology in the significantly improved group was higher than in the total group (39.3% *vs*. 27.5%) and the percentage of organic etiology was lower in the improved group than in the total group (18% *vs*. 25.2%). The age of the improved group was younger than the total group (38 y *vs*. 48 y). The study of Virag et al. [11], showed a higher percentage of improvement in comparison to our study, which may be attributed to the fact that their study mainly included patients with psychogenic etiology of erectile dysfunction while our work included only patients with organic venous erectile dysfunction. Virag et al. [11], data weakly suggest that a significant improvement of the natural erections following intracavernous injection therapy is more likely to occur in younger men with a psychogenic etiology of impotence.

Our study also proved that the age is a crucial factor for improvement of the venous leakage after the treatment course as we classified our patients into two groups; post ICI normal and abnormal EDV groups. We found that the mean age of the normal group was (34.5 ±7.35) while the mean age of the abnormal group was (41.27 ±8.79) and the p value was 0.031, which indicates that the younger the age, the better the response to ICI.

In a comprehensive review by Sharlip [10], of trial data on 2,817 men treated with various IC vasoactive agents either alone or in combination, about 9% of men achieved natural erections and no longer required IC injections. An additional 16% reported a reduction in the frequency or dosage of IC injections required for satisfactory sexual function.

Our study was in agreement with previous studies [9-12], which all showed good a response of erection after repeated IC self-injection. The last two studies included a nearly equal number of patients compared to ours (35 & 30) respectively; on the other hand, the study of Awad et al [9], that showed a statistically significant improvement of peak systolic velocity before and after ten doses of IC self-injection is not in agreement with our study that showed no significant difference regarding the peak systolic velocity of the cavernosal arteries, but showed statistically significant difference in end diastolic velocities. Our study showed that disturbances in the level of testosterone do not affect the response of the patients to ICI, because from among the patients with low testosterone levels that were included in our study, some of them showed improvement and others did not.

Reported complications of ICI have included hematomas, burning pain after injection, urethral damage, cavernositis or local infections, fibrotic changes of the corpora cavernosa, curvature, and prolonged erections or priapism. Prolonged erections may be seen during the dose titration phase and were reported in two (15%) patients treated [12]. Due to proper titration, we have not encountered any of these problems with our patients.

CONCLUSIONS

We found that the repeated intracorporeal self-injection may aid in achieving good erection and improving the element of venous leakage to the point that the patients could avoid further use of ICI. Therefore, an early rehabilitation course using repeated ICI is recommended for patients with venous leakage especially those who are young in age. On the other hand, further longer-term studies on larger numbers of patients is highly recommended to prove the effect of repeated ICI and identify the different factors that may contribute to improvement. Finally, penile prosthesis should not be rushed in young patients with diagnosed venous leakage unless multiple trials of ICI are done.

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