DOPPLER EVALUATION OF ERECTILE DYSFUNCTION IN DIABETIC PATIENT WITH INTRACAVERNOUSAL ALPROSTADIL (CAVERJECT®) INJECTION

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ABSTRACT

Objective: Erectile dysfunction (ED) is a common enough male problem. It is secondary to organic, psychogenic and combined causes. This study described the normal sonographic anatomy of the penis, sonographic technique for evaluation of ED and the normal phases of erection with intracavernous injection (ICI) of alprostadil (coverject®).

Patients and methods: Twenty five diabetic patients (on oral hypoglycemic drugs for at least 10 year) complaining of prolonged history (>2 years) of ED, aged 35 to 45 years, were included in this study. The treatment started with a minimal dose of 1.125 micrograms and the dosage was titrated to achieve rigid erection. Following the establishment of the effective dose, Doppler US examinations were performed.

Results: 21 patients (84%) had a grade IV erectile response, the remaining 4 patients (16%) have grade III. A significant increase in peak systolic velocity between baseline and 20 µg PGE1 (p<0.001) was observed in all cases. Following ICI of Coverject there was a significant increase in grade of erection (p<0.001) and a significant reduction in the end diastolic volume (EDV) (p<0.001). A reduction of the EDV to below 5 cm s⁻¹ was observed in all patients. Four patients with EDV <5.0 cm s⁻¹ but >0.0 cm s⁻¹ had poor erectile response following ICI while 21 showed persistent EDV reduction <5 cm s⁻¹ with good rigidity.

Conclusion: the important cause of ED in the diabetic patient is psycogenic factor and Intracavernous injections of Caverject are effective therapy for erectile dysfunction

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual relations (1, 2). The last decade has witnessed major advances in the understanding of erection and its underlying mechanisms. A complex hemodynamic process is being delineated; involving four basic elements, namely, sinusoidal relaxation, arterial inflow, venous occlusion and neural control (3, 4). Erectile dysfunction affects as many as 30 million men in America, with an increasing prevalence with age. Impotence affects diabetic patients 10–15 years earlier than the general population, regardless of insulin-dependence status, and it may often be the first clinical sign of peripheral nervous system involvement (1,5,6). Erectile
Dysfunction may be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal and drug-induced), and mixed. Mixed erectile dysfunction is most commonly encountered having both a psychogenic and organic component. Several pathophysiologic states, such as diabetes mellitus, may have detrimental effects upon erectile capacity via multiple pathways. Erectile dysfunction may be a manifestation of generalized atherosclerosis. Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation. Dysfunction of the venoocclusive mechanism that normally allows maintenance of erection can cause erectile dysfunction and may be the result of degenerative changes affecting the penis such as general aging, Peyronie’s disease, and diabetes mellitus.

The transurethral administration of prostaglandin E1 has shown a positive effect in the treatment of a substantial proportion of men with chronic erectile dysfunction. Agents such as PGE1 act directly on the trabecular smooth muscle, binding to specific EP receptors and increasing cAMP synthesis. As such, the direct-acting agents do not require sexual stimulation for efficacy.

Color Doppler sonography is the best method in diagnostic evaluation of patients with erectile dysfunction. It assesses the integrity of the arterial supply to the penis and provides some useful information on the veno-occlusive mechanism. Because the arterial diameter and flow rate change during the different phases of erection CDS is performed after pharmacostimulation with vasoactive agents.

**AIM OF STUDY**

This study aimed to investigate the intracavernous alprostadil injection using color duplex ultrasound or the diagnosis in diabetic men. The ultrasonography results were compared before and after intracavernous injection of alprostadil administration in patients with erectile dysfunction (and analyzed according to the risk factors). To see if there are differences in the mean peak systolic velocities (PSVs) and the mean end diastolic velocities (EDVs) between the two group of patients.

**PATIENTS & METHOD**

**Patients:**

from January 2010 to May 2010, 25 consecutive patients of varying ages from radiological unit of Baghdad teaching hospital, Baghdad, Iraq. with a prolonged history (>2 years) of inability to attain or maintain a satisfactory erection were recruited. All patients underwent physical examination of the external genitalia; evaluation of bulbocavernous reflex, perineal and abdominal sensation was normal. All patients gave informed consent to undergo a Doppler US examination with intracavernosal administration of a single dose of 20 μg PGE1 (alprostadil).

**Procedure:**

**Equipment used:**

1-25 gauge needle and Tuberculin syringe
2-injectable Caverject (penile injection set)
3-alcohol prep pads
4- three non-sterile gloves
5- Ultrasound probe-7 MHz (Philips HD 11, Germany)

Firstly, the dose titration of Alprostadil (Caverject, Upjohn S.A P u u r s , Belgium), is supplied as a sterile, freeze dried powder in a 5 ml vial. After it was reconstituted with one milliliter of bacteriostatic water, each vial contained 20 μgms of Alprostadil, 173 mg per milliliter of lactose and 47 μgms per milliliter of sodium citrate. In the mean time patient will be laying on its back on the examining room table. The penis was pulled
away from the body until the skin was taut. A syringe with 25 gauge ½ inch needle was held at the right angle to the penis and the injection was given at the base of the penis on either side alternatively, avoiding visible veins. Pressure was applied to the injection site for five minutes or until bleeding stopped. The first injection was delivered with a small amount of the drug (starting dose- 1.125 μgm). The optimal dose was one that produced erection suitable for intercourse and not exceeding duration of 60 minutes. Once this was accomplished and after 5 minutes, a Penile Doppler US of the cavernosal arteries on both sides of the penis was done. Fifteen minutes after the injection, we will do the same penile Doppler study of the cavernosal arteries was reported(13). Artificial erection was categorized into four grades by two observers, using the following criteria (14); Grade I: partial tumescence; Grade II: full tumescence with inability to penetrate; Grade III: incomplete rigidity adequate for penetration, but not maximal; Grade IV: full rigidity. The presence of full rigidity (defined as erection grade IV) and flow reversal in diastole (EDV <0.0 cm s\(^{-1}\)) was accepted as an unequivocal response to PGE1. An EDV measurement of <5.0 cm s\(^{-1}\) is generally accepted as excluding venogenic impotence, but in the current study full rigidity, the clinical requirement of the patients, was the end-point (15, 16).

**Doppler ultrasound**

Doppler US examinations were performed with a Philips HD 11 (Philips com.; Germany) using a 7–10 MHz extended frequency linear probe which machine giving comparable spectral Doppler US assessment. All patients underwent the same US examination protocol. A grey-scale US examination of the penis was performed to identify any fibrosis or calcification. The right cavernosal artery was imaged on color Doppler US, in a longitudinal direction, and a "gate" (width 2 mm) placed over the proximal artery to record a spectral Doppler waveform. The baseline PSV was recorded by measuring the highest angle-corrected velocity (<60°) using the internal calipers of the machine and the software measurement package provided by the manufacturers(17). The following measurements were obtained at 5 min, 10 min, 15 min and 20 min following the intracavernosal injection of 20 μg PGE1; 1) PSV in cm s\(^{-1}\), defined as the highest velocity measured on the spectral Doppler waveform. 2) EDV in cm s\(^{-1}\) defined as the lowest velocity on the spectral Doppler waveform. The EDV could be below the baseline demonstrating flow reversal. 3) Grade of erection estimated 15 min after the PGE1 injection. Care was taken to obtain measurements at the same point along the right cavernosal artery at the base of the penis. The same two experienced radiologists performed all the Doppler US investigations including those that preceded the enrolment(13).

**STATISTICAL METHODS**

Analysis of variance with repeated measures for PSV was used to assess the longitudinal change over time from baseline to 10 min, 15 min and 20 min, and over the increasing doses of PGE1. For the other measures (EDV and grade) the longitudinal change over time was only evaluated between baseline and 15 min for which data were completed.

**RESULT**

Twenty five diabetic patients (on oral hypoglycemic drugs for at least 10 years), age between 35 to 45 years (mean age 40.2 years) were included in the study. The majority of patients were young men. 20 patients were married, 3 were single and 2 patients were divorced. All participants were having normal sexual activities at least 2 years previously. None of them had received intacavernosal injections prior to their enrollment in this study. Following intracavernosal injections of Caverject, sufficient erection for coital penetration was
achieved in 21 patients (84%). 4 patients (16%) responded with grade 3 penile tumescence. With tumescence (increase in intracorporal pressure), a characteristic and continuous progression of cavernosal artery velocity and wave form patterns was observed. This was initiated by intracavernosal injection of caverject, is the transition between undetectable and continuous flow. The peak systolic velocity increased from 0 to 30 cm/sec. It was defined as the first waveform phase that could be identified consistently. It was characterized by continuous flow throughout the cardiac cycle. The mean peak systolic velocity was 32 cm/sec, and the peak diastolic velocity was 8.7 cm/sec. Maximal positive diastolic velocity occurred during this phase, whereas peak systolic velocity was maximal in all subjects. Phase 2 is defined by a progressive decrease in the diastolic velocity. Systolic velocity decreased during the midportion of this phase in four subjects. During the second half of this phase, the systolic velocity increased and peak systolic velocity was 32 cm/sec. Phase 3 is identified when diastolic flow approximates zero. The mean systolic velocity was 70 cm/sec. During this phase, patients exhibited maximal peak systolic velocity. The waveform was narrowed and sharply peaked. Phase 4 is defined by reversed diastolic flow. Reversed diastolic flow developed first at end diastole, as intracorporal pressure increased, reverse flow was seen throughout diastole. The mean peak reverse diastolic velocity during this phase was 3 cm/sec, whereas the mean peak systolic velocity remained positive (68 cm/sec). The systolic waveform was narrow and sharply peaked and Peak systolic velocity was maximal during this phase in five subjects and was equal in phases 1 and 4 for one subject. Phase 5 is characterized by the eventual loss of both systolic and diastolic flow signals. Loss of flow reversal was first noted during end diastole, while velocity and the duration of the systolic component decreased continuously. The end stage of the flow cycle and is defined by loss of both systolic and diastolic flow. Doppler US scans in a 45-year-old impotent patient with DM. Images captured in the longitudinal plane at the base of the penis parallel to the cavernosal artery. (a) Evaluation 15 minutes after intracavernosal injection of prostaglandin E1(Caverject) demonstrates The patient had grade III erection. (b) Evaluation after prostaglandin E1(Caverject) 20 minutes demonstrates PSV of 68 cm/sec and EDV of −5 cm/sec. The angle of measurement is corrected to 55°. The patient had penile tumescence. Doppler US scans in a 61-year-old impotent patient with DM. Images captured in the longitudinal plane at the base of the penis parallel to the cavernosal artery. (a) Evaluation 10 minutes after intracavernosal injection of Intracavernous injections of prostaglandin E1(Caverject). The patient had grade III erection. (b) Evaluation after Caverject administration 20 minutes after the beginning of Caverject administration demonstrates a PSV of 64 cm/sec and an EDV of 1 cm/sec. This was the maximal PSV during the entire evaluation.

**DISCUSSION**

Penile erection is a complex neurovascular event that has been the subject of extensive clinical research. In patients with corporovenous occlusive dysfunction, ultrastructural studies have demonstrated a reduced percentage of smooth muscle fiber as a result of exposure to toxic risk factors (hypercholesterolemia, smoking) or chronic ischaemic processes and DM (18). However, it has been hypothesized that anxiety-mediated raised sympathetic tone may maintain the corporeal smooth muscle in a state of contraction, resulting in cavernovenous incompetence from a psychogenic rather than an organic mechanism (19). Failure to respond to intracavernous PGE1 does not necessarily
indicate the presence of an organic problem as anxiety, or the embarrassment of an erection, either during sexual intercourse or during the course of a Doppler US examination may block the effect of pharmacological stimulation. Doppler US is recognized as a reliable investigation to assess penile arterial integrity, although some authors report a lower sensitivity of Doppler US over cavernosometry in the assessment of venogenic impotence (20, 21). In the current study, following 20 µg PGE1, a small number of patients responded with a normal Doppler US pattern and not developed full rigidity. In the majority (n=21) full rigidity developed; a optimal erection, PSV >30 cm s⁻¹ limit (which defines cavernous arterial integrity) and an EDV >0.0 cm s⁻¹. In this study the level of EDV not reaching >4 cm s⁻¹ .An EDV >5 cm s⁻¹ is thought to indicate significant venous leakage, although in the presence of an incomplete erectile response, uncertainty exists when the EDV remains elevated above 0.0 cm s⁻¹ (22, 23). Interpretation may lead to a possible diagnosis of venogenic impotence, leading to further and more invasive investigations. A completely normal unequivocal response would be full rigidity (grade IV) and an EDV <0.0 cm s⁻¹ (reversal of flow in diastole). These findings are highly suggestive that the majority of our patients had a "non-anatomical" corporovenous occlusive dysfunction. In our study, we not only found significant differences in the clinical response of intracavernosal injection of coverject also in changes in PSVs in the cavernosal arteries. Significantly more patients had erection or congestion and a higher PSV with use of intracavernosal injection. Because our study group of 21 patients was the same for the regimen and all other variables were constant, our results indicate that intracavernosal injection is more likely to cause improvement in a patient's erectile dysfunction , and this improvement is the direct result of a greater increase in cavernosal arterial flow. The possible explanation for the clinical and US differences we found between patient before and after intracavernosal injection may be related to patient anxiety. The test-induced anxiety might have been higher with DM patients since it was the first examination performed. Patient anxiety is an important factor that can affect both clinical and Doppler US results. However, it has been documented that patients are understandably more comfortable using sildenafil compared with intracavernosal injection (24) and that intracavernosal injection can increase adrenergic tension, causing a decrease in erection (25). Although psychogenic erectile dysfunction was historically considered to be the most common cause, mixed disorders are most common. Araujo et al. and Shabsigh et al. (26,27)found that Psychogenic erectile dysfunction can be caused by performance anxiety, strained interpersonal relationships, lack of sexual arousability, and overt psychiatric Erectile dysfunction is noted in patients with neurological disorders disorders is the effect of psychological stimuli abates with age. Androgen deficiency results in a decrease in both nocturnal erections and libido. Although testosterone levels do not correspond to severity of erectile dysfunction, in those patients with reduced libido (28). However, erection in response to visual sexual stimulation is preserved in men with hypogonadism, suggesting that androgen is not absolutely essential for erections, due to multiple pathways (29,30). Erectile dysfunction may be a manifestation of generalized atherosclerosis and may even be its initial presentation. Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation (31). Less commonly, local stenosis of the common penile artery may occur in men who have sustained blunt pelvic or perineal trauma (32). Dysfunction of the venoocclusive
mechanism that normally allows maintenance of erection can cause erectile dysfunction (33) and may be the result of degenerative changes affecting the penis such as general aging, Peyronie’s disease, and diabetes mellitus, especially if there has been a long period without rigid erection. Although generally caused by global penile tissue degeneration, venoocclusive dysfunction may also be the result of congenital or trauma-induced formation of large venous channels draining the corpora cavernosa. Venous leak can be seen in anxious men with excessive adrenergic tone causing structural alterations of the cavernous smooth muscle and endothelium and insufficient trabecular smooth muscle relaxation (34). Young patients are deemed to be more prone to intracavernosal PGE1 response failure due to a high adrenergic tone (35). Other authors advocate audio-visual sexual stimulation combined with genital self-stimulation to augment the vasoactive erectile response during Doppler ultrasound. A significant decrease of the EDV after serial administration of intracavernous drugs combined with genital plus audio-visual sexual stimulation has been reported (36). In conclusion our results seem to indicate that the intracavernous PGE1 injection effective and safe therapy for men with erectile dysfunction, Doppler US examination is safe and can provide useful further information in a significant number of impotent patients when appropriately selected, the diabetic patient exposed to multiple factor causing erectile dysfunction (like psychogenic effect) rather than venoocclusive mechanism and its more reliable to be educate the patient about the disease. We advocate the use of a re-dosing protocol at any time with a full PGE1 dose with other drugs like phentolamine or saldinafile a dynamic when Doppler US study with shows a pattern consistent with venous leakage. The application of this protocol in our practice has enabled a consistent reduction in the number of Doppler US diagnoses of venous leakage erectile dysfunction.

<table>
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<tr>
<th>TIME</th>
<th>RTPSV cm/s</th>
<th>RT EDV cm/s</th>
<th>LT PSV cm/s</th>
<th>LTEDV cm/s</th>
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<td>36± 10.6</td>
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<td>15 min</td>
<td>70 ± 10.8</td>
<td>3.9 ±1.44</td>
<td>72 ± 21.7</td>
<td>4 ± 1.3</td>
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<tr>
<td>20 min</td>
<td>68 ± 23.4</td>
<td>2.4 ±0.23</td>
<td>66 ± 13.9</td>
<td>3 ± 1.7</td>
</tr>
</tbody>
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Table 1 shows the mean and standard deviation of patients with systolic and diastolic velocity Baseline
Figure 1.

Figure 2.
REFERENCES

Doppler Evaluation Of Erectile Dysfunction In Diabetic Patient With Intracavernous Alprostadil (Caverject®) Injection

تقييم الدوبلر لضعف الانتصاب في المرضى المصابين بالسكري باستخدام الحقن الجوفي بعقار البروستاديل

الخلاصة

ضعف الانتصاب هو أحد مشاكل الرجال المهمة، وهو ثانويً إلى الأسباب المشتركة والنفسية المنشأ والعضوية. وصفت هذه الدراسة التشريح الطبي للقضيب بواسطة جهاز الأشعة فوق السمعية، لتقييم ضعف الانتصاب والمراحل الطبيعية للانتصاب بالحقن الجوفي بعقار البروستاديل.

خمسة وعشرون مريض من مرضى السكري ويعمر يتراوح بين 50-35 سنة يعانون من ضعف الجنسي (ضعف الانتصاب) لمدة أكثر من ستة أشهر، لمعالجة بدأها مع جرعة أقل ما يمكن من 125 مايكلوغرام وترتفع الجرعة حتى إنجاز الانتصاب الكامل. أظهرت فحوص الدوبلر بعد الجرعة الفعالة.

أظهرت النتائج أن 21 مريض (84%) كان عندهم الدرجة الرابعة من الانتصاب، المرضى الباقون (6%) عندهم الدرجة الثالثة، ولاحظت في كل الحالات زيادة هامة في السرعة الإنبساطية البالغة الذروة بين الخط الأساس و 20 مايكلوغرام من عقار البروستاديل (0.01%)، وكان هناك زيادة هامة في درجة الانتصاب (0.01%) وتفخيص هام في السرعة الإنبساطية إلى تحت 5 سيتيمتر/ثانية لوحظ في كل المرضى، أربعة مرضى مع تخفيف السرعة الإنبساطية إلى تحت 5 سيتيمتر/ثانية ولكن > 0.00 سيتيمتر/ثانية كان عندهم رد قابل للانتصاب مستويً الذي ينطلق بالحقن الجوفي بعقار البروستاديل بينما 21 مريض كان عندهم انخفاض دائم في السرعة الإنبساطية > 5 سيتيمتر/ثانية ظهروا الظاهرة الجديدة. استنتج من هذه الدراسة أن السبب المهم للضعف الجنسي (ضعف الانتصاب) في المرضى المصابين بالسكري هو الحالة النفسية واستخدام الحقن الجوفي بعقار البروستاديل علاج فعال للضعف الجنسي.

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