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# Evaluation of the sensitivity of different doses of vasoactive drugs in diagnosing erectile dysfunction in impotent patients: a prospective case-control study

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**Introduction** Erectile dysfunction (ED) is one of the most common sexual disorders worldwide affecting about 30 million men in the United States, and an estimated 100 million men worldwide. Penile duplex doppler ultrasound (PDDU) is performed using an intracavernosal injection (ICI) of a vasoactive agent to demonstrate both arterial insufficiency and veno-occlusive dysfunction. This article aims to evaluate the sensitivity of different doses of different vasoactive agents used to diagnose ED in impotent patients.

**Material and methods** This study recruited 90 subjects with ED and 100 healthy subjects as controls. All of the subjects were assessed using the International Index of Erectile Function score (IIEF-5) while degree of erection was assessed by the Erection Hardness Score (EHS). Two penile duplex tests were done for each candidate two weeks apart.

**Results** None of the sample population achieved a normal clinical response (EHS >2) to 10 ug PGE1. In contrast, 60 controls (60%) had a normal response (EHS >2) to 10 ug PGE1. This difference in response between the sample and control populations to 10 ug PGE1 was of high statistical significance 11 ($p < 0.001$). In contrast, 54 (60%) out of the 90 cases had normal clinical response (EHS >2) to 0.25cc Trimix (everywhere). Interestingly, 96 controls (96%) demonstrated normal response (EHS >2) to 0.25cc Trimix. This difference in response between the sample and control populations to 0.25 cc Trimix was also of high statistical significance ($p < 0.001$).

**Conclusions** Our study demonstrated a statistically significant association between the response to Trimix over PGE1 and peak systolic velocity (PSV) and end diastolic velocity (EDV). Thus, we conclude that 0.25 cc Trimix is more sensitive than 20 ug PGE1 in diagnosing ED for impotent patients and also provides a more potent response.

Key Words: penile duplex doppler ultrasound ‹› erectile dysfunction ‹› prostaglandin E1 ‹› Trimix

## INTRODUCTION

Erectile dysfunction (ED) is one of the most common sexual disorders worldwide affecting about 30 million men in the United States [1], and an estimated 100 million men worldwide [2, 3]. However, men with ED usually suffer in silence due to the associated stigma [4]. ED is defined as the persistent and/or recurrent inability to attain and/or maintain a penile erection necessary for sexual intercourse [5]. Penile duplex doppler ultrasound (PDDU) is performed using an intracavernosal injection (ICI) of a vasoactive agent to demonstrate both arterial insufficiency and veno-occlusive dysfunction [6]. PDDU is an important tool in the diagnosis of ED as it helps to rapidly localize and visualize the cavernosal artery [7].

ICI plays a major role in the diagnosis of ED, alone or in conjunction with PDDU, because it helps detect

vascular abnormalities and differentiation between vasculogenic causes of impotence [8]. Mihmanli et al. (2007) stated that few studies have assessed the method of standardizing the dosage of vasoactive agents and how to correlate their efficacy with patient response and satisfaction [9]. In this prospective, case-control study, we aimed to compare the sensitivity of different doses of vasoactive drugs (PGE1 & Trimix) in diagnosing ED in ED patients by determining the most sensitive dose able to induce a maximum erection among study and control patients. As the most effective and ideal combination of different pharmaco-active drugs is yet to be found, information is needed to choose an effective and less costly alternative to PGE1 able to effectively diagnose vascular ED with the least amount of side effects [2].
Thus, we were able to adjust the most sensitive dose of vaso-active agents to diagnose ED in impotent patients during penile duplex.

## MATERIAL AND METHODS

### Study design and participants

This was a prospective case-control study consisting of 190 participants attending our outpatient andrology clinic from January 2017 to July 2018. The sample group consisted of 90 subjects diagnosed with ED as confirmed by an IIEF-5 score <22, whereas the control group consisted of 100 sexually healthy subjects whose potency was confirmed by an IIEF-5 score ≥22.
All of the participants provided written informed consent and signed it before being included in our study. This study received approval from our local ethical committee. The guidelines for strengthening the reporting of observational studies in epidemiology (STROBE) were strictly applied in the study.

### Inclusion criteria of the patients

Men aged 20–60 years old who complained of ED.

### Exclusion criteria of the patients

All patients with penile fibrosis, history or clinical evidence of hypogonadism, or acute or chronic illness that suggest pure neurogenic erectile dysfunction were excluded from the study.
Patients suffering from acute or chronic hematological disorders or smokers as well as those taking medications affecting sexual health such as antipsychotics and some antihypertensive drugs, were also excluded from this study.

### Inclusion criteria of the controls

The control group was composed of potent men within the age group of 20–60 years old, who were attending our clinic for other complaints than ED such as infertility, scrotal pain and urethral discharge.

### All of the participants were subjected to the following:

Detailed personal and sexual histories were taken. Additionally, past history in the form of medical diseases that may be a risk factor for ED, pelvic trauma or surgery and drug intake, especially those affecting sexual function, was also taken. All of the subjects were assessed by the abridged 5-item version questionnaire of the international index of erectile function (IIEF-5) to determine their potency [10]. Two penile duplex tests (SONOLINE G40, Diagnostic Ultrasound Systems, Siemens AG, Erlangen, Germany) were done for each candidate. Clinical responses and haemodynamic parameters were observed in all participants. Furthermore, all of the participants were subjected to a general examination for signs of hypogonadism and pervious operations. Also, a full genital examination was done to detect and exclude patients with acquired penile deviation, peyronie's disease or penile fibrosis from the study. Measurements of prolactin and total testosterone were performed in the early morning. Hormonal levels were measured using an electro chemiluminesence immunoassay analyzer [Roche Co., Cobas e 602, Japan]. The normal reference values were as follow; serum prolactin = 4.04–15.2 ng/ml and testosterone (total) = 2.5–8.4 pg/ml. The standard dorsal approach for the duplex examination was adopted. We used a high-frequency (7.5 MHz) linear probe to obtain a transverse view. Then we adopted an oblique – longitudinal approach once tumescence commenced. It should be noted that an angle of 60° cephalad in the transverse plane permits visualization of the beginning of the cavernosal artery, running toward the probe that could be seen at a Doppler angle of 0°. Further, we corrected the angle and obtained our measurements at the penile base toward the penoscrotal junction. Spectral measurement and image acquisition began two to three minutes after injection as the cavernosal arteries became more visible [11, 12]. Moreover, we aimed to get hemodynamic data of an erection of a quality similar to an erection achieved during sexual intercourse, as is the goal of a vascular examination of the penis [12].
After injection, we gently massaged the site of injection to avoid hematoma formation as much as possible [13, 14]. The first session was done by using

10 ug PGE1 as a starting dose; if no or poor response after 10 to 15 minutes, re-dosing with another 10 ug PGE1 was done in the same setting. After 2 weeks, the second session was done by using 0.25 cc Trimix as a starting dose; if no or poor response after 10 to 15 minutes, re-dosing with an extra 0.75 ml was done in the same session. Each 1 cc of Trimix solution contains PGE1 at 10 ug/ml, papaverine at 30 mg/ml, and phentolamine at 1.0 mg/ml [7]. Each subject of the two groups was subjected to two penile duplex studies as described above. Notably, the degree of erection of all the participants was evaluated by the erection hardness score (EHS) [15, 16].

### Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Mann Whitney U test for independent samples. Within group comparison of numerical variables was done using the Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, a Chi- square ($\chi^2$) test was performed. The exact test was used instead when the expected frequency was less than 5. Paired comparisons were done using the McNemar test. P values less than 0.05 was considered statistically significant. All statistical calculations were done using the computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

## RESULTS

The mean age of the sample and control groups was 42.1 ±9.94 years and 33.84 ±6.74 years, respectively. The difference in mean age was of high statistical significance (P <0.001) (Table 1). Furthermore, 33 (36.7%) patients within the sample group were diabetics, 9 (10%) were hypertensive and 48 (53.3%) did not suffer from any systemic illness whereas all members of the control sample were healthy. This difference in the general health status was of high statistical significance (p <0.001) (Table 1). Moreover, 27 (30%) patients from the sample group suffered from mild to moderate ED, 27 (30%) suffered from moderate ED, 18 (20%) suffered from mild ED, and 18 (20%) suffered from severe ED. On the other hand, all of the controls were potent.

**Table 1.** *Socio-demographic characteristics of the participants*

| | Sample (n = 90) | | | | Controls (n = 100) | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Minimum | Maximum | Mean | SD | Minimum | Maximum | Mean | SD | |
| Age (years) | 22 | 58 | 42.10 | ±9.94 | 21 | 44 | 33.84 | ±7.64 | <0.001 |
| Chronic illness | Diabetes | | 33 (36.7%) | | All the controls were free (100%) | | | | <0.001 |
| | Hypertension | | 9 (10%) | | | | | | |
| | Free | | 48 | | | | | | |
| IIEF-5 scores | N | | Percentage (%) | | All the controls were potent (100%) | | | | <0.001 |
| Mild (21–18) | 18 | | 20% | | | | | | |
| Mild-moderate (12–17) | 27 | | 30% | | | | | | |
| Moderate (8–11) | 27 | | 30% | | | | | | |
| Severe (1–7) | 18 | | 20% | | | | | | |

SD – standard deviation; IIEF-5 – The International Index of Erectile Function

**Table 2.** *Clinical response to vasoactive agents (prostaglandin E1 & Trimix) in the participants*

| | | Sample Group (n = 90) | | Control Group (n = 100) | | p-value |
|---|---|---|---|---|---|---|
| | | Normal response (EHS >2) | Abnormal response (EHS ≤2) | Normal response (EHS >2) | Abnormal response (EHS ≤2) | |
| PGE1 | 10 ug | 0 (0%) | 90 (100%) | 60 (60%) | 40 (40%) | <0.001 |
| | 20 ug | 42 (46.6) | 48 (53.4) | 28 (70%) | 12 (30%) | <0.001 |
| Trimix | 0.25 cc | 54 (60%) | 36 (40%) | 96 (96%) | 4 (4%) | <0.001 |
| | 1cc | 18 (50%) | 18 (50%) | 4 (100%) | 0 (0%) | 0.114 |

PGE1 – prostaglandin E1

This difference in the level of potency between the sample and control groups was also of high statistical significance (p <0.001) (Table 1). Remarkably, none of the sample group (100%) achieved normal clinical response (EHS >2) to 10 ug PGE1. In contrast, 60 controls (60%) revealed normal response (EHS >2) to 10 ug PGE1 while 40 controls (40%) demonstrated an abnormal response (EHS ≤2); no statistical difference was noted in their mean age, 34.05 ±7.61 years, 32.75 ±9.64 and p 0.915, respectively. This difference in the response to 10 ug PGE1 between the cases and the controls was of high statistical significance (p <0.001) (Table 2). When re-dosing with another 10 ug PGE1 for the non-responders within the sample and control groups, only 42 out of the 90 sample patients (46.6%) achieved a normal clinical response (EHS >2) and the remainders (53.4%) still had an abnormal clinical response (EHS ≤2), whereas 28 controls (70%) demonstrated a normal response (EHS >2) to 20 ug and only 12 controls (12%) still showed an abnormal response (EHS ≤2). This difference in the response to 20 ug PGE1 between the sample and control groups was of high statistical significance (p <0.001) (Table 2).

In contrast, 54 (60%) out of the 90 sample patients had a normal clinical response (EHS >2) and the remainders (40%) had an abnormal clinical response (EHS ≤2) to 0.25 cc Trimix, whereas 96 (96%) out of the 100 controls demonstrated a normal response (EHS >2) (Table 2). This difference in the response to 0.25 cc Trimix between the sample and control groups was of high statistical significance (p <0.001) (Table 2). When re-dosing with another 0.75 cc Trimix for the non- responders within the sample and control groups, only 18 (50%) out of the 36 sample patients obtained a normal clinical response (EHS >2) and the remainders (50%) still had abnormal clinical response (EHS ≤2) whereas the only 4 controls who were non responders to 0.25 cc Trimix all demonstrated a normal response (EHS>2) (Table 2). This difference in the response to 1 cc Trimix between the sample and control groups was of no statistical significance (p 0.114) (Table 2). Our study has shown that the mean peak systolic velocity (PSV) of the sample patients who responded to Trimix was statistically higher than those who responded to PGE1 (50.63 ±15.33, 39.86 ±14.80, p <0.001, respectively) (Table 2).

Also, the mean end diastolic velocity (EDV) of the sample patients who responded to Trimix was statistically lower than those who responded to PGE1 (1.5 ±3.01, 2.81 ±3.70, p <0.001, respectively). In the same context, our study has shown that the mean PSV of the controls who responded to Trimix was statistically higher than those who responded to PGE1 (57.39± 16.28, 48.42 ±15.69, p <0.001, respectively) (Table 3). Also, the mean EDV of the controls who responded to Trimix was statistically lower than those who responded to PGE1 (0.16 ±0.44, 1.28 ±2.37, p <0.001, respectively). Moreover, no statistical difference was observed in the right and left PSVs between the sample and control participants who were non-respondent to modified 20 ug PGE1: 34.45 ±14.09, 45.88 ±18.9, p 0.254, 34.62 ±13.25, 46.63 ±17.7, p 0.254, respectively (Table 3).

Furthermore, no statistical difference was observed in the right and left EDVs between sample and control group participants who were non-respondent to modified 20 ug PGE1: 5.31 ±3.71, 7.38 ±0.94, p 0.171, 4.99 ±4.04, 6.96 ±0.88, p 0.211, respectively (Table 4). The difference in the resistive index (RI) between sample and control group participants who were non-respondent to modified 20 ug PGE1 did not demonstrate any statistical significance: 0.88 ±0.09, 0.82 ±0.09, p 0.352, respectively (Table 4). Interestingly, the means of erection duration (in hours) were statistically shorter in the sample and the control group participants who responded to

**Table 3.** *Comparison of hemodynamic responses to prostaglandin E1 and Trimix in the participants*

| | | Sample Group (n = 90) | | p-value | Control Group (n = 100) | | p-value |
|---|---|---|---|---|---|---|---|
| | | PGE1 | Trimix | | PGE1 | Trimix | |
| PSV | Minimum | 12.10 | 21.96 | <0.001 | 30.53 | 42.60 | <0.001 |
| | Maximum | 82.75 | 90.09 | | 88.38 | 94.59 | |
| | Mean | 39.86 | 50.63 | | 48.42 | 57.39 | |
| | ±SD | ±14.80 | ±15.33 | | ±15.69 | ± 16.28 | |
| EDV | Minimum | 0 | 0 | <0.001 | 0 | 0 | <0.001 |
| | Maximum | 12.57 | 13.27 | | 8.08 | 1.31 | |
| | Mean | 2.81 | 1.50 | | 1.28 | 0.16 | |
| | ±SD | ±3.70 | ±3.01 | | ± 2.37 | ±0.44 | |

PSV – peak systolic velocity; SD – standard deviation; EDV – end diastolic velocity

**Table 4.** *Doppler findings between the sample and control participants who were non-respondent to modified 20 ug prostaglandin E1*

| | Sample Group (N = 48) | | | | | Control Group (N = 12) | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Minimum | Maximum | Mean | SD | Median | Minimum | Maximum | |
| RT PSV | 34.45 | 14.09 | 34.03 | 12.42 | 61.12 | 45.88 | 18.90 | 49.47 | 25.44 | 62.72 | 0.254 |
| LT PSV | 34.62 | 13.25 | 32.28 | 11.77 | 61.44 | 46.63 | 17.71 | 49.47 | 27.67 | 62.75 | 0.254 |
| RT EDV | 5.31 | 3.71 | 5.31 | .00 | 13.36 | 7.38 | .94 | 7.58 | 6.36 | 8.21 | 0.171 |
| LT EDV | 4.99 | 4.04 | 5.06 | .00 | 11.77 | 6.96 | .88 | 6.68 | 6.25 | 7.95 | 0.211 |
| RI | .88 | .09 | .88 | .73 | 1.00 | .82 | .09 | .80 | .74 | .91 | 0.359 |

SD – standard deviation; RT PSV – right peak systolic velocity; LT PSV – left peak systolic velocity; RT EDV – right end diastolic velocity; LT EDV – left end diastolic velocity; PSV – peak systolic velocity; EDV – end diastolic velocity; RI – resistive index

**Table 5.** *Comparison of hemodynamic responses to prostaglandin E1 and Trimix in the participants*

| | | Trimix | | | PGE1 20 ug | | |
|---|---|---|---|---|---|---|---|
| | | Control Group | Sample Group | p-value | Control Group | Sample Group | p-value |
| Erection duration | Minimum | 1 | 0.53 | <0.001 | 0.5 | 1 | <0.001 |
| | Maximum | 4 | 4 | | 3 | 4 | |
| | Mean | 1.46 | 0.93 | | 1.7 | 1.02 | |
| | ±SD | ±0.82 | ±1.18 | | ±0.76 | ±1.01 | |

PGE1 – prostaglandin E1; SD – standard deviation

Trimix than those who responded to 20 ug PGE1: 0.93 ±1.18, 1.46 ±0.82, p <0.001, 1.01 ±1.01, 1.7 ±0.76, p <0.001, respectively (Table 5). However, it should be noted that 6 patients showed priapism >4 hours on PGE1 20 ug, while 6 patients showed priapism >4 hours on 0.25 cc Trimix and 6 patients also showed priapism >4 hours on 1 cc Trimix. Contrarily, only 4 control patients showed priapism on 20 ug PGE1 while 8 and 16 control patients showed priapism on 0.25 cc and 1 cc Trimix, respectively. Management of priapism was carried out in all cases by injecting 30 mg ephedrine HCL after which penile tumescence was achieved without the need of blood evacuation.

## DISCUSSION

PDDU has been considered the primary investigation of choice in ED as it differentiates between psychogenic and vasculogenic causes and also determines whether the cause is arterial insufficiency or veno-occlusive disease [1]. ICI of a low dose vasoactive agent is commonly used to determine if vascular abnormalities are present and whether PDDU will be indicated [17]. Several previous studies have proficiently described a standardized diagnostic approach for vasculogenic ED.

In 2013, a study conducted by Pereira et al. had shown the pivotal role of computerized tomography angiography and digital subtraction angiography in diagnosing arteriogenic ED due to the fact that stenotic and occlusive lesions of the internal iliac artery and internal pudendal artery could be revealed [18]. Thus, the Yamaki classification is radiologically reproducible and allows for easy recognition of the internal pudendal artery in patients with arteriogenic ED [18]. Similarly, due to the complexity and heterogeneity of PDDU evaluation, Sikka et al. (2013) recommended further invasive diagnostic tests involving penile angiography and cavernosography/cavernosometry to establish veno-occlusive dysfunction [6]. On the other hand, Butaney et al. (2013) who conducted a 30-question electronic survey that was distributed to members of the International Society for Sexual Medicine (ISSM), had found that most of the respondents reported utilizing a standardized penile duplex ultrasound protocol [19]. However, widespread variation is still present among practitioners especially in the technique and interpretation of results which limits accurate diagnosis and appropriate treatment of penile conditions [19]. Remarkably, our study demonstrated statistically higher response to Trimix than PGE1 as none of the sample participants had responded to 10 ug PGE1. Thus, it can be concluded that Trimix is more potent than PGE1 in inducing erection in ED patients and consequently more sensitive to diagnosing ED in these patients. Similarly, a study conducted by Bechara et al.

(1996) that was carried out on 32 patients had demonstrated that only 7 patients responded to prostaglandin E1 versus 16 to Trimix [20]. Furthermore, Bennett et al. (1991) reported that 0.25 cc Trimix had been efficacious for diagnosis and treatment of the majority of patients with mild to moderate arteriogenic and/or venogenic and diabetic impotence [21].

Moreover, Syam et al. (2005) stated that the clinical efficacy of Trimix as a vasoactive combination is clinically more effective than PGE1 [2]. It should be noted that although administrating oral sildenafil with audiovisual sexual stimulation prior to penile duplex proved efficacious as it led to a significant increase in blood flow in the cavernosal arteries, more patients responded to Trimix than to sildenafil and the clinical response was significantly better [22]. In contrast, Chandek Montesa et al. (1992) reported PGE1 ICI is the first choice approach in the diagnosis and treatment of ED in males, due to its safety and degree of acceptance [23]. Also, Amar et al. (1993) and Wilkins et al (2003) had revealed that PGE1 is a more suitable agent than other vasoactive drugs in the diagnosis and treatment of ED [24, 25].

Moreover, our study revealed a significant association between the response to Trimix over PGE1 and PSV and EDV. In contrast, Syam et al. (2005) found a significant difference between PGE1 and Trimix and EDV only [2]. Remarkably, we re-dosed the non-responders of the sample and control groups up to 20 ug PGE1 and 1 cc Trimix in the same settings, respectively. Consistently, two previous studies had shown the importance of re-dosing while performing PDDU. The first one was conducted by Aversa et al. (2000) and concluded that re-dosing of the PGE1/ phentolamine (PHE) mixture was a safe and effective procedure to maximize erectile response during dynamic PDDU and had a better diagnostic sensitivity than re-dosing of PGE1 alone [26]. The second one was conducted by Gontero et al. (2004) and demonstrated the importance of PHE re-dosing to avoid a false diagnosis of veno-occlusive ED [27]. Moreover, Patel et al. (2012) recommended very low doses of PGE1 (5 ug) when testing cavernosal arteries of drug naive patients with no ED to avoid the risk of priapism [14]. Also, the same authors proposed a re-dosing protocol of an extra 5 ug PGE1 in patients who did not show a proper response to the first dose.

## CONCLUSIONS

Administration of 0.25 cc Trimix is more sensitive than 20 ug PGE1 in diagnosing erectile dysfunction for patients complaining of any degree of erectile dysfunction, and also elicits a more potent response. In addition, 1 cc Trimix should be avoided in psychogenic ED patients as it may cause priapism.

Finally, re-dosing with a higher dose of a vasoactive agent is recommended if penile duplex study results are strongly mismatched with the clinical diagnosis.

### Study limitations

The main limitation of our study was the age disparity between the sample and control groups which was due to the age nature of the disease, as ED is mostly a complaint of older men, while most of the men recruited in the control group were mainly complaining of infertility, for which medical help is sought at a younger age.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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