INTRODUCTION

Erectile dysfunction (ED) or impotence is defined as the inability to reach or maintain penile stiffness/erection that is sufficient for satisfactory sexual intercourse. Its incidence and prevalence are expected to increase significantly in the Indian population along with the increase in various lifestyle diseases.\(^1\) ED occurs mainly due to psychogenic and/or organic aetiologies.\(^4\) Organic causes of ED include vasculogenic, neurologic, pharmacologic, endocrinologic, urologic and mechanical factors such as Peyronie’s disease.\(^5,6\) Vascular insufficiency due to either arterial or venous or both arterial and venous insufficiencies is a common cause of organic ED.\(^4,5\)

Accurate diagnosis of vasculogenic ED is imperative as aetiology specific, targeted treatment options are now available.\(^5,7\) Arteriography with selective internal iliac angiography and dynamic infusion cavernosometry with cavernosography (DICC) are considered the gold standards for evaluation of arteriogenic and venous impotence; respectively.\(^6,8,9\) However, these invasive techniques cannot be recommended as screening tools for evaluation of ED. Several studies in the past have investigated the role of penile duplex ultrasound and Doppler spectrum analysis for the diagnosis as well as post-therapy response evaluation of vasculogenic ED.\(^5, 6, 8,15\) These investigators have used minimally invasive pharmaco-erection technique with intracavernosal injection (ICI) of vasoactive agents such as...
papaverine alone or in combination with phentolamine and prostaglandin PGE1 (Trimix); for the evaluation of vascular insufficiency, Intracavernosal injections are painful and are associated with the risks of extravasation, ecchymosis, hematoma and priapism. Hence, studies are also being conducted to explore the utility of safer, oral vasoactive agents such as PDE5 inhibitor sildenafil for penile Doppler ultrasound investigation of patients with ED.

On this background, the present study proposes to evaluate the clinical utility of oral sildenafil citrate along with visual sexual stimulation (VSS) for non-invasive duplex Doppler ultrasound evaluation of penile hemodynamics in patients with ED.

**MATERIALS AND METHODS**

An Institutional Ethics Committee approved, observational study conducted between April 2017 and May 2018, included 36 patients referred from the department of urology for penile duplex Doppler ultrasound of ED. In the beginning, a detailed medical and sexual history was obtained from all these patients. They also underwent thorough physical examination, essential biochemical and hormonal investigations and completed the International Index of Erectile Function-5 (IIEF-5) scoring questionnaire. The criteria for IIEF-5 scoring were set as follows: a score of 22-25 was considered as no ED; 17-21 indicated mild ED; 12-16 indicated mild to moderate ED, 8-11 indicated moderate ED, and a score of 5-7 indicated severe ED. Patients satisfying the following inclusion criteria were enrolled in the study: 1) male patients of all ages; 2) investigated for complaints of ED and 3) with IIEF-5 score less than 25.

Patients with history of trauma, those with history of recent myocardial infarction, coagulation defects or poor cardiac performance and known cases of Peyronie’s disease; were excluded from this study. An informed consent was obtained from all the study participants.

The penile Doppler ultrasound (PDU) examinations were conducted in an appropriate environment; respecting the privacy of patients. Grey-scale and duplex Doppler ultrasound of all cases was performed at rest and in the erection/tumescence phases; on an EPIQ 7 Ultrasound Colour Doppler system (Philips Healthcare, Amsterdam, The Netherlands) using a high frequency linear transducer (8-15 MHz).

One of the two experienced radiologists blinded to the IIEF-5 score of the patients, performed ultrasound scanning. The transducer was placed on the ventral penile surface especially during the erection phase. Initially, gray scale imaging of flaccid penile shaft was done in transverse and sagittal planes to rule out fibrosis or calcifications. Slow flow sensitivity was optimized to assess the arterial response as well as the venous flow with a small field of view (FOV). Pulse repetition frequency (PRF) values of 1,000–1,500 Hz were employed with a low wall filter. Longitudinal scans were performed on the cavernosal arteries with a sample volume size of 1mm. Both cavernosal arteries were evaluated in all patients. Electronic cursors were used to measure the baseline, pre-medication diameters of cavernosal arteries in longitudinal projection along the proximal penile shaft. Identification of blood flow through the cavernosal vessels on the colour Doppler image was followed by spectral analysis of these vessels. Doppler evaluation was performed with the transducer positioned at the base of the penis maintaining an optimal Doppler angle between 30° and 50°. Pre-medication, peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI) measurements were recorded. Mean values of the measured cavernosal arterial diameters and Doppler parameters were reported.

Thereafter, oral sildenafil citrate (50-100 mg) was administered in order to obtain pharmaco-erection. Audiovisual sexual stimulation (AVSS) was provided for enhancing the drug response. Continuous monitoring was done for 30–90 min post-medication as the time interval between pharmaco-stimulation and erection varied from patient to patient. Cavernosal arterial diameters and penile hemodynamic parameters including PSV, EDV and RI were recorded 45 minutes post oral sildenafil or upon obtaining pharmaco-erection; whichever was earlier. They were measured every 10 minutes until 90 min or until diminution of tumescence.

Post-medication erectile response was graded using the clinical Erection Hardness Grading Scale (EHGS) as follows: grade 1: increase in size of penis, but not hardness (rigidity); grade 2: increase in size and slight increase in rigidity, but insufficient for sexual intercourse; grade 3: increase in rigidity, sufficient for sexual intercourse, but not fully rigid; and grade 4: fully rigid erection.

This study used diagnostic criteria of waveform dampening and PSV <25 cm/s for diagnosing arterial insufficiency. Presence of persistent diastolic flow and a mean EDV of >/= 5 cm/ sec were used as the indicators of venous insufficiency. Patients with cavernosal artery PSV of >/= 25 cm/s and EDV of < 5 cm/sec were categorized as normal on the PDU evaluation (Figure 1).
Pre-medication PDU images showing normal flow (a) and baseline spectral waveform (b) within the cavernosal artery. Post- sildenafil PDU images demonstrate increased cavernosal arterial diameter (c) and increased PSV with end diastolic flow reversal (d), suggesting normal response to sildenafil.

**Statistical Analysis**

The results were analysed statistically using SPSS 16.0 (SPSS for Windows, Version 16.0. Chicago, SPSS Inc) software. Quantitative data was presented as means, standard deviation and range. Pre and post Sildenafil cavernosal artery diameters, PSVs and EDVs were compared using paired t test. A p-value <0.05 was considered statistically significant. For cavernosal artery diameter and PSV the post-medication values were greater than the pre-medication values, hence one tailed hypothesis was used. Whereas for EDV the post-medication values were either greater or lesser than pre-medication values, hence two tailed hypothesis was used.

**RESULTS**

The mean age of the 36 study participants was 53.69 years (age range 38–69 years). Age distribution of the patients is summarized in Table 1. Majority of the patients (44.44%) were in the age group of 50-59 years.

<table>
<thead>
<tr>
<th>Age group in years</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>2</td>
<td>5.56</td>
</tr>
<tr>
<td>40-49</td>
<td>9</td>
<td>25.00</td>
</tr>
<tr>
<td>50-59</td>
<td>16</td>
<td>44.44</td>
</tr>
<tr>
<td>60-69</td>
<td>9</td>
<td>25.00</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100.00</td>
</tr>
</tbody>
</table>

In this study, the pre-medication IIEF-5 score recorded mild ED in 11 (30.56%) patients, mild to moderate ED in 13 (36.11%) patients, moderate ED in 11 (30.56%) patients and severe ED in 1 (2.77%) patient.

The post oral sildenafil, clinical erectile response assessment using the EHGS revealed a score of grade 1 in 12 (33.33%) patients and grade 2 in 15 (41.67%) patients. Six (16.67%) patients achieved a grade 3 response, whereas three (8.33%) patients showed grade 4, fully hard rigid erection. Patients with EHGS scores of grade 3 and grade 4 showed mean PSVs of 42.08 cm/s and 42.67 cm/s, respectively.

In the present study, the pre-medication cavernosal artery 0.50 mm to 1.30 mm with a mean of 0.98 ± 0.24 mm. Post oral sildenafil, cavernosal artery diameters varied from 0.50 mm to 1.80 mm with a mean of 1.30 ± 0.29 mm (Figure 2a). There was a statistically significant difference in the pre and post-medication cavernosal artery diameters (P<0.00001) (Table 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-medication baseline Mean values</th>
<th>Post oral sildenafil medication Mean values</th>
<th>Diffence</th>
<th>t-value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavernosal artery diameter in mm</td>
<td>0.98±0.24</td>
<td>1.30±0.29</td>
<td>0.32</td>
<td>6.1893</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSV in cm/s</td>
<td>14.45±8.4</td>
<td>22.47±14.3</td>
<td>8.02</td>
<td>4.8646</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDV in cm/s</td>
<td>2.85±7.32</td>
<td>3.36±7.37</td>
<td>0.51</td>
<td>2.0343</td>
<td>0.04954</td>
</tr>
</tbody>
</table>

The pre-medication PSV varied from 6.0 cm/s to 39.0 cm/s and the mean PSV was 14.45 ±8.41 cm/s. Post sildenafil PSV ranged from 6.7 cm/s to 55.0 cm/s with a mean of 22.47±14.32 cm/s. A t-value of 4.86 and P-value 0.00001 (P<0.05) indicated that the difference in these results was statistically significant (Figure 2b, Table 2).
Range of the pre-medications EDV recorded was 1.0 cm/s - 6.0 cm/s with a mean EDV of 2.85±1.32 cm/s. The post-sildenafil EDV ranged from 0.0 cm/s to 6.20 cm/s with a mean of 3.36±1.37 cm/s (Figure 2c). As depicted in Table 2. The difference in the pre and post- medication EDV measurements was found to be statistically significant.

On the PDU evaluation, 23 (63.89%) of the 36 patients, with low PSV values (<25 cm/s) in the cavernosal artery were diagnosed to have arterial insufficiency (Figures 3, 4a-d)).

Three (8.33%) patients were considered to have venous insufficiency (Figure 5a-b), 1 (2.78%) patient was diagnosed to have combined arterial and venous insufficiency and 9 (25%) patients were considered normal (Figures 1, 3).
Eleven of the 23 patients diagnosed to have arterial insufficiency on PDU, showed post sildenafil EHGS score of grade 4 or grade 5 scoring.

DISCUSSION

Normal penile erection is a complex mechanism involving psychological, endocrinologic, neurologic and vascular systems. In erectile dysfunction one or more of these components are either damaged or deficient.

Vasculogenic impotence is a common and potentially curable aetiology of organic ED. Accurate diagnosis of vasculogenic ED is thus imperative. Adequate knowledge of the penile hemodynamics leading to normal erection is essential for the evaluation of vasculogenic ED.

Vascular anatomy of the penis is unique with artery of the penis branching into the cavernosal artery and the dorsal artery of the penis. Cavernosal arteries provide blood flow to the corpora cavernosa and are involved in the initiation and maintenance of erection. The corpora cavernosal sinusoids contain the venous sinusoidal occlusion mechanism producing rigid erections, amongst these, pharmaco penile Doppler ultrasound is an established first-line investigation to evaluate penile arterial and veno-occlusive function.

Ultrasound evaluation of vasculogenic ED was pioneered by Lue et al. Schwartz et al evaluated erectile function in normal subjects with color flow Doppler sonography and described a consistent spectral waveform/ intracorporeal pressure pattern characteristic of intact arterial and venous sinusoidal erectile mechanisms. They arbitrarily divided spectral waveform variations and intracorporeal pressure changes into phases.

In 1982, Virag first reported treatment of ED with intra cavernosal injection (ICI) of papaverine. Thereafter, several studies have evaluated the efficacy of PDU in the diagnosis of ED using ICI of papaverine for pharmaco-erection. Papaverine is a nonselective phosphodiesterase (PDE) inhibitor and potent smooth muscle relaxant which acts directly on the penile arteries and cavernosal sinusoids.

However, ICI of vasoactive agents such as papaverine, PGE1, and phenolamine, is associated with complications including pain, burning sensation, ecchymosis or hematoma formation at the injection site. Fear of injection may cause stress, anxiety, dizziness along with increased sympathetic stimulation resulting in a false-positive interpretation of arterial insufficiency. Patients with normal hemodynamic function may have prolonged erections and priapism. Repeated injections may at times result in penile cavernosal tissue fibrosis.

To avoid these complications, investigators have been evaluating use of non-invasive, oral vasoactive agents such as sildenafil citrate for pharmaco stimulation during the PDU of ED. Arslan et al, Bacar et al and Speel et al in their respective studies concluded that oral sildenafil with visual
sexual stimulation (VSS) could achieve arterial response comparable to that after ICI of papaverine. Vishwarpoo B et al found oral sildenafil to be as effective as injection papaverine in evaluating ED and have recommended its use with genital self-stimulation in the evaluation of ED, especially in young men with psychogenic impotence. Erdogru et al and Copel et al had a different opinion about the efficacy of Sildenafil. They recorded a significantly better clinical response to ICI of vasoactive agents as compared to sildenafil in association with VSS. Observations of Yang Y suggest that although PDE5-Is such as sildenafil and papaverine ICI show similar effects on the PDU parameters in detecting arterial ED, more patients achieve better clinical responses to ICI.

In this context, present study investigated the potential use of oral vasoactive agent sildenafil citrate as a non-invasive alternative to ICI of papaverine, for the PDU evaluation of ED. Sildenafil citrate is a highly effective oral agent in the treatment of ED. It is a Phosphodiesterase type 5 inhibitor (PDE5-I) which maintains erection by inhibiting the catabolism of cyclic guanosine monophosphate and increasing its levels.

The action of PDE5-Is on the cavernosal smooth muscles needs to be augmented with AVSS as the nitric oxide-cyclic guanosine monophosphate pathway needs to be activated by sexual stimulation. So, adhering to the protocol used by similar studies conducted in the past, AVSS was provided in our study along with oral sildenafil to obtain pharmaco-erection.

In our study, a statistically significant difference was noted in the pre and post-medication cavernosal artery diameters ($P < 0.00001$). However, inconsistent and overlapping differences were recorded in the post oral sildenafil diameters of the cavernosal arteries, across different clinical response categories. Thus in conjunction with the observations of Quam et al and Benson et al, this study did not consider cavernosal arterial diameter as an indicator of arterial function.

The differences in the pre and post-medication PSV and EDV measurements were also found to be statistically significant ($P < 0.05$). Using diagnostic criteria of PSV <25 cm/s, 23 patients were diagnosed with arterial insufficiency. Of the 23 patients diagnosed with arterial insufficiency on PDU, 10 (43.47%) patients showed moderate ED; 11 (47.82%) patients showed mild to moderate ED; one (4.34%) patient showed severe ED and one (4.34%) patient recorded mild ED on the IIEF-5 analysis (Figure 7).

The three patients diagnosed with venous insufficiency (mean EDV of $>5$ cm/sec) recorded normal PSV measurements. In the present study, one patient showed PDU parameters indicating mixed arterial and venous insufficiency. However the final PDU interpretation of this case was indeterminate results, as venous competence cannot be assessed on PDU in a patient with arterial insufficiency.

None of the study participants complained of any significant adverse reactions post sildenafil administration. The results of this observational study indicate that sildenafil citrate can be used as an effective vasoactive agent for non-invasive PDU evaluation of vascalogenic ED. These observations are in conjunction with earlier existing comparable studies. Sildenafil has the added advantage of being a cost-effective, safer substitute for ICI, with higher patient compliance and convenience. Moreover, most of the complications associated with ICI are avoided.

A time-consuming stimulation protocol which needs to be supplemented with AVSS to obtain pharmaco-erection is the major disadvantage of oral sildenafil. Hence if sildenafil is to be used as a substitute for ICI of papaverine, its characteristics of erection induction should be considered so as to avoid potential diagnostic pitfalls.

**Limitations of Study**

The limitation of our study is a lack of comparison with intracavernosal or other oral vasoactive agents.

**CONCLUSION**

The authors of this study conclude that oral sildenafil citrate when combined with AVSS induces a sufficient erectile response for assessing the penile hemodynamic parameters on duplex Doppler ultrasound. It may be used as a non-invasive, safer, first-line screening test along with PDU for the evaluation of vascalogenic ED. More invasive ICI can be reserved for patients with indeterminate PDU results or inadequate erectile response.

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**References**


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