Combination of Vacuum Erection Device and PDE5 Inhibitors as Salvage Therapy in PDE5 Inhibitor Nonresponders with Erectile Dysfunction

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ABSTRACT

Introduction. Oral phosphodiesterase type 5 inhibitors (PDE5i) have improved treatment options for erectile dysfunction (ED). In case of unresponsiveness to PDE5i, alternative therapies are considered.

Aim. To evaluate whether combination of vacuum erection device (VED) and PDE5i is effective as salvage therapy in subjects with ED in whom PDE5i alone failed.

Methods. From September 2007 to May 2008, we evaluated 69 men (aged 36–82 years) in whom PDE5i treatment at the highest recommended dose, with at least 4–6 attempts at intercourse during a 3 months period, had failed. The clinical efficacy of combination therapy was evaluated using the International Index of Erectile Function-5 (IIEF-5) questionnaire, Sexual Encounter Profile (SEP)-2, SEP-3, and Global Patient Assessment Scale (GPAS).

Main Outcome Measures. Scores on IIEF-5, SEP-2, SEP-3, and GPAS before and after combination therapy were measured.

Results. After 4 weeks of combination therapy, the mean IIEF-5 score increased significantly over baseline from 9.0 to 17.6 ($P < 0.001$). Of the 34 subjects with a SEP-2 response of "no" at baseline, 27 (79%) responded "yes" after combination therapy ($P < 0.001$). Of the 50 subjects with a SEP-3 response of "no" at baseline, 35 (70%) responded "yes" after combination therapy ($P < 0.001$). Furthermore, of the 42 subjects with a GPAS response of "not at all" or "slightly" improved at baseline, 31 (74%) responded "moderately" or "greatly" improved after combination therapy ($P < 0.001$). One subject (1.5%) experienced device-related intermittent penile pain, which resolved after 4 days without any action.

Conclusions. Statistically significant improvements over baseline were seen in IIEF-5, SEP-2, SEP-3, and GPAS measures following 4 weeks of combination therapy of PDE5i and VED. This study supports the use of PDE5i with VED in men in whom PDE5i alone failed. This combination therapy may be offered to patients not satisfied with PDE5i alone before being switched to more invasive alternatives. **Canguven O, Bailen J, Fredriksson W, Bock D, and Burnett AL. Combination of vacuum erection device and PDE5 inhibitors as salvage therapy in PDE5 inhibitor nonresponders with erectile dysfunction. J Sex Med 2009;6:2561–2567.**

Key Words. Combination Therapy; Patient Satisfaction; Penile Erection; Phosphodiesterase; VED

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1]. The introduction of oral phosphodiesterase type 5 inhibitors (PDE5i) (i.e., sildenafil citrate, tadalafil, and vardenafil hydrochloride) has greatly enhanced ED treatment, and studies have demonstrated high tolerability and success rates for improved erectile function (EF).

To date, PDE5i are the first treatment choice for ED among physicians [1,2]. The efficacy of PDE5i demonstrates the importance of the nitric

oxide (NO)–cyclic guanosine monophosphate (cGMP) pathway in EF because these agents counteract the degradation of NO-generated cGMP. If used properly, PDE5i have a rapid onset of action to facilitate EF. In most published clinical trials, the efficacy of PDE5i as judged by successful sexual intercourse ranges from 52% to 94% [3–5]. Because not all patients respond to PDE5i, additional therapies are being investigated, such as soluble guanylyl cyclase activators and NO donors, which act on NO-independent and NO-dependent pathways, respectively [6].

Alternative treatment choices for ED include vacuum erection devices (VEDs), intracavernosal injectable agents, and intraurethral vasoactive agents [2]. Surgical treatments are still reserved for men who cannot use or fail to respond to these treatments. Patients who are not completely pleased with EF following the use of PDE5i and who are not interested in invasive therapy are offered the option of a VED before pursuing invasive alternatives. The VED mechanism depends on its ability to boost arterial inflow by a vacuum effect while decreasing venous outflow from the penis by applying a rubber constriction band after penile blood engorgement [7].

In this prospective open-label study, we tested the efficacy of combining VED and PDE5i for ED after failure to achieve an adequate erection using PDE5i alone.

Methods

Study Protocol

Patients who had been prescribed a maximum dose of at least one PDE5i (20 mg for tadalafil or vardenafil hydrochloride, 100 mg for sildenafil citrate) for ED were surveyed by mail or phone to determine their satisfaction with this therapy. Patients were defined as nonresponders by self-report after four to six unsuccessful attempts using the maximum drug dose over at least a 3 months period. Patients have received and were required to follow instructions for the proper use of PDE5i, including the need for sexual stimulation and the avoidance of alcohol as well as fatty food intake. Only those who declared that dissatisfaction was primarily because of inadequate efficacy, and not related to unwanted side effects, were considered eligible for this study.

Participants were also required to demonstrate competency with the use of VED and have a body mass index of less than 35.0 kg/m^2 at the time of enrollment. The latter was required because very overweight men have difficulty seeing their penis while using the VED and, thus, require more time to learn the correct process than this rather short study allows.

Patients were not screened with Sexual Encounter Profile Questions 2 or 3 (SEP-2 or SEP-3) prior to inclusion in the trial, and, as such, some subjects responded positively at baseline to one or both SEP questions despite declaring dissatisfaction with oral medications upon enrollment. It was suspected that some subjects reporting dissatisfaction with PDE5i were in fact able to have successful intercourse and still not be completely satisfied with their sexual experience. The study was designed to include these patients, despite the fact that they may have experienced partial or even functional responses to PDE5i.

Exclusion criteria were a history of any definitive treatment for prostate cancer (e.g., radical prostatectomy, radiation therapy, androgen deprivation) or unstable cardiovascular disease (e.g., unstable angina, recent myocardial infarction, cardiac failure, or life-threatening arrhythmia) within the past 6 months. Men with an anatomical deformity of the penis such as severe penile fibrosis or curvature, Peyronie's disease, or history of penile surgery (except for circumcision) were excluded from study. Men with a history of sickle cell disease, multiple myeloma, leukemia, or any other hematologic disorders, men using medications that may cause priapism, and ED caused by low serum testosterone levels (<300 ng/dL) were also excluded.

All patients had to anticipate having the same female sexual partner (vaginal intercourse was a required study activity) throughout the study for consistency in recording responses to efficacy questionnaires. At the time of enrollment, the patient was required not to have participated in a clinical drug study within the last 30 days prior to entering this study. Prior to the administration of study questionnaires, the investigator obtained informed consent for participation.

Data were collected at visit 1 (baseline; study entry) and visit 2 (4 weeks after baseline; study end). During visit 1, a medical history was taken and baseline safety assessments were made, including a physical examination. Patients were instructed to continue taking the same PDE5i as they were taking prior to enrollment throughout the study so as not to introduce an additional variable to the trial. All questionnaires (the International Index of Erectile Function-5 [IIEF-5], SEP-2 and SEP-3, and the Global Patient Assess-

ment Scale [GPAS]) were administered at both visits. Patients were required to have completed a minimum of four attempts at sexual intercourse in order for results to be considered valid for the 4-week period. Patients self-reported whether they completed the required attempts, and the number of PDE5i doses used per subject were not accounted for in the trial. The study was approved by respective Institutional Review Boards of the participating medical centers.

Treatments

Men were instructed to take one tablet of PDE5i at a maximum dosage at least 1 hour before sexual activity and 2–3 hours after a meal. Instruction in the use of a VED included personal tutoring as well as watching an instructional video (Osbon Erecaid ESTEEM, Timm Medical Technologies, Eden Prairie, MN, USA).

Treatment Evaluations

The clinical efficacy of combining PDE5i and VED was evaluated using the IIEF-5 questionnaire, which is an abbreviated version of the IIEF [8]. In addition to completing the IIEF-5 questionnaire, men were assessed using SEP-2, SEP-3, and GPAS questionnaires [9], which rated performances and satisfaction with current ED treatment regardless of the IIEF-5 score. IIEF-5 and SEP questions were chosen in order to keep study questionnaires simple and brief while still using validated instruments. Questions asked were, for SEP-2, "Were you able to insert your penis into your partner's vagina?" and for SEP-3, "Did your erection last long enough to successfully complete intercourse?" The GPAS is based on a 4-point Likert scale and is not a validated assessment tool. However, it was chosen for its simplicity as well as for the ability of patients to use a more continuous scale to monitor their progress. Its role in this trial was particularly useful to collect subjective patient responses relative to the use of tension rings during the study. The GPAS asked, "Has the treatment you have taken over the past four weeks improved your erections?" with response choices of "not applicable, not at all, slightly, moderately, and greatly." At visit 2, patients were asked to respond to GPAS both with and without the use of tension rings.

Statistics

All efficacy analyses were performed on an intent-to-treat basis. Responses to the IIEF-5 were treated as continuous variables and are presented as means. Variables such as SEP-2, SEP-3, and GPAS are presented as counts and percentages. McNemer's and paired *t*-tests were used and a probability of 5% or less was considered significant.

Results

Patient Population

In total, 69 subjects from four sites participated in this study. Men aged ≥18 years who had a minimum of 3 months history of mild, moderate, or severe ED of organic, psychogenic, or mixed causes (as determined by the investigator) were eligible to participate in the study. The diagnosis of ED was established according to the National Institutes of Health statement on ED [10]. Subjects were mostly white (87%) with an average age of 64 years. Sixty subjects (87%) had ED for at least 1 year, with 25 (36%) of those having ED for more than 5 years. Fifty-eight subjects (84%) had gradual onset ED, unassociated with any specific event. All subjects had previously received at least one oral PDE5i, with 91% receiving sildenafil citrate, 64% receiving vardenafil hydrochloride, and 67% receiving tadalafil. Additionally, 14 subjects (20%) had previously used intracavernosal injection (ICI) therapy. In all subjects, the main disease associations were hypertension and hyperlipidemia, and, to a lesser extent, diabetes mellitus (Table 1). Fifty-seven subjects (83%) were married, and 53 subjects (77%) had been with their current partner for more than 5 years (Table 2).

IIEF-5

The mean IIEF-5 score at visit 1 was 9.0 ± 5.74. After use of combination therapy (PDE5i + VED) for 4 weeks, the mean IIEF-5 score increased to 17.6 ± 7.18. The change in IIEF-5 after visit 2 was similar in all subgroups, including patients with hypertension and diabetes mellitus. This increase is statistically significant compared with visit 1 ($P < 0.001$). The mean change from visit 1 in the IIEF-5 score was 8.6, with a 95% confidence interval of 6.8–10.4.

Table 1 Erectile dysfunction disease associations

Disease state	N (%)
Hypertension	38 (55.1)
Hyperlipidemia	30 (46.2)
Diabetes mellitus	16 (23.2)
Medication related	6 (9.2)

Table 2 Summary of interpersonal relationship and sexual activity history

Characteristics	N (%)
Marital status	
Single, never married	2 (2.9)
Married	57 (82.6)
Divorced or separated	4 (5.8)
Widowed	6 (8.7)
Time with current partner	
<6 months	1 (1.4)
6 months–1 year	7 (10.1)
1–5 years	8 (11.6)
>5 years	53 (76.8)
Frequency of sexual activity	
<4 times per month	52 (75.4)
5–10 times per month	11 (15.9)
>10 times per month	6 (8.7)

Of particular note, 63 subjects responded with "very low," "low," or "moderate" at visit 1 to the patient confidence question ("How do your rate your confidence that you could get and keep an erection?"). Of these patients, 36 (57%) responded "high" or "very high" at visit 2 ($P < 0.001$). Furthermore, the patient satisfaction question stating, "When you attempted sexual intercourse, how often was it satisfactory for you?" yielded 63 subjects that responded "almost never," "a few times," or "sometimes" at baseline. Of these patients, 36 (57%) responded "most times" or "always" after vacuum therapy ($P < 0.001$).

IIEF-5 scores were also analyzed in relationship to affirmative responses to SEP-2 and SEP-3 at baseline. In 35 patients with a positive SEP-2 at baseline, the mean IIEF-5 score increased from 13.2 to 19.5 ($P < 0.001$), and in 19 patients with a positive SEP-3 at baseline, the mean IIEF-5 score increased from 15.0 to 18.9 ($P < 0.05$). In 18 patients with positive responses to both SEP-2 and SEP-3, the mean IIEF-5 score improved from 15.5 to 18.9 ($P < 0.05$). These data suggest that the addition of VED therapy in patients with functional but suboptimal responses to PDE5i has the potential to treat ED more effectively.

SEP

Improvements in SEP question responses were found after combination therapy for 4 weeks. All 35 subjects with a SEP-2 response of "yes" at visit 1 maintained that response at visit 2. Of the 34 subjects with a SEP-2 response of "no" at visit 1, 27 (79%) responded "yes" at visit 2 ($P < 0.001$). Of the 19 subjects with a SEP-3 response of "yes" at visit 1, 15 subjects (79%) maintained that response at visit 2. Of the 50 subjects with a SEP-3 response of "no" at visit 1, 35 (70%) responded "yes" at visit 2 ($P < 0.001$).

GPAS

Improvement was also observed after combination therapy for 4 weeks according to the GPAS measure. Of the 42 subjects with a GPAS response of "not at all" or "slightly" improved at visit 1, 31 (74%) responded "moderately" or "greatly" improved at visit 2 ($P < 0.001$).

Safety

Overall, participants responded well to combination therapy. One participant (1.5%) experienced a device-related adverse event, which was intermittent penile pain of mild severity that resolved after 4 days without any action. There were no adverse events associated with the use of tension rings during the trial.

Discussion

The advent of effective oral therapy with PDE5i has revolutionized the management of ED, and this therapeutic option is recognized as first-line treatment. Although PDE5i are currently the most widely used therapy and have excellent overall efficacy rates (52–94% for successful sexual intercourse), a substantial portion of patients have inadequate responses [3–5]. Vacuum therapy alone has a reported efficacy rate of 65–90%, and like oral medication, a significant number of patients have inadequate responses to VEDs as well [11]. It is commonplace for non-oral ED therapies like ICI, intraurethral therapies, and VEDs to be grouped together in treatment algorithms and presented as equally appropriate alternatives when PDE5i fail or are contraindicated. However, because of the noninvasive nature of VEDs coupled with their high efficacy rates for patients of varying etiologies, VEDs do represent an acceptable alternative primary treatment option following failed oral therapies and prior to consideration of injectable or intraurethral therapies [12]. This study provides evidence that the combination of VED and oral therapies can indeed be considered prior to more invasive alternatives.

Statistically significant improvements were seen after 4 weeks of combined therapy according to IIEF-5, SEP-2, SEP-3, and GPAS measures. These improvements did not diminish in significance upon subgroup analysis, as both hypertensive and diabetic subsets were equally as successful

as the entire study population. Despite successful results from the majority of patients in the study, four patients reported a negative SEP-3 response after a positive response at baseline. There is no easy explanation as to why these patients responded poorly to combination therapy. It is possible that these patients would benefit from additional training with the VED, but additional follow-up would be required to confirm this impression.

The combination of VED and oral medications has been studied previously by Chen and colleagues [13]. In this study, 161 men with ED of varying etiologies for more than 6 months were randomized to monotherapy with either a PDE5i (i.e., sildenafil citrate) or a VED. Patients who were unsatisfied with either initial monotherapy after 2 months were switched to the alternate monotherapy thereafter for an additional 2 months and then reevaluated. Patients were withdrawn from further study if they were satisfied with either monotherapy, as determined by the Global Assessment Question (GAQ). The remaining cohort of 41 patients was instructed to use the two therapies in combination. All 41 patients responded positively to the GAQ, and IIEF-EF domain scores obtained for this group increased from 10.2 at baseline to 27.4. Furthermore, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction domain scores improved significantly in this group despite the fact that no change was seen in these domain scores following either monotherapy. It is noteworthy that this group of patients was significantly younger than the patients who were satisfied with either monotherapy, possibly indicating the greater expectations that younger patients have regarding treatment success.

A major limitation of the study by Chen et al. was that patients were aware of the trial design at the beginning of the study, and it is possible that an inordinate number of patients responded negatively to GAQ following the first monotherapy. This is supported by the fact that success rates from the initial monotherapy groups for both sildenafil citrate and VED were lower than the success rates reported in the peer-reviewed literature (56% and 37%, respectively). It is also possible that the chance to try, what was, at the time, a novel oral therapy may have influenced some patients to report failure with the VED in order to try sildenafil citrate. These trial inconsistencies, coupled with the differences between U.S. and Israeli patient populations with regards to comorbidity profiles and treatment expectations, provide the basis for a contemporary trial to confirm the utility of combination therapy in U.S. patients who have failed PDE5i monotherapy because of insufficient efficacy.

While IIEF-5 was used as the primary assessment in our study, rather than IIEF-EF domain, there are striking similarities in EF improvement when comparing the results from Chen et al. to our findings. However, significant differences exist between the patient populations of the two studies. Approximately two-thirds of the subjects in our study had previously used vardenafil hydrochloride or tadalafil, and 91% of our subjects had used sildenafil citrate. Another 14 subjects (20%) had previously used ICI therapy as well. In contrast, patients from the Chen et al. trial presented with no previous treatment history for ED. Sixty subjects (87%) in our study had ED for at least 1 year, and 25 of these (36%) report having ED for more than 5 years. When considering that patients in our study were much more likely to have failed multiple therapies, and that many had suffered from ED in excess of 5 years, it is possible to infer that the combination of VED and oral therapies is more successful in difficult-to-treat patients than Chen and colleagues had previously demonstrated. Furthermore, the larger combination therapy population in our study provides more robust evidence for clinicians to consider when treating patients who have failed oral therapy.

The efficacy of combining sildenafil citrate with VED was also investigated in men dissatisfied with the results of a VED alone. Raina et al. conducted a study to determine whether sildenafil citrate may augment the treatment efficacy and response rate when used in combination with VED for patients with ED following radical prostatectomy [14]. The IIEF-5 score revealed statistically significant improvement in each domain, and 24 patients (77%) reported that combination therapy enhanced their erections. These data also support the success of combined therapy in a difficult-to-treat patient population.

The management of ED with a combination of existing treatment modalities appears to be synergistic in light of their diverse mechanisms of action. VEDs have also been combined with other ED therapies before the development of PDE5i. Chen et al. and Marmar et al. evaluated VEDs in combination with ICI for men with ED after treatment when either method alone failed [15,16]. In these studies, the investigators concluded that VEDs may augment a partial response to ICI and

that the combination provides an acceptable alternative before more invasive therapy is offered to patients.

The influence of uncontrolled methodological factors must be acknowledged as a limitation of our trial. During their first visit, patients were given specific instructions regarding how to use the VED and were informed about its impact on erections. It is possible that some patients may have been influenced positively by study participation and active treatment of any kind. Because our study lacked a VED treatment arm only, we are unable to assess whether reinstruction and coaching using VEDs also produced a positive perception. The same consideration would apply to a PDE5i treatment only arm. An ongoing trial, which includes these study design features, may affirm whether the combination is truly superior to either treatment used alone. To establish the improvement of EF further, partner satisfaction may also be investigated in future studies.

An additional limitation to our trial involves the inclusion of patients based on self-reported failure with PDE5i. While the receipt of proper instructions for using PDE5i was required prior to inclusion, patients were not required to respond negatively to SEP-2 or SEP-3 at baseline. As such, some subjects responded positively to SEP-2 and/or SEP-3 despite being dissatisfied with PDE5i prior to inclusion.

Our findings demonstrated that the combination of PDE5i and VED had a positive effect on patient satisfaction and EF as measured by IIEF-5. While multimodal treatment strategies may require more patient involvement and motivation, the benefit of improved EF responses as shown in our study lends support to the combination of PDE5i and VEDs for the management of ED.

Conclusions

Statistically superior results were seen in IIEF-5, SEP-2, SEP-3, and GPAS measures following 4 weeks of combination therapy consisting of PDE5i and VED as compared with PDE5i alone. These results suggest that this combination therapy may be effectively used for PDE5i failures and may be considered prior to initiating more invasive alternatives.

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Conflicts of Interest: Arthur L. Burnett, MD, and James Bailen, MD are Consultants at TIMM Medical Technologies, Inc.

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