Association Between Dosage Frequency and the Treatment Outcomes of Sildenafil in Young and Middle-aged Men With Erectile Dysfunction: A Chinese, Multicenter, Observational Study

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OBJECTIVE To evaluate the correlation between the dosage frequency of sildenafil and its treatment outcomes in men with erectile dysfunction (ED).

METHODS Data were from a 4-week, multicenter, observational study of men (1699), between 18 and 60 years of age, with a clinical diagnosis of ED defined as the Sexual Health Inventory for Men (SHIM) score ≤21. The erectile function and quality of sexual life were evaluated at the baseline and the endpoint of sildenafil treatment (after 4 weeks) by using SHIM, Self-Esteem and Relationship Questionnaire, 36-Item Short Form Health Survey, Erection Hardness Score, and the global efficacy question.

RESULTS Nine hundred thirty-five patients were enrolled in the ≤1 weekly, 573 in the 2-3 weekly, and 158 in the 4-7 weekly dosage frequency cohorts. After 4 weeks of treatment, a higher dosage frequency of sildenafil was associated with a better SHIM, Self-Esteem and Relationship Questionnaire, and 36-Item Short Form Health Survey score improvement (all $P < .0001$). Hyperlipidemia is a poor prognostic factor (odds ratio, 3.59; $P = .04$), whereas hypertension (odds ratio, 0.25; $P < .01$) and coronary heart disease (odds ratio, 0.56; $P = .05$) are sensitive to sildenafil treatment.

CONCLUSION Higher dosage frequency of sildenafil is associated with a better improvement of sexual function and quality of life of men with ED, and the concomitant treatment of hyperlipidemia is recommended. UROLOGY 86: 62–67, 2015. © 2015 Elsevier Inc.

Erectile dysfunction (ED) is defined as the inability of the man to attain or maintain an erection sufficient for satisfactory sexual performance. Reports suggest that ED is associated with decreased self-esteem, impaired sexual relationship, and compromised quality of life.[1,2] Aging has been shown to be independently related to the prevalence and severity of ED.[3] Besides aging, a variety of physical and psychosocial comorbidities including diabetes mellitus (DM), cardiovascular disease, spinal cord injury, and depression contribute to the occurrence and severity of ED.[4,5] It is widely approved that phosphodiesterase type 5 inhibitors (PDE5Is; sildenafil, tadalafil, and vardenafil) are currently the first-line therapy for ED. Numerous clinical trials have been carefully performed, established, and validated the high efficacy and good tolerability of PDE5Is worldwide.[6,7]

The successful treatment of ED with PDE5Is relies on several potential factors. The basal severity and etiologic diagnosis of ED were identified as the major prognostic factors associated with treatment outcomes.[8] Moreover, dosing conditions including a high-fat meal, coadministration drugs, and inadequate dose influence treatment outcomes as well.[9,10] However, the influence of dosage frequency of PDE5I on its treatment outcomes has not been well studied yet. Interestingly, several recent studies showed that low-dose tadalafil (2.5 or 5 mg) once daily demonstrated higher efficacy than on-demand 20-mg tadalafil.[11] Vardenafil per night also improved sexual function of ED patients who previously were refractory to on-demand PDE5Is treatment.[12] Another study with nightly dosing of sildenafil for 1 year demonstrated sustainability of improvement of erectile function and endothelial function after the treatment.[13] However, there are also some conflicting results. Zumbé et al compared and showed no significant difference in erectile function improvement between once daily and

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on-demand vardenafil in the treatment of mild-to-moderate ED.[14] Park et al study showed that once daily and on-demand udenafil (a selective PDE5I, approved in 13 countries) did not demonstrate a significant difference, and the treatment efficacy was not maintained after treatment of ED patients with DM.[15] Therefore, further studies are needed to determine whether the dosage frequency influence the treatment outcomes of PDE5Is.

In the present multicenter observational study, we aimed to assess treatment outcomes of sildenafil, which is the most commonly used PDE5I in the Chinese population, among 3 different dosage frequency groups in men with ED to optimize and personalize the treatment.

METHOD

Study Design

It was a multicenter observational study designed to evaluate the effect of the dosage frequency of sidenafil on the treatment outcomes of men with ED. There were 51 medical centers involved in this study across 11 Chinese cities (including Beijing, Shanghai, Guangzhou, Hangzhou, Nanjing, Shenyang, Dalian, Wuhan, and so forth), which were centrally coordinated by Chinese Andrology Association. The local institutional ethics committee reviewed and approved the study.

Patients

Patients were eligible to participate in the study if they had ED, were 18-60 years old, and in a stable relationship with an identical female partner. ED was defined as having a score of Sexual Health Inventory for Men (SHIM) $\leq$21.[16] Patients were excluded if they have used PDE5Is before entering this trial. Written informed consent was obtained from all the participants.

In the commencement of the study, we obtained detailed basic clinical characteristic information (including age, ED duration, ED severity, hypertension, DM, coronary heart disease (CHD), and hyperlipidemia) of each participant. Eligible patients received sildenafil at different dosage frequency at the discretion of the investigators and the preference of each patient for a period of 4 weeks. Sildenafil should not be taken more than once every 24 hours. If there is related side effect, the drug intake should be stopped. The single dose of sildenafil is 25, 50, and100 mg (25 and 50 mg are splitted from 100 mg by pill splitter). Precise single dose and dosage frequency information was documented for each patient (Supplementary Fig. 1).

Main Outcome Measures

Sexual Function. We measured and assessed the sexual function by using SHIM score before and after 4 weeks of treatment and the Erection Hardness Score (EHS), as well as the global efficacy question (GEQ) after the treatment. Responses to each of the 5 items of SHIM were rated from 1 to 5 and summed to produce a total score ranging from 5 to 25, with higher scores indicating a better sexual function. According to the scores, patients with ED were categorized into the following 4 grades: no ED (22-25), mild ED (12-21), moderate ED (8-11), and severe ED (5-7). EHS is a reliable single-item scale ranging from 0 to 4: whenever sexual stimulation occurs as EHS0, penis does not enlarge; EHS1, penis is larger but not hard; EHS2, penis is hard but not hard enough for penetration; EHS3, penis is hard enough for penetration but not completely hard; EHS4, penis is completely hard and fully rigid.[17] Percentages of EHS3 or EHS4 in patients are recorded after 4 weeks of treatment. In the present study, EHS score was dichotomized as a binary variable with EHS1 or EHS2 indicating not enough erectile hardness and EHS3 or EHS4 indicating enough erectile hardness. The GEQ asked "Did the treatment improve your erections?" with a response of yes or no.

Psychosocial Status. Psychosocial status of ED patients was evaluated by means of Self-Esteem and Relationship (SEAR) questionnaire before and after the 4 weeks of treatment.[18] SEAR consists of 14 items (each item is scored 1-5) addressing 2 domains: sexual relationship (items 1-8) and confidence (items 9-14) with higher scores indicating better function.[18] The confidence domain is composed of 2 subscales: self-esteem (items 9-12) and overall relationship (items 13 and 14). The overall score (items 1-14) is calculated from the 2 domains and subscales.

Health-related Quality of Life. Health-related quality of life was evaluated by using the 36-Item Short Form Health Survey (SF-36) before and after the study.[19] SF-36 includes 3 dimensions (General Health, ranging from 1 to 6; Vitality, ranging from 4 to 24; and Mental Health, ranging from 5-30) with a total score of 10-60. A higher score represents a high level of life quality.

Statistics

Data were analyzed by Public Health College of Peking University Health Science Center (Beijing, China). Analysis was performed on an intention-to-treat basis, which means all variables of all the participants were analyzed. The mean score changes of SHIM, SEAR, SF-36, and the percentage of patients had a "Yes" answer in GEQ or achieved EHS3 or EHS4 were calculated. A logistic regression model, including age, duration of ED, hypertension, DM, CHD, and hyperlipidemia in each dosage frequency groups as covariates, was fitted for analysis of binary efficacious variables of the response to the GEQ and EHS score. The logistic regression model was constructed using a stepwise selection method.

The data were expressed as the mean $\pm$ standard deviation. Statistical analyses were carried out using the 2-tailed nonparametric Kruskal-Wallis test run on SPSS 13.0 software. Levels of significance were expressed as P values, and $P \leq .05$ is considered as statistical significance.

RESULTS

Study Participants

From June 2008 through June 2009, a total of 1956 patients aged $\leq$60 years attended the initial screening. Totally, 290 patients (82 had prior use of PDE5Is, 105 had an SHIM score >21, 70 received no PDE5Is as first-line treatment after diagnosis of ED, and 33 received tadalafil or vardenafil) were excluded from the study. Of the remainder, 935 patients were enrolled in the $\leq$1 weekly dosage frequency cohort, 573 in the 2-3 weekly dosage frequency cohort, and 158 in the 4-7 weekly dosage frequency cohort (Supplementary Fig. 1). No severe adverse effects among all the patients were observed during the study.