

Evaluation of the efficacy of once-daily use of Tadalafil vs. On-demand use. Is there a cumulative effect?

Hasan Jamshidian, Armin Borhan, Soheil Kooraki, Arash Borhan
 Department of Urology, Tehran University of Medical Science, Imam-Khomeini Hospital, Tehran, Iran.
 Corresponding Author: Armin Borhan. Email: daneshyariran@yahoo.com

Abstract

Objective: To assess and compare the efficacy of on-demand versus daily dosages of tadalafil in the treatment of erectile dysfunction.

Methods: The case-control double-blind study was conducted at the Department of Urology, Tehran University of Medical Science, Imam Khomeini Hospital, from March 2008 to January 2010. It comprised 100 males suffering from erectile dysfunction who were randomised into two groups; one receiving on-demand tadalafil (10mg), and the other receiving once-daily dose of tadalafil (10mg). The erectile function domain of the International Index of Erectile Function was evaluated initially at the baseline and then at 24 weeks after treatment. To evaluate the possible cumulative effect of tadalafil, the index was measured in the group taking daily tadalafil at 12 weeks after the initiation of the treatment. SPSS 13 was used for statistical analysis.

Results: The study showed significant improvement in the mean erectile function domain measured after 24 weeks in both daily (17.08 ± 3.896 vs baseline 12.64 ± 2.92 ; $p < 0.001$) and on-demand (15.46 ± 3.64 vs baseline 13.48 ± 2.86 ; $p < 0.001$) groups. Data showed significant difference in mean scores between on-demand and daily groups ($p = 0.03$). In daily group, the mean domain measured at the 24th week showed significant improvement compared to the mean score of the 12th week ($p < 0.001$).

Conclusion: Treatment with daily tadalafil was associated with a significantly higher erectile function domain score compared to the on-demand use. The significant difference between mean scores of 12th week and 24th week in the daily group points towards the possible cumulative effect of tadalafil.

Keywords: Erectile dysfunction, Tadalafil, Cumulative effect. (JPMA 62: 1195; 2012)

Introduction

Erectile dysfunction (ED) is a common problem in men which might strongly impact one's quality of life.^{1,2} In 2000 it was estimated that 150 million men were suffering from ED.³ Since ED could potentially lead to psychological and mental problems, there has been always a demand for the best possible treatment options.^{2,4,5} In recent years, the development of phosphodiesterase 5 (PDE5) inhibitors such as sildenafil and tadalafil has furthered the management of ED.⁶⁻⁸ Although PDE5 inhibitors have an efficacy of 60-70% when used before sexual intercourse, the fact that it is required to be taken before a planned-sex, leaves many patients dissatisfied.^{9,10} In 2003, tadalafil was approved for the treatment of ED and with a half-life of 17.5 hours and bioavailability of 80%, it soon became the first choice of ED treatment in many countries. Tadalafil is recommended with a dosage of 10-20mg before sexual activity.^{11,12} In a study, 147 patients with ED, who were under treatment with sildenafil, were asked to replace their medication by tadalafil. Of the patients, 133 preferred to remain on tadalafil, while only 14 patients returned to sildenafil ($p < 0.001$).¹³ Recently,

some studies have shown that daily use of tadalafil could produce considerable results versus on-demand use and, therefore, result in higher treatment satisfaction of the patient and his partner.^{7,14,15} We evaluated the hypothesis that tadalafil could yield better results when used on a daily basis rather than on an on-demand basis for the treatment of patients with ED. Also, we evaluated the possible time-dependent effect of tadalafil in the treatment of ED.

Patients and methods

This was a randomised placebo-controlled double-blind study which was conducted from March 2008 to January 2010 at the Urology Department of Tehran University of Medical Science, Imam Khomeini Hospital, Iran. Men at least 18-year-old who were expected to have the same sex partner for the following six months were enrolled. The subjects had a convincing history of ED for at least 3 months and they were not under any kind of treatment for the problem. The International Index of Erectile Function (IIEF) questionnaire was used to enroll the patients. Demographic information were first noted down before the patients were

fully examined by an expert urologist. Subjects were excluded if they had penile anatomical abnormalities which could interfere with the sexual function; spinal cord injury; sexually transmitted diseases; cardiovascular diseases, diabetes mellitus, uncontrolled hypertension or ischaemic heart disease; any history of substance abuse; psychological problems and the history of any surgical procedures performed on the pelvic region such as prostatectomy. Patients who were taking nitrate compounds or androgens were not included in the study. Moreover, patients who developed any adverse effects of tadalafil such as headache, back pain and leg pain which required the discontinuation of the medication, were also excluded.

Patients were randomised into two groups using a randomisation box. The first group was given once-daily 10mg tadalafil, while a placebo pill was given to those in the group before sexual activity on an on-demand basis (the daily tadalafil group). The second group was given long tadalafil before sexual activity, while once-daily placebo pill was administered to them. (the on-demand tadalafil group). All patients were under either of the two medication regimens for a period of 24 weeks. The on-demand before-sex administration of tadalafil was limited to twice a week in order to prevent the conversion of the on-demand effect to the daily effect. The placebo pill was a combination of starch and lactose and had a shape and colour similar to that of tadalafil. Both the patient and the examiner were blinded to the randomisation of the subjects.

The IIEF questionnaire was used to assess the efficacy of the treatment. Questions 1-5 and 15 of the questionnaire which deal with the erectile function domain, were selected to measure the outcome of the study. This constituted a 6-question rating scale (IIEF6) which was applied to all the subjects before the treatment and 24 weeks later. Subjects who were taking daily tadalafil were assessed once more 12 weeks subsequent to beginning of the treatment. All the questionnaires were filled by the same analyst and the patients along with the physicians were blind. The scale score of 25-30 was considered normal; a score of 19-24 was regarded as mild dysfunction; while scores of 13-18 and 7-12 were considered as mild-to-moderate and moderate ED, respectively. A score of 6 or below was interpreted as having

severe dysfunction.¹⁶ Subjects who had a baseline score below 25 were eligible for the study, which was approved by the ethics committee of the university. After explaining the study process in detail to the subjects, written informed consent was obtained from all of the participants.

Statistical analysis was performed using SPSS 13.0. Variables had normal distribution according to Kolmogorov-Smirnov test results. Therefore, parametric tests — paired T-test and independent T-test — were used to evaluate the inter-group and within-group differences. All statistical tests were 2-tailed and the level of significance was chosen at p-value less than 0.05. All quantitative variables were expressed as mean ± standard deviation.

Results

Initially, 143 patients were considered for the study. Of them, 17 (11.8%) and later 26 (18.18%) were excluded based on the primary exclusion criteria, while those who met the primary inclusion criteria, opted out of the study at various stages. As such, the final sample size was 100 patients who were randomised into two groups. There was no significant difference in the mean age between the two groups (50.72±9.40 years ranging from 30-70 in the on-demand group vs. 51.90±1.19 years ranging from 26-75 in the daily group; p = 0.58). The mean duration from the onset of the ED was 29±17 and 32±19 months in the on-demand and daily groups respectively, which posed no significant difference (p=0.40).

The baseline IIEF6 showed that in the on-demand group, 32 (64%) and 18 (36%) subjects were in the mild-to-moderate and moderate categorisations respectively. In the daily group, 1(2%), 23(46%) and 26(52%) patients suffered from mild, mild-to-moderate and severe ED respectively (Table). Data did not show any evidence of the significant difference in the mean baseline score between two groups (13.48±2.86 in the on-demand group vs. 12.64±2.92 in the daily group; p = 0.15).

In the subjects who were on the once-daily tadalafil, the mean IIEF6 score measured 12 weeks after treatment onset showed significant difference in comparison with the baseline score (15.24±3.56 vs. 12.64±2.92, p <0.001). The mean score was further improved when measured 24 weeks after the beginning of the treatment (17.08±3.89 vs. 12.64±2.92, p <

Table: severity of the erectile dysfunction is evaluated in the two groups separately before and in the 24th week. The severity for the daily group was also assessed 12 weeks after beginning of the medication.

| | | Normal | Mild | Mild-to-moderate | Moderate | Severe |
|--------------------------|----------|--------|---------|------------------|----------|--------|
| Daily Group (group1) | Baseline | 0 | 1(2%) | 23(46%) | 26(52%) | 0 |
| | Week 12 | 0 | 10(20%) | 31(62%) | 9(18%) | 0 |
| | Week 24 | 2(4%) | 14(28%) | 30(60%) | 4(8%) | 0 |
| On-Demand Group (group2) | Baseline | 0 | 0 | 32(64%) | 18(36%) | 0 |
| | Week 24 | 0 | 10(20%) | 31(62%) | 9(18%) | 0 |

0.001). There was also a considerable difference between the 12-week and 24-week mean scores in this group ($p < 0.001$).

There was a significant difference between the mean baseline and 24th-week IIEF6 scores in the group taking on-demand medication (15.46 ± 3.64 vs. 13.48 ± 2.86 ; $p < 0.001$). The data showed a meaningful difference in the mean scores of the 24th-week IIEF between two groups ($p = 0.03$).

Discussion

Erectile dysfunction is a multifactorial and chronic disease related to several underlying diseases as cardiovascular, neurological, endocrine and psychological disorders.¹ Historically, anticipated sexual activity was the leading cause of pharmacological ED treatment. In this case, just before sexual activity, men needed to inject vasoactive drugs into the penis or apply vacuum device. Some of these complications were minimised by using oral PDE5 inhibitors.⁸ However, the treatment worked only when the intake and intercourse occurred within a limited time window. In this study, we compared on-demand dose and daily use of tadalafil in the treatment of ED. The results that showed tadalafil could significantly improve ED either used on a once-daily basis or on-demand basis, but the best results were achieved when the medication was administered on a daily-basis. Our results were in line with a study that showed that the mean IIEF erectile function domain score improvement was significantly higher in the group taking once-daily tadalafil than those who were on the on-demand regimen. It reported that 84% of the subjects who were on the daily regimen completed the sexual intercourse as against 69% of those who were on the on-demand regimen.¹⁷ However, in contrast to our findings a study performed on patients with mild-to-moderate ED found no evidence of the superior effect of the daily fixed verapamil (a PDE5 inhibitor) over on-demand use.¹⁸ PDE5 inhibitors have anti-proliferative effects and could potentially improve vascular endothelial function.¹⁹ So, in some cases sildenafil is being used for the treatment of primary pulmonary hypertension.²⁰ Regarding this fact, our study showed that chronic use of tadalafil for the treatment of ED might have a cumulative effect; through observing that there was a significant difference in the IIEF6 scores recorded at 12th and 24th weeks following the given treatment. Similarly, in a study, chronic administration of sildenafil significantly improved ED. The study suggested that sildenafil did not act through nitric oxide (NO) or cyclic guanosine monophosphate (cGMP) pathways and, so, tachyphylaxis to the chronic effect could not be a matter of concern.¹⁹

Our study did have some limitations. Because of cultural issues, patients were not completely comfortable about discussing their sexual activities and, therefore, some

were refusing to answer the IIEF questions. Six patients dropped out of the study for this very reason. Furthermore, the satisfaction of the patients' female partners was not questioned by the study. Besides, the side effects of tadalafil were not completely inspected even when 11 subjects discontinued tadalafil because of headache or leg pain and, therefore, opted out of the study. Indeed, other studies have also not reported serious adverse effects of tadalafil. In a multi-centre clinical trial, the most common adverse effects of on-demand tadalafil were regarded as headache (15%), dyspepsia (8%) and back pain (5%).¹⁴ As such, daily use of tadalafil seemed to be satisfactory for most of the patients as it enabled them for spontaneous sexual activity rather than imposing the stress of on-demand medication for a planned sex.

Conclusion

The study found evidence in favour of the superior effect of once-daily tadalafil against on-demand medication for the treatment of erectile dysfunction. The significant difference between mean IIEF scores at 12th and 24th weeks in the daily group indicates possible cumulative effect of tadalafil.

Acknowledgements

We would like to thank the nursing, administrative and secretarial staff of the Urology Department and the clinic at the Imam Khomeini Hospital for their contribution to the maintenance of patient record without which this project would have been impossible.

References

1. Wespes E, Amar E, Hatzichristou D, Hatzimouratidis K, Montorsi F, Pryor J, et al. EAU Guidelines on erectile dysfunction: an update. *Eur Urol* 2006; 49: 806-15.
2. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993; 270: 83-90.
3. McKinlay JB. The worldwide prevalence and epidemiology of erectile dysfunction. *Int J Impot Res* 2000; 12 Suppl 4: S6-11.
4. Costa P, Costa P, Grivel T, Giuleano F, Pinton P, Amar E, Lemaire A. [Erectile dysfunction: a sentinel symptom?]. *Prog Urol* 2005; 15: 203-7.
5. Wagner G, Fugl-Meyer KS, Fugl-Meyer AR. Impact of erectile dysfunction on quality of life: patient and partner perspectives. *Int J Impot Res* 2000; 12 Suppl 4: S144-6.
6. Cour F, Cour F, Fabbro-Peray P, Cuzin B, Bonierbale M, Bondil P, deCrecy M, et al. [Recommendations to general practice doctors for first line management of erectile dysfunction]. *Prog Urol* 2005; 15: 1011-20.
7. Porst H, Porst H, Giuliano F, Glina S, Ralph D, Casabe AR, Elion-Mboussa A, et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2006; 50: 351-9.
8. Hatzimouratidis K, Hatzichristou D. Phosphodiesterase type 5 inhibitors: the day after. *Eur Urol* 2007; 51: 75-88.
9. Montague DK, et al. Chapter 1: The management of erectile dysfunction: an AUA update. *J Urol* 2005; 174: 230-9.
10. Costa P, Avances C, Wagner L. [Erectile dysfunction: knowledge, wishes and attitudes. Results of a French study of 5,099 men aged 17 to 70]. *Prog Urol* 2003; 13: 85-91.
11. Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002; 168: 1332-6.

12. Francis SH, Corbin JD. Molecular mechanisms and pharmacokinetics of phosphodiesterase-5 antagonists. *Curr Urol Rep* 2003; 4: 457-65.
 13. Stroberg P, Murphy A, Costigan T. Switching patients with erectile dysfunction from sildenafil citrate to tadalafil: results of a European multicenter, open-label study of patient preference. *Clin Ther* 2003; 25: 2724-37.
 14. Carson CC, Rajfer J, Eardley I, Carrier S, Denne JS, Walker DJ, Carson CC, et al. The efficacy and safety of tadalafil: an update. *BJU Int* 2004; 93: 1276-81.
 15. Skoumal R, Chen J, Kula K, Breza J, Calmfirescu N, Basson BR, et al. Efficacy and treatment satisfaction with on-demand tadalafil (Cialis) in men with erectile dysfunction. *Eur Urol* 2004; 46: 362-9.
 16. (Online) (Cited 2010 April 4). Available from URL: www.cornellurology.com/faculty/IBPH-IIIEF-Assessments.pdf.
 17. McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med* 2005; 2: 415-25.
 18. Zumbe J, Zumbe J, Porsi H, Sommer F, Grohmann W, Beneke M, Ulbrich E. Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: findings of the RESTORE study. *Eur Urol* 2008; 54: 204-10.
 19. Behr-Roussel D, Gorney D, Mevel K, Caisey S, Bernabe J, Burgess G, et al. Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis. *Eur Urol* 2005; 47: 87-91.
 20. Chockalingam A, Gnanavelu G, Venkatesan S, Elangovan S, Jagannathan V, Subvamaniam T, et al. Efficacy and optimal dose of sildenafil in primary pulmonary hypertension. *Int J Cardiol* 2005; 99: 91-5.
-