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Original Research

Daily Dose of 5 mg Tadalafil Safely Improves Erectile Function and Liver Function Enzymes in Smokers

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Abstract

Background: Smokers are known to have a higher risk of erectile dysfunction. We examined how daily consumption of low-dose tadalafil affected erectile function and circulation in smokers and assessed the medication safety. **Methods**: Men aged over 20 years with current smoking status were selected to complete four weeks of treatment with 5 mg tadalafil daily. Erectile function was measured using the International Index of Erectile Function (IIEF), and additional tests included measuring various serum parameters, electrocardiogram, and nail capillary blood flow. **Results**: The IIEF scores, capillary blood flow, and serum liver function enzyme levels significantly improved. There were no reported adverse side effects. **Conclusions**: Smokers who were administered 5 mg tadalafil daily for four weeks had improved International Index of Erectile Function scores, dilated capillary vessels, and improved blood liver function enzyme levels; proving not only safety of usage and its effectiveness but also possible features that can indicate usages of the drug in other purposes.

Keywords: erectile dysfunction; liver function; smokers; tadalafil

1. Introduction

Smokers are known to be at a higher risk for vascular diseases, such as coronary artery disease, myocardial infarction, stroke, and hypertension [1]. Smoking affects the circulation to all parts of the body, including the genitals, and free radicals from the smoke can cause endothelial damage in the blood vessels, which in turn can cause disease [2]. Penile erection, which occurs through functional dilation of the blood vessels, can also be affected by smoking. Studies have shown that the chances of oxidative stress from smoking are closely associated with the causes of erectile dysfunction (ED) [3]. Some studies have shown that ED can also be improved when smoking is ceased [4].

Phosphodiesterase type-5 (PDE-5) inhibitors are mild vasodilators, which are commonly used to improve ED. Tadalafil, sildenafil, and vardenafil are examples of PDE-5 inhibitors, which are ingested at a dose of 10 mg to 20 mg, 30 min before intercourse, once per day.

A previous study has proven the efficacy and safety of the daily intake of tadalafil at a lower dosage of 5 mg daily [5]. This method of regular intake is considered to be better than the ordinary on-session methods because the individual taking the medication everyday may avoid the thought that a patient is dependent on drugs for correct erectile function on each occasion.

While other studies have shown efficacy of lower-dose tadalafil in improving lower urinary tract symptoms and sexual performance in patients with erectile dysfunction, we aimed to study whether the daily intake of lower-dose tadalafil improves erectile function readiness in smokers who are prone to ED.

2. Materials and Methods

2.1 Design of the Study

The efficacy of 5-mg once-daily tadalafil was evaluated in a four-week open-label pilot study, conducted at our hospital.

Our hospital's ethical review board authorized the protocol (2019-07-006) and consent forms, and all patients provided signed informed consent prior to enrollment. The study followed the protocol and ethical principles outlined in the Declaration of Helsinki, which were amended in 2000, as well as pertinent regulations.

2.2 Study Population

Eligible participants were men aged $\geq$20 years who identified themselves as smokers and volunteered to participate in the study. Recruitment was done on any male patients of ages above 20 who have visited Soonchunhyang University Hospital regardless of visiting purposes. Their sexual habit prior to inclusion of the study was dismissed as screening measure as they were expected to improve from the baseline anyhow. Patients had to be in monogamous, heterosexual relationships and agree not to receive any other ED therapy during the study. The exclusion criteria were as follows: (1) myocardial infarction in the past 90 days; (2) coital unstable angina or angina pectoris; (3) heart failure classified as class 2 by the New York Heart Association within the previous six months; (4) stroke within the previous six months; (5) genetic degenerative retinal diseases, including retinitis pigmentosa; (6) hypersensitivity to PDE-5 inhibitors; (7) concurrent administration of other PDE-5 inhibitors; (8) certain genetic disor-

ders (galactose intolerance, glucose-galactose malabsorption, and Lapp lactase deficiency); (9) non-arterial anterior ischemic optic neuropathy; and (10) concurrent administration of guanylate cyclase stimulation.

2.3 Measures of Efficacy

The protocol included four treatment-free weeks, followed by four weeks of treatment. Tadalafil 5 mg was administered at approximately the same time each day. Treatment compliance was considered to be at least 80% of the prescribed dosages.

During the initial appointment, individuals were asked about their smoking history, which was measured in pack-years. Nicotine levels were measured using the urine cotinine test, which also represented their smoking habit. The study participants completed the Fagerstrom Test for Nicotine Dependence.

The International Index of Erectile Function (IIEF) is a 15-item, self-managed survey used worldwide to diagnose ED, and this was used to measure the primary efficacy of tadalafil [6]. The IIEF has been certified as a concise and dependable measure for evaluating erectile performance, it is easy to administer in research and clinical settings and is psychometrically validated.

Recruitment criteria for this study included those whose answers scored $\geq$21 in the IIEF-5, which is a concise version of the IIEF. The scale of this score represents the status of ED as being severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), or no ED (22–25). Since the participants were only those who had a score of $\geq$21, an improvement in the IIEF score was interpreted as an improvement in performance and satisfaction in those who already had normal sexual function.

Additional tests included assessing the physiological status of the patients after eight hours of fasting through blood tests, urine tests, and electrocardiogram (ECG). Blood tests included chemistry (blood urea nitrogen, creatine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase, C-reactive protein, and fasting blood sugar), total blood count and differentials (differential white blood cell, hemoglobin, and platelet), lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride), and prostate-specific antigen (PSA).

An exploratory examination of the effect of tadalafil on capillary pressure was also performed. Capillary tests can be used to noninvasively assess microvessels [7]. The nail vascular test was used to analyze capillary abnormalities around the nail. It is helpful in assessing the health of blood vessels throughout the body [8]. After placing a drop of immersion oil on the nail to visualize the blood vessels, the second and fourth values on both sides of the nail were measured using a microscope at 200$\times$ magnification. Images of the capillaries of each patient's fingernails were transferred and stored on a computer using a halo-vision stereo microscope (digital camera Polaroid, No. 812401TT, Minneapolis, MN, USA) for analysis. Based on the center with the highest resolution on each of the fingers, three apical limbs and capillary widths were measured along with the speed and flow of blood within the capillaries.

Treatment emergent adverse events were defined as any adverse event that occurred or worsened after the patient was allocated to therapy. All reported events were analyzed to assess treatment safety.

2.4 Statistical Analysis

It was determined that a cohort of 30 participants, with an anticipated dropout rate of 30%, were required to reach minimum statistical significance (two-sided alpha = 0.05, beta [1-power] = 0.1).

All data are presented as mean $\pm$ standard deviation, with statistical significance set at $p < 0.05$. The paired *t*-test was used to compare IIEF before and after tadalafil use. A comparison of laboratory tests was also performed using the *t*-test. The statistical R program (version 4.0; R Project for Statistical Computing, Vienna, Austria) was used to conduct the analyses.

3. Results

3.1 Study Participant Characteristics

Overall, 30 patients were enrolled in the study. Six patients opted out of the study and 24 patients (mean age, 42.22 $\pm$ 9.7 years; body mass index, 25.9 $\pm$ 3.0 kg/m^2; systolic blood pressure, 137.5 $\pm$ 13.1 mmHg; diastolic blood pressure, 86.8 $\pm$ 8.7 mmHg; and pulse, 82.9 $\pm$ 10.8) completed the study. Participants had a smoking history of 22.4 $\pm$ 10.3 pack-years, nicotine levels of 42 $\pm$ 5.4 ppm, and nicotine dependency of 3.3 $\pm$ 2.4 (score out of 10).

3.2 Primary Measure of Efficacy

3.2.1 IIEF

According to the IIEF self-administered survey, there was a statistically significant increase in score from 46.8 to 56.1 ($p < 0.005$).

3.2.2 Capillary Measurements

Fingertip capillary measurements showed significant increases in the apical limb width from 12.10 to 14.7 μm (p = 0.011) and flow from 15,583.80 to 21,476.10 μm^3/s (p = 0.033). The width increased from 44.9 to 46.3 μm and the speed from 103.8 to 107.5 μm/s, but these findings were not statistically significant.

3.2.3 Liver Function Enzymes

After four weeks of daily tadalafil, ALT levels significantly decreased from 30.6 U/L to 26.2 U/L. Additionally, AST levels decreased from 27.5 U/L to 24.4 U/L, but this was not statistically significant (p = 0.087).

3.2.4 PSA

No statistically significant changes in pre- and post-measurements were observed for PSA (0.9–1.0 ng/mL).

3.2.5 Blood Pressure and ECG

Systolic blood pressure, diastolic blood pressure, and pulse rate before and after tadalafil use demonstrated no clinical differences. There were no significant differences in ECG (heart rate: 80.0 to 79.0 bpm, PR interval: 184.7 to 188.3, and QT: 357.9 to 349.2, before and after the medication, respectively), further supporting the safety of daily low-dose tadalafil.

4. Discussion

4.1 ED

ED is diagnosed when a person has insufficient penile erection for vaginal penetration [9]. According to a cross-sectional and community-based investigation, the pervasiveness of ED demonstrates a gradual increase with age [10]. The number of ED cases worldwide is estimated to reach 322 million by 2025 [11,12].

A range of factors can cause sexual dysfunction in elderly men, including psychological or physical conditions, underlying diseases, and medications taken for their treatment. Additionally, testosterone levels commonly decrease due to various aspects of the lifestyle of an aging man. These include certain daily habits and androgen deficiency. A study showed 24% of men aged between 30 and 79 years had testosterone levels below 300 ng/dL. In addition, 5.6% of patients had symptomatic androgen deficiency [13]. Additionally, nonendocrine causes of ED, such as neurogenic, vasculogenic, iatrogenic, and endocrine pathways, have also been suggested.

Men with ED commonly experience anxiety and depression associated with their sexual performance. Therefore, these symptoms affect not only the sex life, but also their overall quality of life [14].

4.2 Physiology Underlying ED

The central mechanism of penile erection consists of the L-arginine-nitric oxide-cyclic guanosine monophosphate pathway [15]. Sexual stimulation activates neurological pathways that cause nitric oxide to be released directly from the endothelial cells and nerves into the penis. Nitric oxide binds to guanylyl cyclase upon entering the cytoplasm of smooth muscle cells. When nitric oxide interacts with guanylyl cyclase, the enzyme undergoes a conformational shift, allowing it to catalytically produce 3,5′-cyclic guanosine monophosphate (cGMP) out of guanosine 5′-triphosphate. The provocation of penile erection begins intracellularly with cGMP. cGMP-dependent protein kinase (PKG) is activated by cGMP, which then phosphorylates numerous proteins. These protein kinase interactions cause a decrease in calcium levels in cells, enabling relaxation of arterial and trabecular smooth muscles, resulting in dilatation of arteries, constriction of veins, and penile erection firmness.

The effects of nitric oxide and cGMP on smooth muscle contraction seem to be controlled through PKG rather than by cyclic AMP-dependent protein kinase. In smooth muscles, PKG has multiple distinct physiological substrates. All of these targets are phosphorylated, which results in a decrease in intracellular Ca^{2+} concentration or sensitivity to Ca^{2+}, thereby reducing the tone of smooth muscle [6].

4.3 PDE-5 Inhibitors' Mechanism of Action

As cGMP is required for penile erection, increasing intracellular cGMP levels could be a viable treatment for insufficient smooth muscle relaxation. By degrading cGMP, PDE-5 commonly prevents penile erection [15].

The cGMP-specialized PDE-5 enzyme is widely expressed in a variety of cells and tissues. The nitric oxide-cGMP pathway is amplified when PDE-5 is inhibited, resulting in relaxation of vascular [16] and non-vascular smooth muscles [17], weakening leukocyte adhesion [18], decreasing platelet activation, and suppressing cell proliferation [19,20]. In this study, the increase in nail capillary circulation represents blood flow improvement from vascular dilation due to PDE-5 inhibitors. Apical limb width is representative of vasodilatory effects, and an increase in the width results in increased blood flow through the vessel.

However, the vasodilation is not generalized. The degree of vasodilation is dependent on the physiological stimulus of nitric oxide. Local places where a comparatively high nitric oxide production signals a higher requirement for blood perfusion will yield higher efficacy in PDE-5 inhibitors [21]. For example, sildenafil relaxes smooth muscle in isolated strips of the corpus cavernosum by boosting the passage of the usual, cGMP-dependent relaxation processes endogenously, but does not function without nitric oxide [15].

4.4 Tadalafil's Specificity

In clinical trials, tadalafil dramatically improved all effectiveness outcomes across disease etiologies and severity levels in individuals of various ages. Tadalafil is effective for up to 36 h, which allows patients to decide when they want to engage in sexual activities, resulting in favorable quality of life outcomes [22].

Phosphodiesterase type-5 is found in a variety of organs, such as the bladder, and vascular smooth muscles [23]. Phosphodiesterase type-6 (PDE-6) isoenzyme is mainly found in the eyes of mammals, where it regulates phototransduction in the retinal rod and cone [24]. As PDE-5 and PDE-6 share similar amino acid sequences and catalytic domains, the first generation of PDE-5 inhibitors, such as sildenafil and vardenafil, can also act as a PDE-6 inhibitor [25]. Tadalafil, on the other hand, seems to be a

more selective PDE-5 inhibitor [26]. PDE-6 inhibition has been associated with visual impairments, such as functional blindness, vision problems, and increased light sensitivity [27].

4.5 Liver Function Enzymes

We hypothesize that the improvement in liver function enzymes in our study can be attributed to two factors: (1) hemodynamic improvements in the liver and (2) cross-activity of different PDEs.

4.5.1 Hemodynamics

Lee *et al*. [28] found that oral treatment with 50-mg sildenafil increased cGMP levels in cirrhotic hepatic veins, but not in peripheral veins, resulting in a significant reduction of resistance in sinusoids, but not in peripheral vasculatures. Therefore, there may be situations in which PDE-5 inhibitors affect hepatic hemodynamics, while the systemic circulation is mostly unaffected.

PDE-5 inhibitors boosted flow in the portal vein and parenchyma without increasing portal pressure in normal rat livers, according to Halverscheid *et al*. [29]. Their findings indicated that reduced nitric oxide bioavailability in cirrhotic livers causes a constriction of sinusoids, contributing to portal hypertension. It is possible that PDE-5 inhibitors could reverse this effect.

In our study, tadalafil's PDE-5 inhibition could have reduced sinusoidal resistance and increased blood flow to the liver. This could improve the condition of the liver parenchyma, resulting in lower leakage and, consequently, serum levels of liver function enzymes.

4.5.2 Cross-activity

Tadalafil is >10,000 times more effective at inhibiting PDE-5 than PDE-1–4 and 7, and >9000 times more effective at inhibiting PDE-5 than PDE-9–10. However, the similarities between homologous catalytic domains of different PDEs allow for the cross-reactivity of PDE inhibitors [30]. It is possible that the daily administration of 5 mg tadalafil in our study also inhibited PDE types other than PDE-5, particularly PDE-3, which are present in considerable amounts in the liver.

4.6 Limitations and Future Direction

Our study included a limited number of participants, which also limited the statistical significance of our findings. The inclusion of only those who had normal erectile function in the study prevented assessing the efficacy of low-dose tadalafil in people with abnormal levels of ED. There was no means of measuring the amount of damage caused by smoking in the study population, thus the level of improvements achieved by tadalafil could not be assessed in relation to either the length of smoking history or anticipated resultant systemic damage.

Future studies should elaborate on improvement in the liver function enzymes following the use of PDE5 inhibitors and attempt to expose their mechanism of action. Possible liver diseases, such as liver cirrhosis and fatty liver, that could benefit from the improvements should be examined as well.

5. Conclusions

A daily dose of 5 mg tadalafil safely improved sexual performance and satisfaction in smokers. The regimen also improved liver aminotransferase levels.

Tadalafil may be advantageous over other PDE-5 inhibitors because it has less cross-reactivity with other PDE types and reduces the risk of some adverse effects, including retinopathy.

Future studies are required to assess the efficacy of tadalafil in the treatment of abnormal liver function and hepatic diseases, such as liver cirrhosis, and avascular necrosis of the femoral head.

Author Contributions

DSK—designed the research study, performed the research and analyzed the data. BWY—provided help and advice on experiments, performed the research and analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Soonchunhyang University Hospital Seoul (approval number: 2019-07-006).

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Conflicts of Interest

The authors declare no conflict of interest.

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