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Does the Daily Dose of Tadalafil for the Treatment of Erectile Dysfunction Increase Penile Sensation?

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What's known on the subject? and What does the study add?

This topic has not yet been studied in the literature yet. Our study demonstrates a quantative increase in penile sensation with the use of tadalafil.

Abstract

Objective: To investigate the effect of tadalafil, used for treating erectile dysfunction (ED) at a daily dose of 5 mg for 12 weeks, on penile sensation.

Materials and Methods: Our study included 30 male patients who applied to our andrology outpatient clinic with the complaint of ED and were prescribed tadalafil at a daily dose of 5 mg for 12 weeks. Before treatment, serum levels of testosterone and luteinizing hormone (LH) were measured. Demographic and clinical characteristics were recorded. Pre- and post-treatment electromyography (EMG) examinations for penile sensation and International Index of Erectile Function (IIEF-5) scoring were performed for each patient.

Results: The mean age was 53±9 years. The mean body mass index was 27±2. Before treatment, serum levels of testosterone and LH were within the normal range. There were 8 (29%) patients with diabetes mellitus and 7 (25%) patients with hypertension. The pre- and post-treatment IIEF-5 scores were 13±3 and 19±3, respectively. Nerve conduction velocities (NCV) increased from 35.5 m/sec to 38.05 m/sec. Latency values decreased from 2.32 ms to 2.14 ms. There was a statistically significant improvement in IIEF-5 scores and EMG results for penile sensation after treatment (IIEF-5, NCV and latency; $p<0.001$, $p<0.001$ and $p=0.001$, respectively).

Conclusion: In this study, we showed that tadalafil at a daily dose of 5 mg used for treating ED provides an increase in penile sensation.

Keywords: Erectile dysfunction, oral phosphodiesterase-5 inhibitors, penile sensation

Introduction

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve and/or maintain an adequate penile erection for sexual activity (1,2). It significantly affects the quality of life of many male individuals (3). It is also one of the most common sexual health problems, affecting an estimated 18 million men in the ultrasound alone (4). Epidemiological data have shown a high prevalence and incidence of ED worldwide (5).

Most men have multiple risk factors for ED, one or more of which may be more predominant, including psychological, neurological, hormonal, arterial, or cavernosal disorders, or a combination thereof (6).

Traditional electrodiagnostic studies for men with ED include pudendal somatosensory -evoked potentials and delays in bulbocavernosus reflexes. Neither of these two methods alone measures the functions of peripheral sensory nerves. The dorsal nerve of the penis (DPN) is the terminal sensory branch of the pudendal nerve, which carries sensory data from the glans and shaft of the penis (7,8). Sensory and tactile stimulation of the penis play an important role in erectile and sexual function. Interruption of sensory stimulation causes decreased libido, ejaculatory dysfunction, and loss of impotence (9,10).

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Erection occurs through three different stimuli: Genital stimulation (contact and reflexogenic), central stimulation (non-contact or psychogenic), or stimulation to the central nervous system (night-time) (11). DPN carries sensory innervation from the penile shaft and glans. Therefore, tactile stimulation has an important role in erection (12). Sensory electromyography (EMG) to DPN showed the early occurrence of sensory disturbances in the distal penis (2).

Recently, inhibitors of the phosphodiesterase-5 (PDE-5) enzyme have been the most widely used treatment for ED. Tadalafil is an effective and well-tolerated treatment for ED (13). Tadalafil at a dose of 5 mg once daily significantly improves ejaculation and orgasm, sexual intercourse and overall satisfaction, and erectile function (14).

In this study, we showed the change in penile sensation in men after treatment with ED. Additionally, this topic has not yet been studied in the literature as far as we know. The inclusion of patients using daily therapy for ED regularly was aimed at a clear assessment of outcomes.

Materials and Methods

This research has a prospective and controlled study design. A signed consent form was obtained from all patients who volunteered to participate in the study. Ethics Committee approval for this study was obtained from the Ethics Committee of Health Sciences University, Antalya Training and Research Hospital (2020-352), and all steps were planned and conducted following the Declaration of Helsinki and its later amendments.

Patients who started treatment for ED in the andrology outpatient clinic were referred to the study by the secretariat. We included patients with a history of at least 6 months of ED who did not receive any treatment, patients with normal serum levels of testosterone and luteinizing hormones, and patients who were recommended to use tadalafil for 12 weeks. Patients with a history of hypogonadism, cryptorchidism, varicocele, peripheral neuropathy, uncontrolled diabetes mellitus (hemoglobin a1c >7%), and past and current illicit drug abuse were excluded from the study. The demographic and clinical characteristics of all patients were recorded.

All patients participating in the study completed the International Index of Erectile Function (IIEF-5) form and underwent penile EMG examination before and after treatment. Patients were divided into two groups as over 50 years old and under 50 years old. A comparative evaluation was made on the effect of age on the outcomes of treatment and penile sensorial EMG.

Electrophysiological studies were planned to be performed between 09:00 and 12:00, at a room temperature of 23 to 25 °C, in a quiet room with dim light, and with the relaxed and awake patient in the supine position. A two-channel electroneuromyography device (Nihon-Kohden-Neuropack, model MEB-2200) was used for recording.

Penile sensorial EMG was examined using Clawson's method. The penis was placed in the concavity of a specially designed Orthoplast penile traction device and stretched to reach its maximum length by pulling from the tip of the glans. A Cunningham incontinence clamp was placed on the glans, and the penis was maintained in tension by holding from the glans. An electroencephalography paste was used for the placement of active and reference steel electrodes. The active recording electrode was placed as proximal as possible to the root of the penis. The reference electrode was placed 4 cm above the active electrode. The proximal part of the dorsal penile shaft was stimulated orthodromically with an active electrode and the dorsal glans with a reference electrode (15).

Statistical Analysis

Categorical data were presented as number and percentages. Continuous data were evaluated by the Kolmogorov-Smirnov test to verify the normality of the distribution of variables. Normally distributed data were presented as mean + standard deviation, while non-normally distributed data were presented as median and IQR (25-75th). An independent simple t-test was used to compare two independent normally distributed data, while the Mann-Whitney U test was used for the comparison of non-normally distributed data. A paired sample t-test was used to compare two independent normally distributed data, while the Wilcoxon test was used for the comparison of non-normally distributed data. Spearman's Correlation analysis was used to analyze the parameters related to changes in IIEF scores. A p-value of <0.05 was considered statistically significant. Analysis of the dataset was carried out using the IBM Statistical Package for Social Sciences version 23.0 (IBM SPSS Corp.; Armonk, NY, USA).

Results

The study included 30 patients. One patient discontinued the treatment with the complaint of myalgia, and the study was continued with 28 patients since another patient did not come to the follow-up visit. The mean age of the patients was 53±9 years. The mean duration of ED was 6.8 months. There were 8 (29%) patients with diabetes and 7 (25%) patients with hypertension. The demographic characteristics and comorbidities of the patients are given in Table 1.

We showed statistically significant changes in pre-treatment and post-treatment IIEF-5 scores and penile sensorial EMG findings. Pre-treatment IIEF-5 scores of 13±3 were measured as 19±3 after treatment with tadalafil at a daily dose for 12

weeks (p<0.001). This improvement was consistent with the literature. The mean nerve conduction velocities (NCV) in EMG was 35.5 m/sec (33.3-41.2) before treatment, and 38.05 m/sec (34.5-43.6) after treatment (p<0.001). The increase in NCV is the most important finding of penile sensorial EMG showing an increase in penile sensation. Thus, the increase in NCV has been interpreted as an improvement in penile sensation. The changes in latency and amplitude values used in the calculation of NCV are given in Table 2.

Table 1. Demographic and clinical characteristics of the patients

Age, years	**53±9**
BMI, kg/m^2	27±2
Alcohol consumption, n (%)	2 (7)
Smoker, n (%)	10 (36)
Comorbidity, n (%)	
Diabetes mellitus	8 (28.6)
Hypertension	7 (25.0)
Coronary artery disease	1 (3.6)

BMI: Body mass index

The delta equation (Δ = the amount of change) was created for the IIEF-5 score and penile sensorial EMG findings as post-treatment value minus pre-treatment value. Factors that may be related to this change were evaluated. There was a significant correlation between age and IIEF-5 score and penile sensorial EMG findings. As age increases, the improvement in the IIEF-5 score (r=-0.614, p<0.001) and all penile sensorial EMG findings decrease (for Δ NCV, Δ Latency, Δ Amplitude, r=-0.746 p<0.001, r=0.637 p<0.001, r=-0.755 p<0.001, respectively). There was a significant correlation between the IIEF-5 score and NCV (r=0.663, p<0.001) and Amplitude (r=0.659, p<0.001). As improvement in IIEF-5 increases, so does improvement in NCV and Amplitude (Table 3).

The mean amplitude value in penile sensorial EMG was 4.47±1.32 before treatment, whereas it increased to 5.07±1.60 after treatment (p<0.015). Additionally, the mean latency value was 2.14±0.42 before treatment, whereas it increased to 2.32±0.38after treatment (p<0.001). The latency and amplitude parameters in the penile sensorial EMG are used to calculate NCV. The increase in these values after treatment was interpreted as an improvement in penile sensation. As a result, it has been shown that the improvement in IIEF-5 provides an improvement in penile sensation (Figure 1).

Table 2. Comparison of IIEF scores and EMG findings before and after PDE-5 inhibitor therapy

	Pre-treatment	Post-treatment	p-value
Overall			
IIEF-5	13±3	19±3	<0.001
NCV, m/s	35.5 (33.3-41.2)	38.05 (34.5-43.6)	<0.001
Latency, ms.	2.14±0.42	2.32±0.38	<0.001
Amplitude, uV	4.47±1.32	5.07±1.60	<0.015

IIEF-5: International Index of Erectile Function-5; NCV: Nerve conduction velocity, EMG: Electromyograph, PDE-5: Phosphodiesterase-5

Table 3. Possible factors related to improvement in IIEF scores and EMG findings

		Δ IIEF-5	Δ NCV	Δ Latency	Δ Amplitude
Diabetes mellitus	Correlation coefficient	-0.131	-0.029	-0.010	-0.338
	p-value	0.506	0.882	0.960	0.078
Hypertension	Correlation coefficient	-0.084	-0.312	0.148	-0.220
	p-value	0.670	0.107	0.451	0.261
Smoker	Correlation coefficient	0.014	0.138	-0.162	-0.176
	p-value	0.943	0.482	0.411	0.371
BMI	Correlation coefficient	-0.221	0.009	0.018	-0.187
	p-value	0.258	0.965	0.926	0.341
Age	Correlation coefficient	-0.614**	-0.746**	0.637**	-0.755**
	p-value	0.001	0.000	<0.001	0.000
Δ IIEF	Correlation coefficient	-	0.663**	-0.555	0.659**
	p-value	-	0.000	0.002**	0.000
	n	28	28	28	28

BMI: Body mass index, IIEF: International Index of Erectile Function, EMG: Electromyography, NCV: Nerve conduction velocity, Δ: Post-treatment values minus pre-treatment values, **Correlation is significant at the 0.01 level (2-tailed)

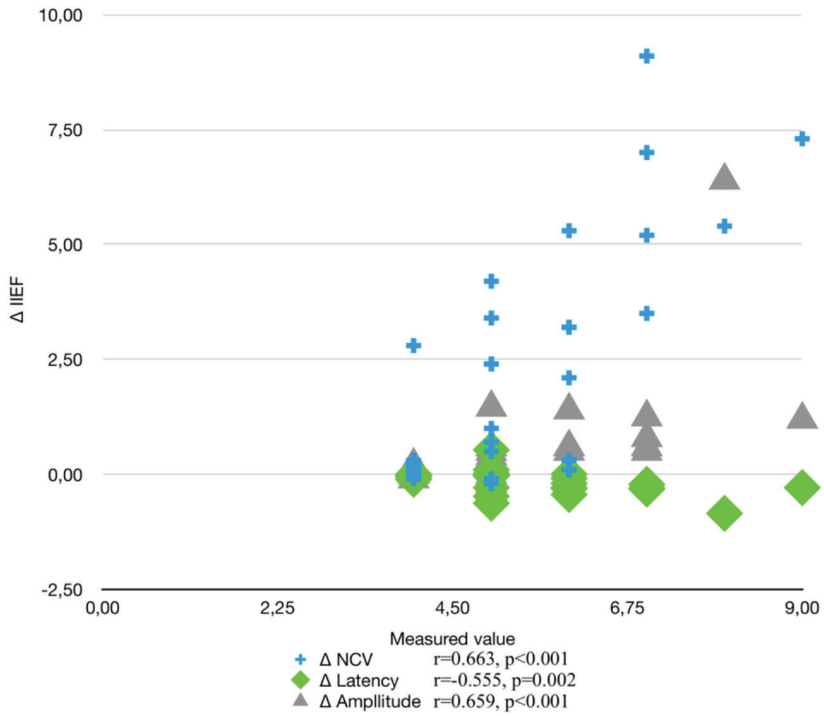

Figure 1. Graph showing the correlation between changes in IIEF-5 score and penile sensorial EMG findings

IIEF: International Index of Erectile Function, EMG: Electromyography, NCV: Nerve conduction velocity

Discussion

Currently, PDE-5 inhibitors are used as first-line therapy in patients presenting with ED. Our literature search did not find any studies reporting normal values of penile sensation during a normal erection. In our study, we performed sensorial measurements in patients with ED. Penile sensorial EMG can provide valuable additional information in the differential diagnosis of ED, particularly allowing the identification of different neurogenic lesion sites (16).

Başar et al. (17) injected intracavernosal papaverine in 15 patients with ED and compared the results of penile EMG and biopsy examinations. They demonstrated low -amplitude values in 5 patients with diabetes mellitus. Penile sensorial EMG is a less-invasive, valuable method for patients with ED, whereas penile biopsy examination did not reveal any specific results. Kayigil and Ergen (18) reported lower amplitude values in the EMG of the corpus cavernosum (CC-EMG) in 45%-65% of patients with ED.

In another study, Herbaut et al. (19) included 24 patients, 16 with normal findings on neurological examination, and 8 with diabetic neuropathy. They investigated the sensory conduction velocity in the dorsal penile nerve at rest and after injection of prostaglandin E1. They reported that the mean NCV values increased from 32.3+/-6.7 m/s to 47.4+/– 8.2 m/s after the injection of prostaglandin E1. They also reported an increase in NCV in patients with improvement in ED.

We also showed an increase in NCV after 12 weeks of daily treatment with tadalafil compared with pre-treatment values. The mean NCV in EMG was 35.5 m/s (33.3-41.2) before treatment, and 38.05 m/s (34.5-43.6) after treatment (p<0.001). The increase in NCV is the most important finding of penile sensorial EMG showing an increase in penile sensation. Thus, the increase in NCV has been interpreted as an improvement in penile sensation.

Itoga et al. (20) showed a reduction in proinflammatory cytokines in rats with a 12-week high-dose tadalafil therapy. Jamaluddin et al. (21) compared patients with vasculogenic ED and non-vasculogenic ED, both treated with tadalafil. They have demonstrated the therapeutic effects of tadalafil on non-vasculogenic ED. Chen et al. (22) showed that long-term tadalafil therapy in diabetic rats partially reduced penile oxidative stress lesions through a local antioxidative stress pathway. Accordingly, they reported that the initiation of long-term once-daily tadalafil therapy immediately after the diagnosis of DM may partially prevent the development of diabetic ED in rats.

In our study, we examined patients who received 12 weeks of tadalafil therapy regardless of the cause of ED and performed IIEF scoring and penile sensorial EMG examinations before and

after treatment. A significant correlation was observed between the IIEF score and penile sensorial EMG findings. A statistically significant improvement was observed in IIEF, NCV, and latency values in both age groups. ($p<0.001$, $p<0.001$, $p=0.010$ for ≤50 years of age; and $p<0.001$, $p=0.012$, $p=0.030$ for >50 years of age, respectively). There was a comparable improvement in the IIEF score in both age groups ($p=0.314$), whereas there was a statistically higher improvement in NCV and latency values in the group aged ≤50 years ($p<0.001$, $p=0.001$, respectively). A significant correlation was observed between the IIEF score and EMG findings. As age increases, the improvement in IIEF-5 ($r=-0.614$, $p<0.001$) and all penile sensorial EMG findings decrease (for Δ NCV, Δ Latency, Δ Amplitude, $r=-0.746$ $p<0.001$, $r=0.637$ $p<0.001$, $r=-0.755$ $p<0.001$, respectively). There was a significant correlation between IIEF and NCV ($r=0.663$, $p<0.001$) and Amplitude ($r=0.659$, $p<0.001$).

Study Limitations

Our study has some limitations, including the absence of data on normal values in penile sensorial EMG in individuals with normal erectile function. The literature search did not show any studies reporting normal values on penile sensorial EMG in a healthy male. Additionally, another limitation is the absence of any data on the effects of socioeconomic status on penile sensation in our study.

Conclusion

We demonstrated a direct correlation between improvements in IIEF-5 scores and NCV values with the use of daily tadalafil and showed that age is a factor affecting the improvement in penile sensorial EMG findings. We interpreted that tadalafil exerts its effects on erectile sensation by preventing the development of apoptosis in corporal sinusoids, preserving the proportion of smooth muscles and reducing pro-inflammatory cytokines.

Ethics

Ethics Committee Approval: Ethics Committee approval for this study was obtained from the Ethics Committee of Health Sciences University, Antalya Training and Research Hospital (2020-352).

Informed Consent: A signed consent form was obtained from all patients who volunteered to participate in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., E.İ., M.S., Concept: S.T., E.İ., M.S., Design: S.T., E.İ., M.S., Data Collection or Processing: S.T., E.İ., A.E., M.S., Analysis or Interpretation: S.T., E.İ., A.E., M.S., Literature Search: S.T., M.S., Writing: S.T., E.İ., A.E., M.S.

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