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ORIGINAL PAPER

Effects of long term sildenafil on the acute phase of Peyronie's disease in a combination treatment

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Summary *Objectives: The aim of this study was to investigate the impact of the addition of 50 mg daily sildenafil to pentoxifylline-colchicine combination therapy on the Peyronie's plaque features in patients with the acute phase of Peyronie's disease (PD).*
Methods: In this retrospective and non-randomized clinical study, patients were divided into 2 groups as group 1; (n = 107) who received colchicine and pentoxyfillin plus 50 mg daily oral sildenafil, and as group 2; (n = 79) who received only colchicine and pentoxyfillin. Patients were compared in terms of degree of curvature, pain in erection and erectile function at the baseline and at 6-month follow up. Pain in erection and erectile function were evaluated by visual Analogue Scale (EF-VAS), and the shortened version of the International Index of Erectile Function (IIEF-5). Improvement in the degree of curvature and change in EF-VAS scores were primary endpoints of the study. Change in IIEF-5 score was the secondary endpoint of the study.
Results: The two groups were statistically similar in terms of demographics and baseline features of PD. A statistically significant reduction in degree of curvature and EF-VAS scores was shown in group 1 compared to group 2.There was also a significantly higher IIEF-5 score in group 1 compared to group 2. No significant side effects were detected in both groups during treatment period.
Conclusions: Adding sildenafil to pentoxifylline-colchicine combination treatment seems to improve PD related symptoms in the acute phase PD. PDE5i may contribute to relieve the Peyronie's symptoms in ED patients through their antifibrotic effects.

KEY WORDS: *Peyronie; Oral treatment; Fibrosis; Antifibrotic treatment.*

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INTRODUCTION

Peyronie's disease (PD) is a fibrotic disorder of tunica albuginea with the formation of penile plaque. PD is a relatively common disorder, with an estimated prevalence of 1.5% in men between 30 and 40 years old and as high as 6.5% in older men (1). PD is characterized by progressive deformity and unstable plaque with painful erection in the acute phase;stabilization of the penile plaque and penile curvature are the major findings of the chronic phase which may require at least 6 months and up to 18 months (2-3). The exact etiology of plaque formation remains unclear. The most recognized theory is abnormal wound healing and aberrant fibrosis following minor trauma to the erected penis (4). The association between PD and Dupuytren contraction is a strong proponent of the fibrotic disease theory (5). Although various types of drugs have been used to date in the acute phase of PD, there is currently no satisfactory and approved oral drug therapy. Several experimental models in human cell cultures and rat models have provided new insights into the pathophysiology leading to the investigation of alternative approaches, including the phosphodiesterase type 5 inhibitors (PDE5i) as an anti-fibrotic modality (6-7). PD is associated with erectile dysfunction (ED) in a percentage of patients ranging from 40 % up to 70% (3, 8). Proven anti-fibrotic effect of PDE5i in the experimental studies and high coexistence rate of ED with PD patients suggests that PDE5i may contribute to the treatment of PD. However, very limited clinical studies were reported about this subject in the literature.
We investigated whether the addition of PDE-5i to combination therapy with colchicine and pentoxifylline (PTX) has any benefit on PD-related symptoms in patients with the acute phase of PD and ED.
Material and Methods: This study was conducted according to the ethical standard laid down by the 1964 declaration of Helsinki and its later amendments. Medical and sexual history, physical examination, records of penile color Doppler ultrasonography were retrospectively evaluated. Patients with PD symptoms for no longer than 12 months and accompanied by ED were included into the study. As per our protocol, patients who were receiving any treatment for PD or ED, as well as those with psychosomatic ED, hypertension, coronary artery disease, diabetes mellitus, hormonal disorders, receiving long-term medication for any disease, alcoholism or smoke abuse were excluded. To rule out organic sexual dysfunctions and other underlying diseases, serum fasting blood glucose level, sex hormones and prolactin levels were also evaluated. In this retrospective and non-randomized clinical study, 6-year medical records of 636 patients who were treated for the acute phase of PD in our institute were revaluated. The review also elucidated that 186 of these patients were included into the study. Patients were divided into two groups as group 1, who received PTX (400 mg, twice daily)-colchicine (0.5 mg, plus oral daily 50 mg sildenafil (n=107) and as group 2 received PTX

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(400 mg, twice daily)-colchicine (0.5 mg, twice daily) (n=79) and who were reluctant to use of sildenafil or unable to purchase sildenafil due to financial reasons. Patients with plaque calcification detected on penile ultrasonography were also excluded from the study. Plaque calcification has been identified as a sign of chronic phase and potential poor predictor of response to treatment (9). Disease duration, erectile pain, erectile function, and penile curvature were assessed at the baseline assessment. Penile curvature was measured according to the Kelami's criteria with a goniometer by the same operator following artificial erection stimulated by intracavernosal vasoactive agent. The severity of erectile pain was assessed by erectile function visual Analogue Scale (EF-VAS) score on a scale of 0-10, with 0 being no pain and 10 being severe pain. Erectile function was evaluated through the shortened version of the International Index of Erectile Function (IIEF-5) questionnaire. Each question is scored on a scale of 1 to 5 and 5 is indicating best function. The collected database of baseline and outcomes at sixth month of treatment in both groups were compared in terms of penile curvature, EF-VAS, and IIEF-5 scores. The primary endpoints of the study were the improvement in curvature and change in EF-VAS scores. Change in IIEF-5 score was the secondary endpoint of the study.

Statistical analysis

Mean, standard deviation, median lowest, median highest, frequency and ratio values were used in descriptive statistics of the data. The distribution of the variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney test was used to analyze quantitative independent data. Chi-square test was used for the analysis of qualitative independent data and Fisher test was used when the chi-square test conditions were not met. SPSS 22.0 program was used in the analysis. P value less than 0.05 was considered as statistically significant.

Results

Our retrospective review revealed that 636 patients with acute phase of PD were treated at our center during the study period. As per our protocol, 186 of 636 patients were enrolled in our study. The baseline characteristics of these patients are displayed in Table 1. Mean age was 56.1± 10.2 in group 1 and 53.54 ± 13.4 in group 2. There was no statistical difference between the groups in terms of demographics and PD characteristics at the baseline period. The mean duration of PD symptoms was 9.2 ± 2.1 months in group 1 and 8.9 ± 2.0 month in group 2 (no statistically significant difference between the groups). Change in mean degree of curvature angle was 11.02 ± 2.3° and 6.6 ± 1.7° group 1 and group 2, respectively. Although a significant difference in mean degree of curvature was shown in group 1 at the sixth month of the treatment compared to baseline, no significant change in mean degree of curvature was revealed in group 2 after the treatment period. EF-VAS showed a significant reduction in both groups, with a statistically higher reduction in group 1 patients compared to group 2 patients (Table 2). At sixth month treatment follow up, 68 of 107 patients (64%) in group 1 stated completely relief in pain during erection, while completely relief in pain was described by 37 of 79 patients (47%) in group 2. Mean IIEF-5 scores increased from 12.78 ± 6.46 to 17.89 ± 82 in group 1 and from 11.86 ± 6.21 to 13.02 ± 6.78 in group 2 at the postoperative period. Compared with the baseline values, the mean IIEF-5 scores in group 1 were significantly different at sixth month treatment follow up, while no significant changes were found in group 2 (Table 2). No clinically significant side effects were observed in any patients in both groups.

Discussion

Our study investigated the addition of PDE5i to conventional combined oral therapy in acute-phase PD and found that adding a PDE5i to the conventional treatment of PD patients may be worthwhile, in the improvement of degree of curvature and erectile pain. The acute phase is characterized by painful erections, soft plaques, while the chronic phase is characterized by fibrotic/calcified plaque and stable disease. Although spontaneous remission is reported in 3-13% of PD cases, the disease stabilizes or worsens in majority of the cases (10). To date, various oral medications have been used in the acute phase, including potassium aminobenzoate, colchicine, PTX, vitamin E, tamoxifen, orgotein, and carnitine acetyl ester

Table 1.
Mean baseline clinical characteristics of the patients.

	Group 1 (n = 107)	Group 2 (n = 79)	p
Age	56.1 ± 10.2	53.54 ± 13.4	0.456
Duration of symptoms (months)	9.2 ± 2.1	8.9 ± 2.0	0.836
Erectile Function Visual Analog Scale (EF-VAS) Score	6.89 ± 3.02	6.14 ± 2.78	0.642
Degree of curvature (°)	35.1 ± 16.3	36.6 ± 17.8	0.696
IIEF-5 score	13.78 ± 6.46	14.10 ± 6.77	0.976

Table 2.
Comparison of the groups at pre-treatment and post-treatment evaluation regarding Peyronie plaque characteristics and IIEF-5 questionnaire.

	Group 1 (n = 107)			Group 2 (n = 79)			Post-treatment comparison between the group 1 and group 2
	Pre-treatment	Post-treatment	p	Pre-treatment	Post-treatment	p	p
Degree of curvature (°)	35.1 ± 16.3	24.08 ± 11.2	0.045	36.6 ± 17.8	30.0 ± 14.3	0.067	0.022
Erectile Function Visual Analog Scale (EF-VAS) score	6.89 ± 3.02	3.89 ± 1.06	0.024	6.14 ± 2.78	4.7 ± 1.78	0.039	0.038
IIEF-5 score	12.78 ± 6.46	17.89 ± 82	0.021	11.86 ± 6.34	13.02 ± 6.78	0.123	0.006

(11). The clinical benefits of oral agents such as potassium aminobenzoate, PTX, colchicine, and coenzyme Q10 have been reported in different studies and are considered as a part of single or multimodal therapy for clinical use, but no single oral pharmacotherapy has been approved for treatment by *American Urological Association* (AUA) or *European Urological Association* (EAU) (12, 13). PTX-Colchicine combination is a preferred treatment alternative for PD patients in our clinic, which is associated with low side effect, low price, and proven success rates from previous studies. 10 PTX is an oral drug that works through mechanism that increase collagen metabolism, downregulate TGF-beta, and reduce fibrogenesis and has been used clinically in a variety of inflammatory and fibrotic conditions, such as radiation fibrosis, radiation proctitis, cystic fibrosis, radiation pneumonitis (14, 15). Significant improvements in degree of curvature, plaque volume, pain intensity, and penile rigidity after PTX treatment support the effectiveness of the treatment in PD patients (16, 17). Colchicine, a commonly used oral therapy, can significantly improve pain relief and penile curvature as monotherapy or in combination therapy (18). Colchicine binds to tubulin, blocks mitosis, reduces inflammation and procollagen formation, and increases collagenase production. Colchicine therapy appears to have conflicting results, and most studies show colchicine success in 30% to 50% of PD patients (18-19). Although various oral treatments are effective in PD patients, the lack of consensus on oral treatment increases the trend towards alternative treatments. We assessed the effect of supplementation with 50 mg of sildenafil on the conventional therapy of PD. The use of PDE5i in PD patients is supported by the fact that almost all PD patients suffer from ED and the proven effects of PDE5i on both pathologies. Several *in vitro* studies have shown that PDE5i has a potential anti-fibrotic effect against Peyronie's-like plaque (6-20). NO and cyclic guanosine 3',5'-monophosphate (cGMP) have anti-fibrotic actions with remarkable effects on collagen synthesis and myofibroblast differentiation. PDE-5i shows anti-fibrotic effects by reducing collagen deposits and oxidative stress, inhibiting myofibroblast proliferation and profibrotic factor secretion (3). Transforming growth factor β1 (TGF-β1) is a key profibrotic factor, found in many tissues and demonstrated in human PD plaques, that was also shown at high levels in the serum of PD patients (21). Following inhibition of PDE-5, elevated levels of cGMP and cAMP activate protein kinase G, which play important role in the apoptosis and reduced collagen synthesis. The mentioned anti-fibrotic effects are also mediated by guanylate cyclase inducers by stimulating protein kinase G and inhibiting fibrotic mediators such as angiotensin 2 or activating TGF-β and Rho activation (22, 23). An experimental study showed that sildenafil and oral PTX, a major PDE4 inhibitor that increases cAMP synthesis, inhibited the development of PD-like plaques (24).

Previous studies have shown a strong relationship between ED and PD, ranging from 20% to 70% (3, 8, 25) *Çakan et al.* indicated that one of the most common (68.5%) presenting symptom in PD is ED (26). ED may be the result of PD, or the two diseases may share common pathophysiological features. The possible mechanisms of development ED in PD include avoiding coitus due to performance anxiety, penile pain, difficulty in penetration and vascular insufficiency. Although there are many well-designed experimental studies and animal models regarding the anti-fibrotic effects of PDE5i, clinical trials investigating the effects PDE5i as monotherapy or in a combination treatment are limited. In a retrospective study of patients with isolated septal scarring and no evidence of penile deformity, septal scarring was significantly regressed in the tadalafil group compared with control group (27). *Ozturk et al.* investigated the effect of daily 50 mg of sildenafil on Peyronie's plaque and observed a statistically significant reduction in pain, whereas there was no significant difference in penile curvature between the two groups (28). Subjective and objective improvements in the characteristics of PD receiving daily doses of tadalafil were also reported by *Vernet et al.* (20) It was shown that the addition of 25 mg sildenafil to collagenase histolyticum (CCH) was superior to CCH monotherapy in improving penile curvature (10). In contrast, *Palmieri et al.* reported similar outcomes in tadafil-ESWT group compared to ESWT group (29).

Our study showed a significant improvement in degree of curvature and significant reduction in EF-VAS score in the sildenafil received group, compared to the conventional treatment group. Changes in degree of curvature and pain status were considered as the primary endpoints of the study. As expected, an improvement in the IIEF-5 score, a secondary endpoint of the study, was found to be more pronounced in the sildenafil-treated group. At this point, we did not evaluate the change in plaque size as a criterion for treatment success. Some investigators have suggested that the evaluation of plaque size using any type of imaging is unnecessary, as these measurements are often inaccurate and changes in plaque size after treatment are not associated with changes in overall deformity and do not directly indicate treatment success (30). Treatment of PD mainly depends on the severity of curvature and the degree of ED (12, 13). In addition Peyronie's plaque is not well formed in acute phase of the disease and possible spontaneous remission in plaque size can be expected in the acute phase.

Our study has some limitations which need to be considered while evaluating its findings. First, it is a retrospective, non-randomized study that can be affected by all potential weaknesses stemming from its retrospective design and six months of follow-up period of to evaluate the treatment outcomes is relatively short for this chronic disease.

Conclusions

To our knowledge, this is the first clinical study in the relevant literature investigating the effect of PDE5i in an oral combination therapy in PD patients. We showed that adding daily sildenafil 50 mg to colchicine and PTX combination treatment improves the PD's related symptoms of patients in the acute phase of PD. Considering the proven antifibrotic efficacy of PDE5i, they may contribute to relieving Peyronie's symptoms in patients with ED. Further multicenter prospective studies with larger number of cases are needed to obtain more precise results.

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