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Original Article

Evaluating the efficacy of intraplaque injection of dexamethasone with oral tadalafil in the chordee patients with Peyronie disease

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Abstract: Background: Some studies demonstrated the effect of the combination of modalities in Peyronie's disease (PD) therapy; however, there is no comprehensive study for evaluation of dexamethasone and phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil in the treatment of PD, so the study aimed to evaluate the efficacy of intraplaque injection of dexamethasone with oral tadalafil in the patients with PD. Materials and methods: This double-blinded randomized, controlled trial was conducted on the patients with PD referred to Alzahra and Khorshid hospitals, Isfahan, Iran. Then the patients were randomly divided into two groups as intervention and control groups. In the intervention group, tadalafil (5 mg PO) was administered once daily for 12 weeks and dexamethasone (8 mg) was injected once a week for 12 weeks. In the control group, the verapamil (5 mg: 2 cc) was injected once a week for 12 weeks. Before and after 12 weeks, an ultrasound was performed to assess the size, number and location of the plaque. The degree of penile curvature from the midline, dorsal and lateral curvature was also determined. Results: The means of penis curvature in the intervention and control groups before therapy were 34.09±7.05˚ and 31.09±7.06˚, respectively (*P*=0.097) and also after therapy were 27.3±7.79˚ and 24.6±6.64˚, respectively (P=0.13). The means of plaque count in the intervention and control groups before treatment were 2.0±1.03 and 1.96±1.06, respectively (P=0.9) and after treatment were 1.22±0.71 and 1.40±0.79, respectively (P=0.34). The means of plaque size in the intervention and control groups were 12.31±4.9 cm and 12.45±4.12 cm, respectively (P=0.9) and after intervention 7.8±3.08 and 9.03±3.46 cm, respectively (P=0.15). Conclusion: According to these findings, there was no significant difference between intervention and control groups regarding the degree of penis curvature, and the count and size of the plaque. Therefore, it seems that tadalafil therapy with dexamethasone did not improve PD compared to verapamil.

Keywords: Dexamethasone, Peyronie's disease, tadalafil

Introduction

Peyronie's disease is a noncancerous condition resulting from fibrous scar tissue on the penis and causes curved and painful erections [1-4]. The etiology of PD is multifactorial such as genetic, trauma, and tissue ischemia [5]. The incidence of PD is up to 7% among the general populations and up to 8% among men with erectile dysfunction (ED) [6]. This incidence may be higher than the reported rate, because men may not refer to the physicians due to embarrassment or misbelieving that the disorder is not curable.

The acute phase of PD is characterized by progressive deformation of the erect penis and inflammation. The patients may experience penile pain and curvature deformity of the erect penis during the acute disease phase [7, 8]. But all patients don't experience pain or discomfort in the penis. This phase lasts approximately 6 to 16 months and the majority of men experience disease progression or plaque's stabilization [5, 7, 8]. The transition from acute to chronic phase is specified by the resolution of inflammation and pain. The plaque size and penis curvature are relatively stable with extensive fibrosis [5].

In the stable phase, the gold-standard treatment of PD is surgery. However, non-operative management is the only therapy option in the acute phase of the disease. In addition, oral or

topical treatment may not be efficacious when administered alone; however, some evidence has shown the use of them as part of the combination therapy regimen. Recently various medical therapies like potassium aminobenzoate, tamoxifen, and acetyl-L-carnitine, verapamil, vitamin E, and acetyl-L-carnitine have been used in the treatment of PD [10-12].

Moreover, phosphodiesterase type 5 (PDE5) inhibitors are considered as a potential treatment option for PD [5]. The four available oral PDE5 inhibitors are sildenafil, vardenafil, tadalafil, and avanafil. These inhibitors can inhibit tissue remodeling after acute injury by reducing oxidative stress, inflammation, and fibrosis [7]. The use of PDE5 inhibitors for prolonged periods induces an elevation of nitric oxide and cyclic guanosine monophosphate as antifibrotic agents to decrease collagen deposition, oxidative stress, profibrotic factor release and myofibroblast numbers [4]. These medicines are safe and effective and considered as first-line therapy for PD patients with ED [4].

Tadalafil is a long-acting PDE5 inhibitor in the treatment of chronic PD. Moreover, it is a safe and effective oral treatment for ED [10, 13]. Another study showed favorable safety and efficacy profile of tadalafil for the general ED population. Dell et al. also reported that tadalafil may be play the leading role in stabilizing plaque's fibrosis and penis curvature [5]. Abd et al. also treated PD with the combination of verapamil and dexamethasone and reported that these medicines are safe and reliable regarding painful erections. However, the efficacy of them regarding penile curvature and ED is limited [14]. Kumar et al. also demonstrated that the effect of combination therapy (tadalafil and pentoxifylline) improved erectile function in patients of ED [14]. Atti et al. also revealed improvement of erectile function in the group treated with verapamil plus tadalafil compared to verapamil group and tadalafil group [5, 15, 16].

Although some studies demonstrated the combination of treatment modalities in PD therapy; studies were conducted regarding the effect of dexamethasone and PDE5 inhibitors such as tadalafil in comparison to verapamil in PD therapy is limited [17], therefore this study aimed was to evaluate the efficacy of intraplaque injection of dexamethasone with oral tadalafil in patients with PD compared to verapamil.

Methods

Sample selection

This double-blinded randomized, controlled trial was conducted on chordee patients with PD referred to Alzahra and Khorshid hospitals affiliated with Isfahan University of Medical Sciences, Isfahan, Iran from June 2019 to March 2021. The protocol of study was approved by Ethical committee of Isfahan University of Medical sciences (IR.MUI.MED.REC.1399.827). Also the current study was registered in Iranian Registry of Clinical Trials (IRCT20200825048515N31, https://www.irct.ir/trial/55272). All patients have obtained written consent for participation into study. Inclusion criteria were included the age range between 18 and 65 years, penile curvature (degree) less than 45°, presence of plaque confirmed by ultrasound, and absence of disease in the active phase (at least one year of disease history).

Exclusion criteria were included history of cardiovascular events, hypertensive crisis and uncontrolled diabetes during study, history of neurological disorders, inability to have sexual intercourse, erectile dysfunction, penile fracture, arterial and venous insufficiency, absence of Peyronie plaques in ultrasound, arterial and venous insufficiency, continuous use of nitrate, cardiovascular events in the last 6 months and any factor that the patient needs to take anticoagulants except aspirin and nitrate.

The diagnosis of PD would be made based on touching plaque during the examination. The patients were then referred to a radiologist and color Doppler ultrasound was performed using a Toshiba Aplio Ultrasound System (Japan). Penile vascular flow, size, and location of plaques were determined in these patients. Papaverine injection was performed for all patients. After injecting papaverine, the degree of penile curvature from the midline, dorsal and lateral curvature was determined. The penile deviation was accurately measured in the erect position. For this purpose, the midpoint of the penis was placed in the root area and before the departure along the horizontal axis of the goniometer. The midpoint of the coronal area was placed at the location of the variable axis of the goniometer. Thus the angle between the two axes determined the degree of deviation of the penis.

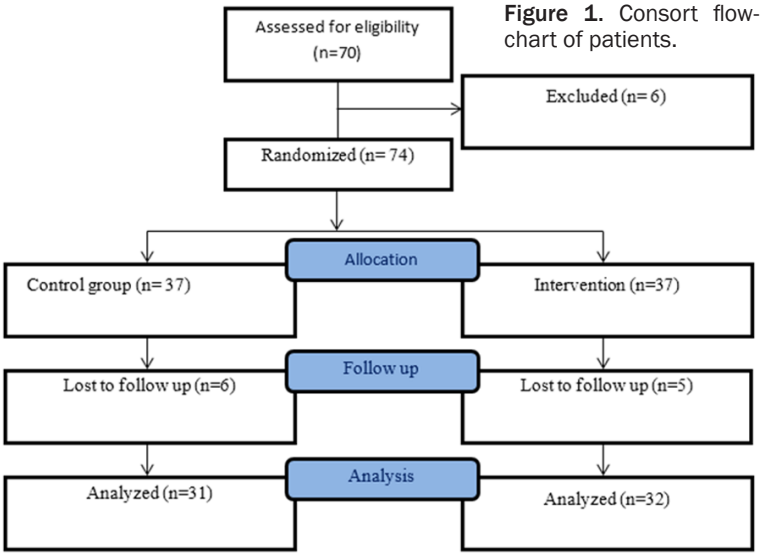

Figure 1. Consort flowchart of patients.

Table 1. The frequency of location of plaque

Location of plaque	Intervention	Control
Dorsolateral	5 (16.1)	3 (9.3)
Dorsal	14 (45.1)	14 (43.75)
Ventral	4 (12.90)	3 (9.37)
Lateral	8 (25.8)	12 (37.5)
Total	31 (100)	32 (100)

Patients treatment

Patients were randomly (using random allocation software) divided into two groups (intervention and control group). In the intervention group, tadalafil (5 mg PO) was administered once daily for 12 weeks and dexamethasone (8 mg) injected once a week for 12 weeks. In the control group, the patients were injected with verapamil (intraplaque) (5 mg) once a week for 12 weeks. All injections were done under sterile conditions. After 12 weeks, patients were examined again and an ultrasound was taken to assess the size, number and location of the plaque.

Statistical analysis

The sample size was calculated via the following formula.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2} \quad \text{(Formulation 1)}$$

N was the sample size and *Z* was a constant (set by convention according to the accepted α error) [1].

Data were entered to SPSS, version 24. The quantitative variables were shown as mean and the qualitative variables were shown as frequency (percentage). Independent t-test was used for comparison of age, degree of penis curvature, plaque count and plaque size between two groups and Chi Square (Fisher exact test) was used to compare of qualitative variables between groups. In addition, relationship of the degree of penis curvature, plaque count and plaque size before compared to after intervention was performed with paired sample t-test. Statistically, $P<0.05$ was assumed significant.

Results

The current study was conducted on 63 patients. **Figure 1** shows consort flowchart of patients. The mean age of patients in the intervention and the control group was 47.70± 10.33 and 49.65±10.03 years, respectively ($P=0.451$). Among 31 patients in the intervention group, 11 patients (35.4%) had diabetes and hypertension. Moreover, among 32 patients in the control group, 10 patients (31.2%) had diabetes and hypertension. In addition, 4 (12.90%) in the intervention group and 7 patients (21.87%) in the control groups underwent microfracture surgery. The most frequency of plaques was related to dorsal position. In addition, the lowest frequency was related to the ventral position (**Table 1**).

As demonstrated in **Table 2**, significant difference was not seen between intervention and control groups in terms of the degree of penis curvature, plaque count and plaque size before therapy ($P>0.05$). In addition, there was no remarkable difference between the intervention and the control groups in terms of the degree of penis curvature, plaque count and plaque size after therapy ($P>0.05$).

Moreover, a significant difference was not seen before intervention between intervention and the control groups regarding degree of penis curvature, plaque count, and plaque size (P> 0.05). However, a significant difference was

Table 2. The mean degree of penis curvature, plaque count and plaque size

Variables		Before	After	*P*-value**
Degree of penis curvature	Intervention	34.09±7.05°	27.3±7.79°	<0.001
	Control	31.09±7.06°	24.6±6.64°	<0.001
	P-value*	0.097	0.13	
Plaque count	Intervention	2.0±1.03	1.22±0.71	<0.001
	Control	1.96±1.06	1.40±0.79	<0.001
	P-value*	0.9	0.34	
Plaque size (cm)	Intervention	12.31±4.91	7.8±3.08	<0.001
	Control	12.45±4.12	9.03±3.46	<0.001
	P-value*	0.9	0.15	

*Independent T test, **Paired samples Test.

seen after intervention between intervention and control groups in terms of degree of penis curvature, plaque count, and plaque size (P< 0.01).

Discussion

Factors that are involved to choose the type of treatment of PD are included the magnitude of penile deformity and duration of disease [18]. Usually, a surgical approach is considered in patients with PD who do not answer to medical or conservative therapy for nearly 1 year [4]. Options for treatment include tamoxifen, pentoxyphyline, vitamin E, and anti-inflammatory reagents [5]. Tadalafil is also a unique phosphodiesterase type 5 inhibitor with a long period of responsiveness. This drug is effective and safe to improve erectile function in populations [13]. Tadalafil can improve erectile function through inhibiting the PDE5 isoenzyme, leading to blocking cGMP degradation. The PDE5 inhibitors act with NO and enhance the levels of cGMP [13, 19], which in the presence of sexual stimulation lead to the erection. The absence of sexual stimulation causes that NO is not released locally and the PDE5 inhibitors do not influence the penis [15, 20], Therefore for initiating the erectile mechanism in the presence of PDE5 inhibitors, sexual stimulation is needed [13].

In the current study, the degree of penis curvature, plaque count, and plaque size decreased under treatment of dexamethasone with oral tadalafil. Park et al., reported that tadalafil (5 mg once daily) could treat PD via reducing the degree of penile curvature, and penile plaque size [21]. Tadalafil may play the main role in stabilizing penis curvature and plaque fibrosis [5]. Palmieri et al. used 5 mg tadalafil and extracorporeal shockwave therapy to manage patients with PD and observed significant improvement in erectile function and quality of life of patients with ED and PD [18]. Porst et al. reported that tadalafil in low doses (2.5 and 5 mg) was effective and well-tolerated. Moreover, tadalafil can be administered due to longer half-time and its use is associated with the patient satisfaction [22].

In this study, there was not a significant difference between tadalafil and verapamil groups regarding the degree of penis curvature, plaque count, and plaque size. It indicated no significant difference between the two therapies regarding the degree of penis curvature, plaque count, and plaque size. There are very few studies in the literature regarding comparing the therapeutic efficacy of PDE5 inhibitors and verapamil in PD treatment. Det Il'Atti et al., treated PD patients with tadalafil and verapamil injection. In this regard, group A was treated with verapamil injection, group B with tadalafil (5 mg once a day), and group C with a combination of tadalafil and verapamil injection, and findings did not demonstrate a significant difference between 3 groups regarding curvature degree which was consistent with our study. No difference was also seen before and after treatment regarding mean plaque size in groups A and B; however, a significant decrease was evident in the third group. They believed that tadalafil may play a central role in stabilizing penis curvature and plaque fibrosis [5].

Kumar et al. assessed the effect of the combination therapy (tadalafil and pentoxifylline) in erectile dysfunction and observed that both

tadalafil and its combination with pentoxifylline improved erectile function in patients of ED [23]. Palmieri et al. reported no significant difference between patients receiving extracorporeal shock wave therapy (ESWT) alone and those receiving daily tadalafil with ESWT regarding curvature degree indicating no effect of tadalafil on curvature degree. Moreover, neither alone ESWT nor tadalafil with ESWT was able to improve plaque size [18]. They also reported that the number of patients with persistent ED in the combinational group was lower than the ESWT group. Therefore, it seems that a combination of tadalafil and ESWT may show the main strategy for conservative management of patients with PD who are complained of ED. In addition, the quality of life sore in patients receiving combination therapy was higher than only ESWT therapy which may be due to the effect on EF [4, 18]. According to these findings, the combination of tadalafil and ESWT was superior to ESWT in an international index of erectile function and quality of life scores [18]. Another study reported that the combination of PDE5 inhibitors with the modulator of selective estrogen receptors may be efficacious in the treatment of PD in the active phase [24]. Therefore, according to these findings, the effect of these therapies on PD disease was dependent on the combination of tadalafil therapy.

Conclusion

According to these findings, there was no significant difference between the intervention and control groups regarding the degree of penis curvature, and the count and size of the plaque. Therefore, it seems that tadalafil therapy with dexamethasone did not improve PD compared to verapamil.

Disclosure of conflict of interest

None.

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