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Effect of PDE5 Inhibitor in Nonsurgical Management of Peyronie's Disease: Preliminary Study

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= Abstract =

Purpose: This study was designed to evaluate the role of PDE5 inhibitors as combination therapy with conventional treatment of Peyronie's disease (PD).

Materials and Methods: From July 2007 to October 2010, 35 Patients were divided into two groups. Group I (N=14) received PDE5 inhibitors in addition to conventional treatment with tamoxifen and acetyl L-carnitine, while group II (N=21) received only conventional treatment. The follow-up duration was at least 12 weeks after the active therapy of PD. Outcomes were assessed by pain relief, successful attempts for sexual intercourse, resolution of the plaque and any occurring complications.

Results: In the efficacy of overall treatment of 35 patients, 94.3% patients experienced successful sexual intercourse, while 5.7% experienced pain on erection, and 25.7% showed a decrease in plaque size. The analysis of parameters before treatment showed no significant difference between groups in terms of successful attempt at sexual intercourse (p=0.583) and pain on erection (p=0.445). Furthermore, there was no difference between groups after treatment in terms of successful attempts at sexual intercourse (p=0.766), pain on erection (p=0.766) and change in plaque size (p=0.445). However, successful intercourse and pain relief after treatment showed significant change irrespective of groups ($p < 0.05$). While the addition of a PDE5 inhibitor did not show any significant improvement in clinical outcome measures, the satisfaction of patient was higher in patients who received combination treatment (p=0.042).

Conclusions: Although the effect of PDE5 inhibitor for pain relief, successful intercourse and resolution of plaque size was not significant, patients who received PDE5 inhibitors had a more satisfaction of treatment of PD. Further prospective studies on the effect of PDE5 inhibitor in PD will be needed.

Key Words: Peyronie's disease, Phosphodiesterase 5 inhibitor, Erectile dysfunction

Introduction

Peyronie's disease (PD) arises from the deposition of collagen and fibrin which creates a plaque in the tunica albuginea of the penis. It leads to curvature of the erect penis and often to pain or erectile dysfunction.[1,2] PD may be present in up to 10% of all men, but primarily affects those in sixties and seventies.[1,3] PD is thought that often the plaque develops as the result of an abnormal wound healing process after trauma to the tunica albuginea, but the current pharmacological treatments of the PD are unsuccessful, because the cause of the PD plaque is unknown and the molecular pathology is poorly understood.[3,4] No sat-

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isfactory medical treatments for PD are currently available, however experimental models have provided new insights into its pathophysiology and etiology, which have facilitated the investigation of alternative therapeutic approaches, including long-term continuous administration of phosphodiesterase type 5 inhibitors as an antifibrotic modality.[5]

Long-term continuous administration of phosphodiesterase-5 (PDE5) inhibitors increase cGMP levels in target tissues, which should prevent development of PD-like plaques in the rat model.[4] The anti-fibrotic role of PDE5 inhibitors is also indicated by the report that treatment with sildenafil every other night for 6 months after radical retropubic prostatectomy seems to prevent the fibrosis of the corpora cavernosa that usually follows this surgery.[6] This preliminary study was designed to evaluate the role of long-term continuous PDE5 inhibitors as an adjunctive combination therapy with conventional treatment of Peyronie's disease.

Materials and Methods

From July 2007 to October 2010, 35 patients with Peyronie's disease were enrolled for this study. Patients were divided into two groups, with group I (N=14) receiving long-term continuous PDE5 inhibitors (Tadalafil 5 mg once daily) in addition to conventional treatment with tamoxifen 20 mg and acetyl L-carnitine 330 mg twice a day, while group II (control; N=21) received tamoxifen and acetyl L-carnitine. Treatment duration was at least 6 months and the follow-up duration was at least 12 weeks after the active therapy of PD. Penile sonography was performed to measure size of plaque and penile curvature angle at penile erection was measured by a protractor. The subjective relief of pain and successful attempts for sexual intercourse were assessed by a global assessment question and the resolution of plaque was measured by a decreased longitudinal length of plaque. Outcomes were assessed by relief of pain, successful attempts for sexual intercourse, resolution of the plaque and any occurring complications. These measures were compared with the conditions of pretreatment for each group. SPSS 12.0 for windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and Pearson's chi-square test was used for analysis of the characteristics. Differences were considered significant at $p < 0.05$.

Results

The mean age of the all patients was 57.5±9.1 years. The mean age of group I was 54.9±10.2 yeras and group II was 59.2±8.2 years (p=0.194). In the efficacy of overall treatment of 35 patients, 94.3% patients (33/35) experienced successful sexual intercourse, (p=0.137) 5.7% (2/35) experienced pain on erection, (p=0.011) and 25.7% (9/35) showed a decrease in plaque size (p=0.466) (Table 1).

Analysis of pretreatment parameters showed no significant difference between group I and II in terms of successful intercourse attempts and pain on erection. 11 patients of group I and 19 of group II experienced a successful sexual intercourse (11/14 vs. 19/21, p=0.583), 5 patients of group I and 5 of group II experienced a pain on erection (5/14 vs. 5/21, p=0.445). Furthermore, after treatment of PD, there was no significant difference between group I and II in terms of successful sexual intercourse, pain on erection and resolution of plaque. 13 patients of group I and 20 of group II experienced a successful sexual intercourse (13/14 vs. 20/21, p=0.766), 1 patient of group I and 1 of group II experienced a pain on erection (1/14 vs. 1/21, p=0.766) and 3 patients of group I and 7 of group II experienced a resolution of plaque (3/14 vs. 7/21, p=0.445) (Table 2).

While the addition of a PDE5 inhibitor did not show any significant improvement in clinical outcome measures, satisfaction rate was higher in patients who re-

Table 1. Efficacy of ovearall treatment after treatment in total 35 patients

Variables	Before treatment	After treatment	p-value
Ability of sexual intercourse	85.7% (30/35)	94.3% (33/35)	0.138
Pain on erection	28.6% (10/35)	5.7% (2/35)	0.11
Plaque size (cm)	2.4±1.5	2.1±1.6	0.466

Table 2. Analysis of group I and II

Variables	Group I*	Group II†	Group III‡
Age	54.9±10.2	59.2±8.2	0.194
Number of patients	14	21	
Sexual intercourse (+) before treatment	78.6% (11/14)	90.4% (19/21)	0.583
Pain (+) before treatment	35.7% (5/14)	23.8% (5/21)	0.445
Sexual intercourse (+) after treatment	92.9% (13/14)	95.2% (20/21)	0.766
Pain (+) after treatment	7.1% (1/14)	4.8% (1/21)	0.766
Resolution of plaque after treatment	21.4% (3/14)	33.3% (7/21)	0.445
Satisfaction of patients	85.7% (12/14)	52.4% (11/21)	0.042

*Group I patients recieved long-term continuous PDE5 inhibitors (Tadalafil 5 mg once daily) in addition toconventional treatment with tamoxifen 20 mg and acetyl L-carnitine 330 mg twice a day. †Group II patients recived conventional treatment with tamoxifen 20 mg and acetyl L-carnitine 330 mg twicea day. ‡p-value $<$ 0.05 to be statistically significant.

ceived combination treatment (12/14 vs. 11/21, p= 0.042) (Table 2).

Discussion

Non-surgical treatments of Peyronie's disease, including vitamine E (Tocopherol), potassium aminobenzoate (Potaba), colchicines, tamoxifen and acetyl-L-carnitine have been used for a long time.[7]

Vitamine E is a commonly used oral drug in Peyronie's disease because of its mild side-effect and low cost. It has natural antioxidant properties and in 1990, Gelbard et al. reported the effects of vitamine E comparing to natural progression of Peyronie's disease. They noted no significant difference between the two groups in pains, plaque, ability for intercourse and over-all perception of disease progression, but at this time vitamine E continues to be primary oral drug despite the lack of benifis.[8]

Potassium aminobenzoate (Potaba) is classified as 'possibly effective' by the Food and Drug Administration for treatment of Peyronie's disease, scleroderma, dermatomyositis in 1959. It has been suggested that Potaba increases utilization of oxygen by tissues and increases activity of monoamine oxidase, which decreases concentration of serotonin, a substance thought to contribute to fibrogenesis.[9] Carson reported a retrospective review of 32 patients treated for at least 3 months with 12 g of Potaba powder daily and followed for 8～24 months.[10] Subjective symptoms analysis demonstrated improvement in penile discomfort in eight of 18 (44%), decreased plaque size in 18 of 32 (56%), and improvement in penile angulation in 18 of 31 (58%) patients. Complete resolution of angulation was reported in eight of 31 (26%) patients. Weidner et al. reported 75 men who underwent a randomized prospective double-blind trial of Potaba 3 g q.i.d. for 1 year vs. an oral placebo.[11] In this study, no significant difference was seen with respect to improvement of curvature or pain between the two groups. The only parameter showing a statistically significant improvement was decrease in plaque size for the Potaba group, but a reduction in plaque size does not correlate with improvement of the most important parameter of curvature.

Oral colchicine therapy is known to induce collagenase activity and decrease collagen synthesis.[12,13] Akkus et al[14] reported that penile curvature was slightly improved in two (11%) and markedly improved in five (26%) of the 19 cases. Seven of nine patients with painful erections reported significant relief. Palpable plaque disappeared in two and decreased in 10 patients. The investigators also performed ultrasound on five patients and described a decrease of approximately 50% in plaque size. However, the authors suggested that a double-blind study is needed to better evaluate the usefulness of this medication, and the primary reported side effect of colchicine is gastrointestinal upset with diarrhea.

Ralph et al[15] reported their experience with oral tamoxifen in 1992. Tamoxifen inhibits release of transforming growth factor-beta (TGF-b) from fibroblasts.[16]

TGF-b has been shown to play a central role in regulating immune response, inflammation, and tissue repair by activating macrophages and T lymphocytes. Tamoxifen results in a reduced inflammatory response and diminished angiogenesis and fibrogenesis.[17] Their regimen included 20 mg of tamoxifen twice a day for 3 months. A total of 80% of patients reported an improvement in pain, 35% showed improvement in deformity, and 34% experienced decreased plaque.[15] However, the most recently published report of a controlled trial of oral tamoxifen (20 mg b.i.d.) vs placebo demonstrated no therapeutic advantage to tamoxifen and several men reported scalp hair loss.[18]

The pathophysiology for the use of acetyl-L-carnitine in patients with Peyronie's disease remains unclear, but it was suggested that this agent restores cells when damaged by inflammation or ischemia and this may be due to inhibition of the toxic coenzyme. Biagiltti et al. reported that 48 men were randomized to receive oral acetyl-l-carnitine vs tamoxifen and overall, the men receiving carnitine did better with respect to curvature than those who took tamoxifen with significantly fewer side effects.[19] They suggested that further evaluation of carnitine in combination with other therapy will be needed.

In addition to these conventional oral therapies of Peyronie's disease, a few studies reported that long-term continuous oral administration of PDE5 inhibitor prevents the development of fibrotic plaque and can reduce the size of plaque.[4,20,21] The mechanism of potential positive therapeutic effect of PDE5 inhibitor in Peyronie's disease suggested that cGMP have anti-fibrotic actions and long-term continuous administration of PDE5 inhibitor, which should maintain or increase cGMP levels in the target tissues, prevents the development of PD-like plaques in the rat model of Peyronie's disease.[20] However, no randomized controlled trials have investigated PDE5 inhibitor use in Peyronie's disease and an article related to the use of PDE5 inhibitors in patients with Peyronie's disease focused on their standard on-demand application for treating erectile dysfunction, and not PD itself.[22] However, our study failed to show any significant difference in treatment outcomes between the two groups. This may be due to the lack of sufficient patient enrollment to present significant treatment effects between patient groups with overall similar regimens. Furthermore, while comparison failed to yield statistical significance, pretreatment sexual intercourse numbers were on average lower in group I, but roughly similar at post treatment assessment. This may have weighed on patient satisfaction of treatment, leading to paradoxical results where no objective difference was shown between objective treatment outcomes, yet subjective treatment outcomes showed significance. As this is a preliminary study, further investigation on a larger scale may present sufficient difference in effect.

Therefore further study of combination treatments with PDE5 inhibitors may help define its future role in patients with PD.

Conclusions

The theraphy of Tamoxifen and Acetyl-L-carnitine as phamacological treatment for Peyronie's disease is effective for pain relief. Although the effect of PDE5 inhibitor for pain relief, successful intercourse and resolution of plaque size was not better than conventional treatment, patients who received PDE5 inhibitors with conventional treatment had a more satisfaction of treatment of PD. Further prospective randomized controlled studies on the effect of PDE5 inhibitor in PD treatment will be needed for the future role of PDE5 inhibitors in patients with PD.

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EDITORIAL COMMENT

The paper by Ham et al highlights the fact that although the effect of PDE5i for pain relief, successful intercourse and resolution of plaque size was not significant, patients who received PDE5i had a more satisfaction of treatment of PD. This study is based on the idea that long term continuous oral administration of phosphodiesterase-5 (PDE5) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and can ameliorate a more advanced plaque.[1-4] Because most of the patients with Peyronie's disease have erectile dysfunction,[4] PDE5 inhibitors can be a good treatment option in terms of preventing fibrous plaque progression and improvement of erectile function. In this meaning, this study is invaluable pioneer study in spite of several limitations, such as small group of patients, no randomized, placebo-controlled study.

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