

A double-blind placebo-controlled study of the efficacy and safety of pentoxifylline in early chronic Peyronie's disease

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OBJECTIVE

To analyse the safety and efficacy of pentoxifylline sustained-release (PTX-SR) treatment in patients with early chronic Peyronie's disease (PD).

PATIENTS AND METHODS

In all, 228 patients with a mean (SD) age of 51 (9) years who had early chronic PD were randomized to receive 400 mg PTX-SR (Apo-Pentoxifylline, Apotex Inc., Toronto, Canada) twice daily (group 1, 114) or similar regimen of placebo (group 2, 114) for 6 months. A medical history was taken and the men had a complete physical examination. The following variables were assessed before and after therapy: penile curvature and penile artery spectral traces (end-diastolic velocity,

EDV, peak systolic velocity, PSV, and resistivity index, RI, of the right and left cavernous arteries assessed with dynamic penile duplex ultrasonography), plaque characteristics (assessed by penile X-ray and penile ultrasonography), pain (assessed by visual analogue scale), erectile function (assessed by the International Index of Erectile Function, IIEF questionnaire), treatment satisfaction (assessed by Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire), and side-effects. Patient perception of penile curvature and plaque size, and mean weekly intercourse attempts were also assessed.

RESULTS

Overall, 36.9% of patients who received PTX-SR reported a positive response, vs only 4.5% in the placebo group. Of patients in PTX-SR group, 12 (11%) had disease progression, vs 46 (42%) in placebo group ($P = 0.01$). Improvement in penile curvature ($P = 0.01$,

and plaque volume ($P = 0.001$) was significantly greater in patients treated with PTX-SR than placebo. The increase in IIEF total score was significantly higher in the PTX-SR group ($P = 0.02$). Mean PSV changes after therapy compared to baseline were statistically significant between PTX-SR (right, +11.4%, left, +11.7%) and placebo-treated (+0.2% and -4.2%, respectively) patients (both $P = 0.04$).

CONCLUSIONS

PTX-SR was moderately effective in reducing penile curvature and plaque volume in patients with early chronic PD. Further studies with different treatment regimens are needed to better elucidate the beneficial effects of PTX-SR in PD.

KEYWORDS

pentoxifylline, Peyronie's disease, treatment, erectile dysfunction

INTRODUCTION

Peyronie's disease (PD) is a localized connective tissue disorder of the tunica albuginea of the penis and surrounding tissue which results in painful erection, penile curvature and erectile dysfunction (ED) [1]. The disorder affects 3.2–8.9% of men in their fifth or sixth decades of age [2]. It has been shown that, of affected men, 80% have ED on testing [3]. Although the exact cause of PD remains unknown, increased levels of TGF β 1 in plaques of patients with PD was reported [4]. While initial reports indicate a high spontaneous improvement rate of 50% [5],

the most current natural history studies suggest that no more than 5–13% of men will have spontaneous resolution of their disease [6,7]. In a retrospective study, Kadioglu *et al.* [6] reported a 30.2% progression rate in men who presented with the acute phase of PD, during an 8-month follow-up. The goal of medical treatment is to end the progression of PD and, if possible, to reverse the fibrotic process. The different phases of PD define the role of its medical and surgical therapy. There are three phases through which the disease processes, i.e. acute, early chronic and chronic [8]. The acute inflammatory or active phase usually lasts 6–18 months and is

characterized by permanent spontaneous pain which increases on erection or there is only pain during erection, and palpable and tender plaque, which is iso- or hypoechoic on dynamic Doppler ultrasonography (US). It is then followed by the early chronic phase characterized by pain during erection; penile curvature with no difficulty with vaginal penetration; palpable hyperechoic plaque(s) with no pain and calcification with a total area of <2 cm² limited to albuginea; and no arterial involvement and venous leakage on dynamic Doppler US. The last phase is the chronic or stable phase, characterized by pain during erection; penile curvature affecting

vaginal penetration and ED; palpable hyperechoic plaque(s) with no pain, with a total area of $>2 \text{ cm}^2$, and calcifications; arterial involvement, and venous leakage on dynamic Doppler US [8]. Oral pharmacotherapy should be considered as a treatment option for acute and early chronic phases. Many oral medicines, including vitamin E, potassium para-aminobenzoate (Potaba), tamoxifen [9], colchicines [10], propionyl-L-carnitine [11], and recently omega-3 [12], have been used, but there is no perfect oral medical treatment available. No medical treatment is currently available that can cure patients with PD [9]. As a result, new oral medical treatments for PD are needed.

Pentoxifylline (PTX), 3,7-dimethyl-1(5'-oxo-hexyl) xanthine, is a nonspecific phosphodiesterase inhibitor, with combined anti-inflammatory and antifibrogenic properties. It downregulates TGF β [13] and increases fibrinolytic activity [14]. An autoimmune cause has also been proposed in the pathogenesis of PD. PTX has been used successfully for the treatment of experimental autoimmune diseases [15]. Cytokines such as TNF, platelet-derived growth factor, and fibroblast growth factor, are known to have a role in fibrosis [16]. PTX down-regulates the release and the production of TNF, inhibits the action of platelet-activating factor on neutrophils, and suppresses the production of platelet-activating factor [17]. Given the favourable properties, and based of its safety profile, we sought to investigate in a randomized placebo-controlled study whether treatment with PTX could produce clinically benefit in patients with early chronic PD. To our knowledge this is the first large randomized clinical trial to examine the safety and efficacy of PTX-SR on early chronic PD.

PATIENTS AND METHODS

In all, 258 patients with early chronic PD were initially considered; the study was carried out from 1 October 2006 to 1 September 2008. Men aged 35–60 years were selected from a tertiary specialized sexual dysfunction clinic. Early chronic PD was defined as pain during erection, penile curvature not affecting vaginal penetration, palpable hyperechoic plaque(s) without pain and calcifications, with a total area of $<2 \text{ cm}^2$ which was limited to the albuginea [8]. The patients were initially

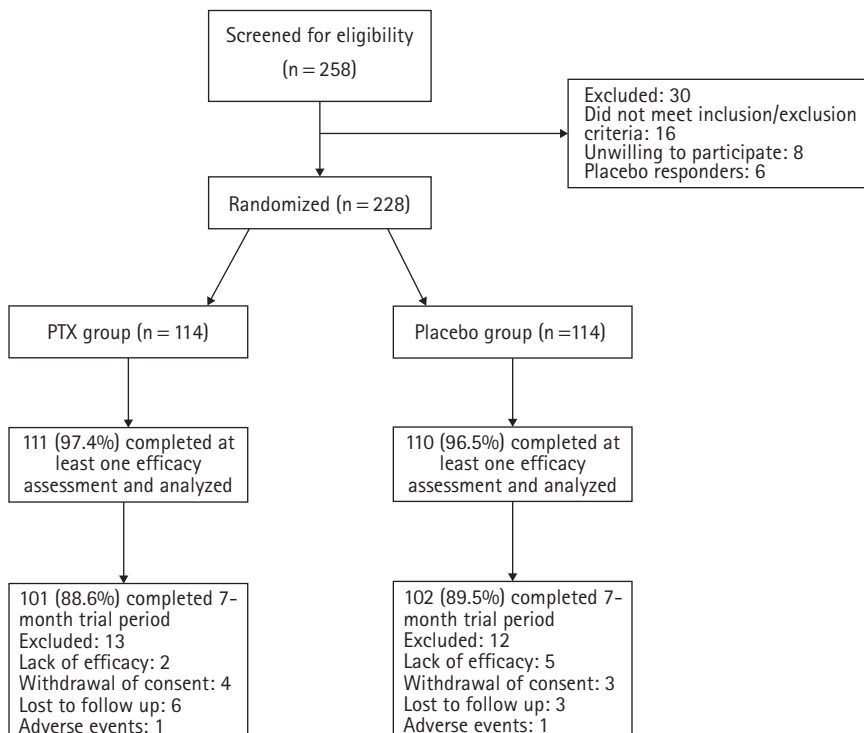
examined clinically, evaluated, and subsequently admitted for screening after giving informed consent. Eligible patients had evidence of disease progression despite previous medical treatments, had ED according to International Index of Erectile Function (IIEF) questionnaire, and were not on any medications for at least 12 weeks. The patients were free from other significant medical or surgical illnesses. Patients for the present study had been treated and had one or more previous treatments for PD that had failed, including oral therapy with Potaba (202, 78.3%), propionyl-L-carnitine (22, 8.5%), colchicine (76, 29.5%), tamoxifen (14, 5.4%) and various vitamins including vitamin E (182, 70.5%). The patients were fully informed of the purpose, procedures and hazards of the trial, and were given the opportunity to leave the trial at any time they desired. The study protocol was in accordance with the Declaration of Helsinki and approved by the Human Ethics Committee.

Inclusion criteria were meeting the criteria for early chronic PD, a case history of ≥ 12 months, previous treatment for PD, presence of ED as defined by an erectile function domain score of the IIEF of <26 [18], no history of penile surgery or pelvic trauma, and were seeking help for PD. Exclusion criteria were any medical treatment for sexual dysfunction (before or during the trial), recurrent PD, endocrinopathy, significant renal impairment (serum creatinine $>1.8 \text{ mg/dL}$), chronic liver disease, alcohol or tobacco use, aged >60 years, supplementation with vitamins or traditional herbs in the previous 3 months, and therapies interfering with PTX.

Each patient provided a complete medical and sexual history and had a physical examination and self-administration of the IIEF [19]. This questionnaire consists of 15 questions that specifically address all five aspects of male sexual function, including erectile function (questions 1–5 and 15, score range 1–30), intercourse satisfaction (questions 6–8, score range 0–15), orgasmic function (questions 9 and 10, score range 0–10), sexual desire (questions 11 and 12, score range 2–10), and overall satisfaction (questions 13 and 14, score range 2–10). Patients were asked to provide a pertinent medical history, including previous treatments; history of symptom duration and progression; history of penile trauma or surgery; status of penile rigidity and ability to engage in sexual intercourse; risk factors such as smoking, drinking, high

blood pressure, hyperlipidaemia, coronary artery disease and diabetes mellitus; and taking any medication. Any history of penile trauma was documented in all participants. The basic laboratory evaluation included a complete blood count and routine biochemistry analyses, kidney and liver function tests, electrolytes, sex hormones and prolactin, and serum lipid measurement. Objective information pertaining to the nature and magnitude of the patient's penile deviation was obtained by dynamic penile duplex US before and after an intracavernous injection with $20 \mu\text{g}$ of prostaglandin E_1 . A second injection was administered as necessary to achieve a maximum erectile response. All patients were able to get full rigidity with an intracavernous injection. Plaque characteristics, including location, size, and fibrous or calcified, were determined with US and plain X-rays. A baseline objective measurement of penile curvature was obtained using a goniometer at maximum penile rigidity. The haemodynamics of penile blood vessels were quantified by measuring peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index (RI) of the left and right cavernous arteries after an intracavernous injection with prostaglandin E_1 . The values used for different vascular status definitions were as follows: pure arterial insufficiency (AI), a PSV of $<25 \text{ cm/s}$; borderline AI, PSV $25\text{--}30 \text{ cm/s}$; pure veno-occlusive dysfunction (VOD), PSV $>30 \text{ cm/s}$ + EDV $>5 \text{ cm/s}$ + RI <0.8 ; mixed vascular disorder, PSV $<25 \text{ cm/s}$ + EDV $>5 \text{ cm/s}$; nonvascular disorder, PSV $>30 \text{ cm/s}$ + EDV $\leq 5 \text{ cm/s}$ + RI >0.8 . The radiologist was unaware of the patient allocation [11,20,21]. For a subjective assessment of penile curvature, patients were asked to sketch the erected penis. A modified Kelami classification was used to evaluate varying degrees of penile curvature and plaque size [22]. Patients were categorized into three groups: class I, plaque length $\leq 1 \text{ cm}$ and curvature of $\leq 30^\circ$; class II, plaque $1\text{--}2 \text{ cm}$ and $30\text{--}60^\circ$ curvature; and class III, plaque $>2 \text{ cm}$ and curvature $>60^\circ$. Patients who did not fall into any of the classifications (e.g. patients with penile curvature $>60^\circ$ and plaque length $<2 \text{ cm}$) were categorized as in a higher class. The disease was classified in each patient from symptoms, an objective assessment, and basal and dynamic penile duplex US. Pain intensity was determined on a conventional 10-point visual analogue pain scale (VAS), where the higher the score, the greater the degree of pain.

FIG. 1. A flow diagram of the patients recruited through the trial.



Before randomized grouping, all the eligible patients received single-blind placebo capsules for 1 week (week -1). Those who showed a decrease of $\geq 20\%$ in pain score (placebo responders) were excluded. The 228 patients who fulfilled the inclusion and exclusion criteria and who consented to the study protocol were randomized and divided into two groups by a computer-generated randomization table in a double-blind fashion and 1 : 1 ratio to receive PTX sustained-release (PTX-SR) 400 mg twice daily (Apo-Pentoxifylline, Apotex Inc., Toronto, Canada) (group 1, 114) or an identically looking matching placebo orally (group 2, 114) for a 6-month period. The rationale for the usual recommended dosage of PTX-SR (400 mg orally three times a day) was based on the fact that PTX is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are reached at 3.3 h [23]. Therefore PTX-SR can be administered at a dosage of 400 mg twice daily to achieve reasonable peak plasma concentrations. This is also in accordance with the information provided by enclosed package. The investigator (M.R.S.), who allocated the patients into the groups, administered the medications and collected the data, and the statistician were all unaware of the type of

treatment the patients received, and of the treatment groups.

Efficacy was assessed every month after the initial dose of PTX-SR on day 1, at the end of the 6-month treatment, and 1 month after stopping treatment. The participants were interviewed in person. The primary endpoints were the improvement in ED, penile curvature, plaque size, and pain. The secondary endpoints were: (i) the mean number of sexual attempts per week; (ii) responses to a Global Assessment Question (GAQ), 'Compared to having no treatment at all for your disease, has the treatment you have been taking during this study improved your erections?'; (iii) treatment satisfaction as assessed using patient versions of the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire; and (iv) improvement in penile artery indices. Subjective changes in pain, penile curvature and sexual function status were recorded during interviews at every follow-up visit. Each patient was asked to complete the IIEF questionnaire at baseline and at each follow-up visit. Duplex US was repeated at the end of the trial (1 month after stopping medication) to assess objective changes in penile curvature and vasculature system. For the

purposes of this trial, disease progression was defined as an increase in plaque volume, and/or penile curvature, and/or penile pain, and/or EDV, and/or a decrease in RI, PSV and/or IIEF score. A positive response to treatment was defined as objective improvement in plaque size and penile curvature.

Safety and tolerability were evaluated by monitoring the vital signs and changes in the physical examination findings, and clinical laboratory data. Data on adverse events, including their severity and relation to treatment, were obtained during follow-up visits on the basis of spontaneous reports, comments volunteered by the participant and direct questioning.

It was considered that randomization of ≥ 200 patients (100 in each group) would allow the detection of a 10° change in penile curvature between the treated and placebo groups, with 90% power and a 5% significance level. Therefore assuming an overall 10% discontinuation rate, 220 patients would be required. Data are presented as the mean (SD). All analyses were done using the intention-to-treat approach; the intention-to-treat population included all randomized patients who took at least one dose of their assigned study medication and who had at least one valid assessment after baseline of primary outcome measures. The data from the intention-to-treat patients were evaluated using the 'last observation carried forward' method to select data such as missing data. All participants who took at least one dose of study medication were included in the safety analyses. For comparisons among the baseline, placebo, and PTX-SR IIEF sexual function domains, the Wilcoxon rank-sum test was used. Other continuous variables were compared using a two-tailed Student's *t*-test and Mann-Whitney *U*-test, whereas categorical data were compared statistically using the chi-square test.

RESULTS

The flow of patients through study protocol is presented in Fig. 1. The mean (SD) patient age and duration of PD at baseline were 51 (9) years and 16 (4.8) months, respectively. Differences in baseline demographic and clinical variables between the PTX-SR and placebo groups were not clinically significant, and the tested groups had basic homogeneity (Table 1); Table 2 lists the associated

comorbidities. At baseline, 75 patients (33.9%) recalled penile trauma. Of 228 randomized patients, 203 (89.0%) completed the whole study protocol, including 101 (88.6%) in the PTX-SR group and 102 (89.5%) in the placebo group. The remaining 25 patients, including 13 in the PTX-SR and 12 in the placebo arm, withdrew from the study because of lack of efficacy (two in the PTX-SR, five in the placebo group), withdrawal of consent (four in the PTX-SR, three in the placebo group), lost to follow-up (six in the PTX-SR, three in the placebo group), and adverse events (one in each group). Of the 228 randomized patients, 140 (61.4%) had dorsal, 10 (4.4%) had ventral, and 129 (56.6%) had lateral curvatures; more than one direction of curvature was detected in 51 (22.4%) patients.

Table 3 shows the objective comparisons in PTX-SR and placebo-treated patients. After 2 months of PTX-SR treatment the beneficial effects began; these gradually and constantly increased during treatment period. Overall, 36.9% of patients who received PTX-SR reported a positive response, as opposed to only 4.5% in the placebo group. Of patients in PTX-SR group, 12 (10.8%) had disease progression, while 46 (41.8%) did so in the placebo group ($P = 0.01$). There were significant differences between PTX-SR and placebo for the improvement in penile deviation ($P = 0.003$). In the group receiving PTX-SR, 37 (33.3%) patients had a measured improvement, 45 (40.5%) showed no change and 29 (26.1%) were found to be worse. Of the patients in the placebo group, nine (8.2%, $P = 0.01$) had a measured improvement in penile curvature, 71 (64.5%, $P = 0.01$) had no change and 30 (27.3%, $P = 0.1$) were worse. A greater percentage of patients had an improvement in penile curvature in the PTX-SR group. Also, in the PTX-SR treatment group, the mean curvature improved, as opposed to worsening in the placebo group (ventral, -40 vs $+26.9^\circ$, $P = 0.001$; dorsal, -22.2 vs $+31.4^\circ$, $P = 0.01$; lateral, -20 vs $+22.2^\circ$, $P = 0.01$; Fig. 2A). In those whose curvature improved, the mean change was 23° for the PTX-SR and -22° for the placebo group ($P = 0.003$). At baseline, all patients had plaque palpable on physical examination. The measurement of plaque size indicated a significant reduction on PTX-SR ($P = 0.001$). At the end of the study, calcifications were noted in eight (7.2%) of the patients who had received PTX-SR and in 26 (23.6%) of those who received placebo ($P = 0.03$). The right and

Mean (SD) or n (%) characteristic	PTX-SR	Placebo	TABLE 1 <i>Baseline demographics and clinical characteristics of the 114 patients in each group; none of the differences were significant</i>
Age, years	51.2 (9.6)	51.4 (10.2)	
Months since onset of PD	20.2 (6.8)	20.6 (6.4)	
Plaque volume, mm ²			
Objective	14 (6.2)	14 (6.3)	
Patient perception	16 (6.4)	16 (5.8)	
Pain during erection	114 (100)	114 (100)	
VAS score	5.5 (2.4)	5.6 (2.1)	
Intercourse attempts (/week)	1.2 (0.4)	1.2 (0.4)	
EDITS score	45.7 (12.4)	45.4 (11.8)	
Penile curvature, °			
Patient perception	35.6 (4.2)	35.8 (4.3)	
Objective			
Ventral	5 (25)	5 (26)	
Dorsal	69 (36)	71 (35)	
Lateral	65 (25)	64 (27)	
IIEF sexual function domains			
IIEF total score	45.8 (12.5)	45.5 (13.1)	
Erectile function	20.4 (5.2)	19.8 (5.4)	
Orgasmic function	8.2 (2.4)	7.6 (2.2)	
Sexual desire	6.4 (1.5)	6.4 (1.3)	
Intercourse satisfaction	6.2 (2.2)	6.6 (2.1)	
Overall satisfaction	5.5 (2.2)	5.7 (2.1)	
Penile artery spectral traces			
Right			
PSV, cm/s	37.7 (0.8)	36.9 (0.7)	
EDV, cm/s	9.4 (0.2)	9.3 (0.2)	
RI	0.77 (0.01)	0.75 (0.01)	
Left			
PSV, cm/s	38.6 (0.7)	38.2 (0.7)	
EDV, cm/s	9.4 (0.2)	9.4 (0.2)	
RI	0.76 (0.01)	0.75 (0.01)	
Vascular status			
Pure arterial insufficiency	24 (21.1)	23 (20.2)	
Borderline arterial insufficiency	22 (19.3)	22 (19.3)	
Pure VOD	28 (24.6)	29 (25.4)	
Mixed vascular disease	6 (5.3)	5 (4.4)	
Nonvascular status	34 (29.8)	35 (30.7)	
Comorbidities:			
Hypercholesterolaemia	18 (15.9)	19 (16.7)	
Diabetes mellitus	9 (7.9)	8 (7)	
Hypertension	21 (18.4)	22 (19.3)	
Coronary artery disease	8 (7)	9 (7.9)	

Comorbidities, n (%)	PTX-SR	Placebo	Total	TABLE 2 <i>Comorbidities in PTX-SR and placebo treated patients at study initiation; none of the differences were significant</i>
Cigarette smoking	28 (25.2)	28 (25.5)	56 (25.3)	
Hypertension	27 (24.3)	25 (22.7)	52 (23.5)	
Serum lipid abnormalities	14 (12.6)	15 (13.6)	29 (13.1)	
Diabetes mellitus	12 (10.8)	11 (10)	22 (10)	
Ischaemic heart disease	9 (8.1)	8 (7.3)	17 (7.7)	
Carpal tunnel syndrome	1 (0.9)	0	1 (0.5)	
Dupuytren's contracture	0	1 (0.9)	1 (0.5)	
Family history	0	0	0	
No risk factors	59 (53.2)	60 (54.5)	119 (53.8)	

TABLE 3 Objective and subjective comparisons of therapeutic efficacy in the two groups at the end of the trial

Mean (SD) or n (%) variable	PTX-SR (111)	% change	<i>P</i> *	Placebo (110)	% change	<i>P</i> *	<i>P</i> †
Objective							
Mean plaque area, mm ²	10 (2.6)	-28.6	0.02	20 (4.0)	+42.9	0.01	0.001
Appearance of calcification	8 (7.2)	+7.2	0.07	26 (23.6)	+23.6	0.02	0.03
Objective penile curvature, °							
Ventral	4 (15)	-40	0.01	9 (33)	+26.9	0.02	0.001
Dorsal	47 (28)	-22.2	0.02	89 (46)	+31.4	0.01	0.01
Lateral	51 (20)	-20	0.02	72 (33)	+22.2	0.02	0.01
Penile artery spectral traces							
Right							
PSV, cm/s	42.0 (0.6)	+11.4	0.04	37.6 (0.5)	+0.2	0.1	0.04
EDV, cm/s	8.2 (0.3)	-12.8	0.04	9.5 (0.2)	+2.2	0.09	0.04
RI	0.85 (0.01)	-10.4	0.04	0.73 (0.01)	-2.7	0.09	0.04
Left							
PSV, cm/s	43.1 (0.6)	+11.7	0.04	36.6 (0.7)	-4.2	0.08	0.04
EDV, cm/s	8.4 (0.2)	-10.6	0.04	9.7 (0.2)	+3.2	0.08	0.04
RI	0.85 (0.01)	+11.8	0.04	0.71 (0.01)	-5.3	0.08	0.03
Vascular status							
Pure arterial insufficiency	20 (18)	-14.7	0.04	21 (19.1)	-5.4	0.07	0.07
Borderline arterial insufficiency	12 (10.8)	-44	0.01	28 (25.5)	+32.6	0.01	0.001
Pure VOD	14 (12.6)	-48.8	0.01	23 (20.9)	-17.7	0.04	0.01
Mixed vascular disease	5 (4.5)	+15.1	0.04	5 (4.5)	+2.3	0.09	0.04
Nonvascular status	60 (54.1)	+81.5	0.001	33 (30)	-2.3	0.09	0.001
Subjective							
Pain during erection	12 (10.8)	-89.2	0.001	19 (17.3)	-82.7	0.001	0.07
IIEF sexual function domains							
IIEF total score	61.4 (6.7)	+34.1	0.01	49.4 (4.2)	+8.6	0.07	0.02
Erectile function	26.2 (2.7)	+28.4	0.02	20.5 (2.8)	+3.5	0.08	0.02
Orgasmic function	8.5 (2.2)	+3.7	0.08	7.8 (2.7)	+2.6	0.09	0.1
Sexual desire	7.5 (1.7)	+17.2	0.03	6.9 (1.4)	+7.8	0.07	0.04
Intercourse satisfaction	11.5 (2.1)	+84.5	0.001	6.7 (2.2)	+1.5	0.1	0.001
Overall satisfaction	7.5 (1.6)	+36.4	0.01	6.0 (2.4)	+5.3	0.08	0.01
Patient perception of plaque area, mm ²	12 (4.3)	-25	0.02	24.6 (4.7)	+53.6	0.01	0.001
Patient perception of penile curvature, °	25.1 (4.1)	-29.5	0.01	44.2 (4.4)	+23.5	0.02	0.01
VAS	1.3 (0.4)	-76.4	0.001	1.5 (0.6)	-67.9	0.001	0.1
Intercourse attempts (/week)	1.8 (0.8)	+50	0.01	1.1 (0.5)	-8.3	0.07	0.01
Per-patient percentage GAQ 'Yes'	62.8	-	-	14.1	-	-	0.01

**P* vs baseline; †*P* placebo vs PTX-SR.

left cavernosal artery PSV, EDV and RI changed at the end of study. Mean PSV changes after therapy compared to baseline were statistically significant between PTX-SR (R, +11.4%, L, +11.7) and placebo-treated (R, +0.2, L, -4.2) patients (both *P* = 0.04; Fig. 2B). There were no statistically significant differences in EDV and RI among the groups.

Table 1 shows the penile vascular status in each group at baseline. When comparing differences in penile artery spectral traces, patients with dorsolateral penile curvature had the highest rate of arterial insufficiency,

at 38.6%. At the end of trial, of patients in the PTX-SR and placebo groups, 60 (54.1%) and 33 (30%) had nonvascular status, respectively (*P* = 0.001; Fig. 2C). Patients with ventrolateral penile curvature had the best penile artery spectral traces, with a nonvascular status recorded in 77% of patients.

Subjective comparisons of the therapeutic efficacy among two groups are also shown in Table 3. All of the patients reported pain on erection at the beginning of the study. After PTX-SR and placebo treatment, 99 (89.2%),

and 91 (82.7%) reported resolution of penile pain, respectively. The difference in improvement in penile pain was not statistically significant (*P* = 0.07). The mean (range) pain scores were 5.5, and 5.6 (1-10) on the 10 point VAS at study entry in the PTX-SR and placebo groups, respectively. There was a significant pain reduction at the end of the study in both groups. The mean reduction of the VAS score was 76.4% in PTX-SR and 67.9% in the placebo group (*P* = 0.1). Patient perceptions of plaque volume were statistically greater in the placebo than in the PTX-SR group (*P* = 0.001). Subjective patient

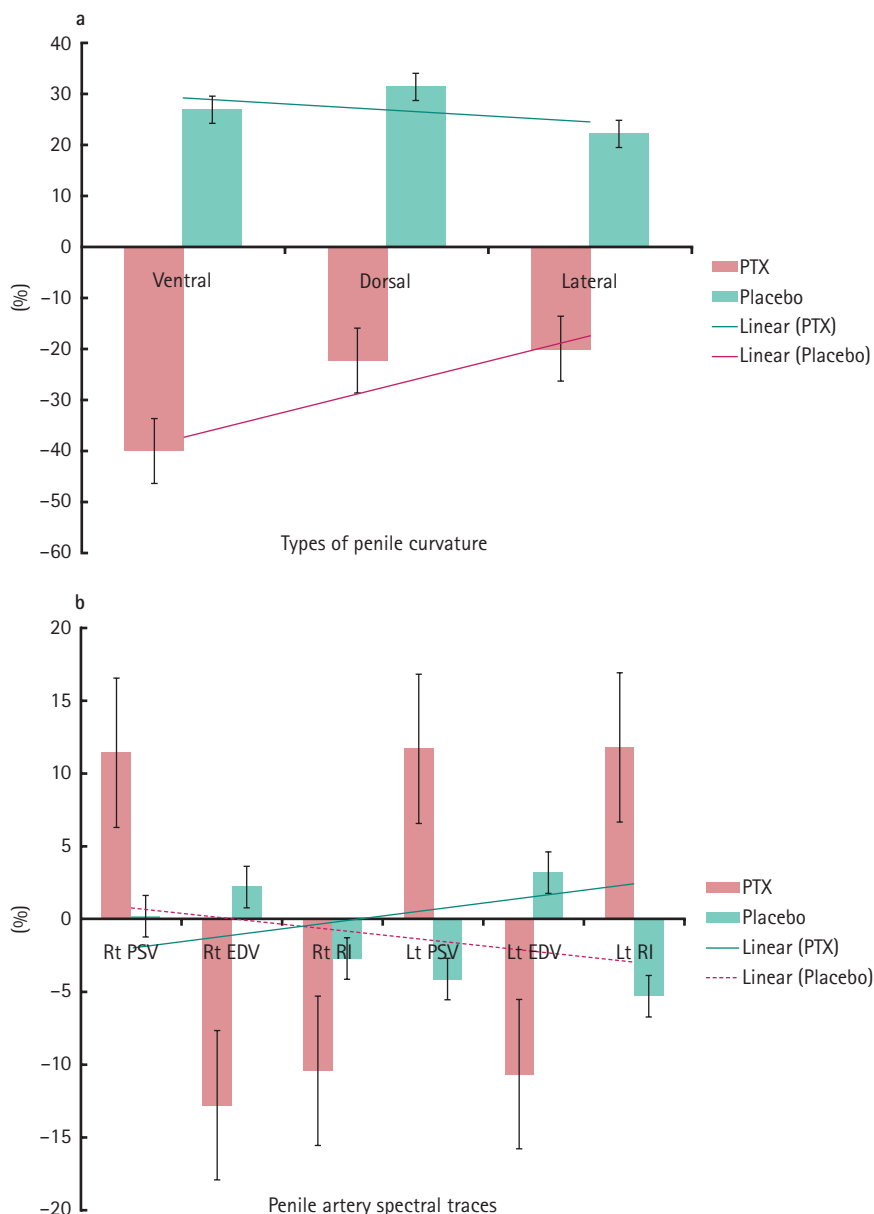
perceptions of penile curvature were in favour of PTX-SR. Patients treated with PTX-SR and placebo reported -29.5° , and $+23.5^\circ$ changes in penile curvature, respectively ($P = 0.01$).

Likewise, there were significant differences in the number of weekly intercourse attempts. At the end of the trial, the mean number of sexual attempts per week was 1.8 (0.8) in PTX-SR and 1.1 (0.5) in the placebo group ($P = 0.01$). For treatment satisfaction and erectile function, all patients were asked to complete the IIEF and EDITS questionnaires (Tables 3,4) There was a significant difference between the PTX-SR and placebo groups in IIEF total score ($P = 0.02$), and IIEF sexual function domains, except orgasmic function (Table 3). After study completion, PTX-SR-treated patients had increased erectile function scores (28.4% vs 3.5%, $P = 0.02$), sexual desire scores (17.2% vs 7.8%, $P = 0.04$), intercourse satisfaction scores (84.5% vs 1.5%, $P = 0.001$), and overall satisfaction scores (36.4% vs 5.3%, $P = 0.01$) (Fig. 2D).

According to the EDITS index scores, 76 (68.5%) patients treated with PTX-SR, and 19 (17.3%) in the placebo group were satisfied (defined as a final EDITS score of >50) with the treatment. The proportion of mean per patient percentage GAQ 'Yes' responses was 62.8% in the PTX-SR and 14.1% in the placebo group ($P = 0.01$; Table 3). There was an objective and subjective improvement in all three Kelami classes (Table 5), with significant differences across the three classes between the groups. Of the patients with Kelami class I penile deformity, 18.5%, and 74.1% had objective deterioration of the curvature in PTX-SR and placebo groups, respectively ($P = 0.001$). In patients with Kelami class II penile deformity, objective curvature deterioration was significant in the placebo group ($P = 0.001$). Of patients treated with PTX-SR, the treatment resulted in an improvement in 39.6% and deterioration in 26.7% with Kelami class III penile deformity; the respective values in the placebo group were 11.8% and 71.6% (both $P = 0.001$).

There was a significant negative correlation between disease duration and a positive response to PTX-SR ($r = -0.68$, $P = 0.001$), and between the Kelami class ($r = 0.72$, $P = 0.001$) and objective improvements and PSV ($r = 0.52$, $P = 0.01$). A positive response to PTX-SR was significantly associated with treatment duration ($r = 0.77$, $P = 0.001$).

FIG. 2. The percentage change in: A, objective estimates of penile curvature at study end; B, penile artery spectral traces at study end; C, penile vascular status (VD, vascular disease; NVS, nonvascular status) at study end; and D, IIEF sexual function domains in both groups at different follow-up times.



The tolerance of the PTX-SR treatment was satisfactory; only one patient discontinued the medication because of adverse effects. There were no adverse effects in any of the vital signs or in the laboratory data. PTX is a peripheral vasodilator and could induce hypotension; consequently, blood pressure should be controlled during treatment with this drug. Nausea followed by vomiting and dyspepsia were the most common adverse

events. No serious adverse event was recorded (Table 6).

DISCUSSION

Theoretically, PTX has anti-inflammatory and antifibrogenic properties, with inhibitory effects on the basic mechanisms of fibrogenesis, e.g. cell proliferation and

extracellular matrix synthesis [24]. These mechanisms of actions might reverse the fibrotic process in PD, and this randomized placebo-controlled study was aimed at answering this question. The PTX-SR group showed a modest but statistically significant improvement in primary and secondary outcome measures compared with the placebo group. There is no evidence from previous reports on the efficacy of PTX for treating PD to make a comparison. Compared to the reported natural progression rate of up to 40% in untreated PD [1,25], the present 11.8% progression rate suggests a therapeutic effect of PTX-SR in preventing disease progression. In addition, PTX-SR was able to halt disease progression in 58 (52.3%) of treated patients. Our results showed that an improvement in pain and a reduction in plaque size and penile curvature paralleled the improvement in EDV and erectile function. The improvement in tissue perfusion by PTX-SR might improve the EDV. PTX has been used widely in human fibrotic conditions, including radiation proctitis, radiation-induced fibrosis [26], alcoholic hepatitis [27], and preventing atherosclerosis in hypertensive patients with type 2 diabetes mellitus [28]. Patients with PD have increased expression and activity of Smad transcription factors of the TGFβ pathway in fibroblasts [29]. PTX inhibits the TGFβ1-mediated pathway of inflammation [30]. Valente *et al.* [31] showed that sildenafil and PTX decrease plaque size in tunical fibrosis induced by TGFβ1 injection.

The pressure for developing an oral treatment for PD has resulted in the off-label use of various medications, e.g. Potaba, tamoxifen, vitamin E [9], colchicine [10], and propionyl-L-carnitine [11]. However, studies with these agents have generally shown them to be unsuccessful or to have limited efficacy in stopping the progression of PD. The management of patients with PD would be improved by the development of a treatment strategy that can reverse the abnormal fibrotic reaction of the tunica albuginea.

Clinically, the present study underscores the safety of PTX-SR therapy and indicates that although a third of men assessed had an improvement in their curvature, about half had their deformity stabilized.

The precise pathophysiological mechanisms that lead to PD have yet to be identified. To develop effective treatments for PD an understanding of the actual pathogenesis of

FIG. 2. Continued

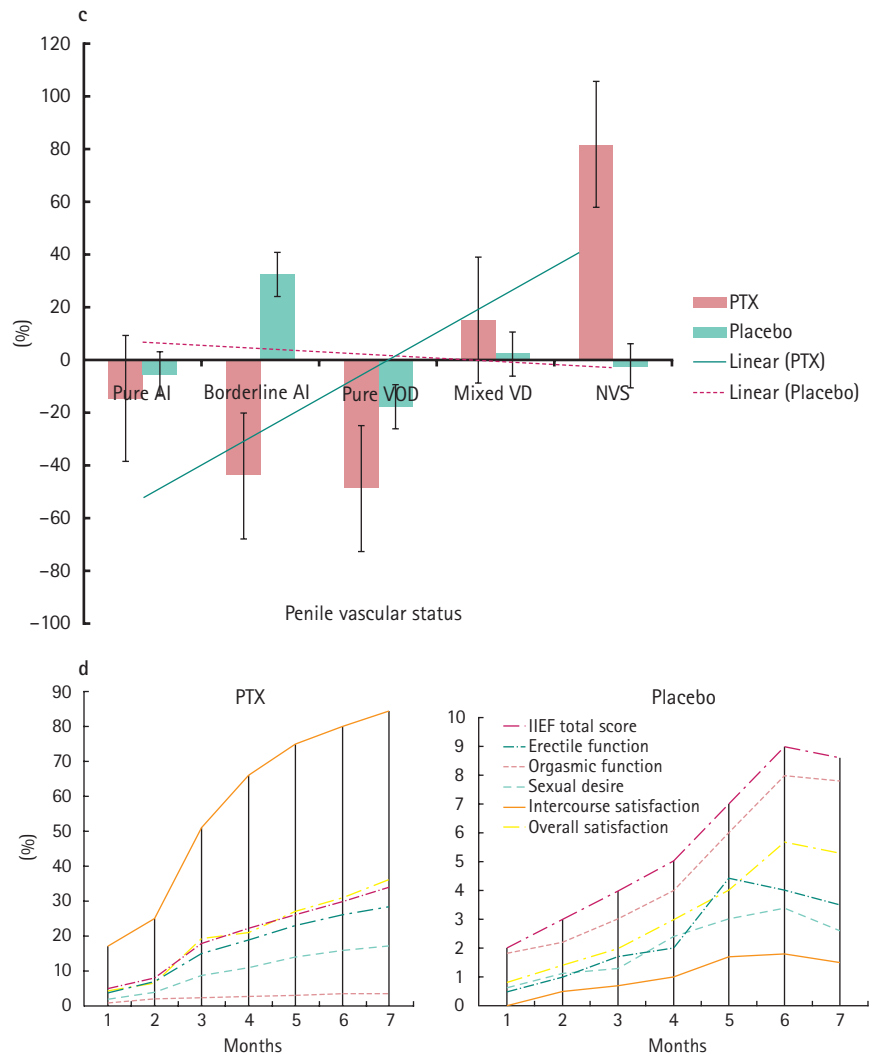


TABLE 4 Comparison between PTX-SR and placebo groups of treatment satisfaction by overall mean EDITS scores after 6 months of treatment

EDITS	Mean (SD, 95% CI)		P
	PTX-SR (111)	Placebo (110)	
Overall EDITS score	64.2 (10.4, 55–76)	38.3 (11.8, 30–46)	0.01
Individual items			
1 Overall satisfaction	2.4 (0.11, 2.0–3.0)	0.9 (0.21, 0.6–1.2)	0.01
2 Expectations	2.3 (0.14, 1.7–2.9)	1.1 (0.14, 0.7–1.5)	0.01
3 Likelihood of continuing	2.4 (0.12, 1.8–3.1)	0.9 (0.24, 0.6–1.4)	0.01
4 Confidence	2.6 (0.10, 2.0–3.2)	1.3 (0.16, 0.7–1.8)	0.02
5 Partner satisfaction	2.5 (0.14, 2.0–3.2)	1.1 (0.17, 0.5–1.6)	0.01
6 Partner desire to continue treatment	2.4 (0.12, 1.8–3.0)	1.2 (0.16, 0.7–1.7)	0.02
7 Naturalness of achieving erection	3.1 (0.12, 2.4–3.7)	2.1 (0.19, 1.6–2.7)	0.02
8 Naturalness of erection hardness	2.6 (0.12, 2.1–3.3)	1.7 (0.17, 1.1–2.3)	0.02
9 Quickness of achieving erection	2.6 (0.12, 2.0–3.3)	1.5 (0.14, 1.0–1.9)	0.02
10 Duration of erection	2.7 (0.11, 2.1–3.3)	1.3 (0.20, 0.8–1.6)	0.01
11 Ease of use	3.8 (0.04, 3.3–4.1)	3.8 (0.06, 3.4–4.1)	0.1

TABLE 5 Subjective and objective changes in different Kelami classes at the end of trial

Change	Kelami Class, n (%) of total or subtotal			Total
	1	2	3	
Objective				
PTX-SR group:				
Overall	54 (53.5)	27 (26.7)	20 (19.8)	101 (100)
Decreased curvature	25 (46.3)*	10 (37)	5 (25)	40 (39.6)
Increased curvature	10 (18.5)*	10 (37)	7 (35)	27 (26.7)
No change in curvature	19 (35.2)*	7 (25.9)	8 (40)	34 (33.7)
Placebo group:				
Overall	54 (52.9)	28 (27.5)	20 (19.6)	102 (100)
Improved curvature	8 (14.8)*	3 (10.7)	1 (5)	12 (11.8)
Increased curvature	40 (74.1)*	18 (64.3)	15 (75)	73 (71.6)
No change in curvature	6 (11.1)*	7 (25)	4 (20)	17 (16.7)
Improved sexual function				
PTX-SR group				
Overall	29 (53.7)*	8 (29.6)	2 (2.8)	39 (38.6)
Placebo group				
Overall	5 (9.3)*	2 (7.1)	1 (5)	8 (7.8)
Subjective				
PTX-SR group:				
Overall	54 (53.5)	27 (26.7)	20 (19.8)	101 (100)
Decreased curvature	35 (64.8)*	12 (44.4)	6 (30)	53 (52.5)
Increased curvature	9 (16.7)*	10 (37)	7 (35)	26 (25.7)
No change in curvature	10 (18.5)*	5 (18.5)	7 (35)	22 (21.8)
Placebo group:				
Overall	54 (52.9)	28 (27.5)	20 (19.6)	102 (100)
Improved curvature	12 (22.2)*	5 (17.9)	2 (10)	19 (18.6)
Increased curvature	36 (66.7)*	16 (57.1)	14 (70)	66 (64.7)
No change in curvature	6 (11.1)*	7 (25)	4 (20)	17 (16.7)

*P > 0.05 class 2 vs class 3.

Adverse events	PTX-SR (101)	Placebo (102)	P	TABLE 6
Nausea	5 (6)	1 (1)	0.04	Adverse events in the two groups, as n (%)
Vomiting	5 (6)	1 (1)	0.04	
Dyspepsia	5 (6)	0	0.03	
Headache	4 (4)	3 (2.9)	0.08	
Diarrhoea	4 (4)	0	0.03	
Tremor	2 (2)	0	0.08	
Dizziness	2 (2)	1 (1)	0.1	
Vertigo	2 (2)	1 (1)	0.1	

this disease is mandatory. At present it seems that a reasonable approach to the nonsurgical treatment of PD might be combined therapy; this should provide synergy between the oral, topical and intralesional drugs. In the present study we have used the criteria of the Oxford Centre for Evidence-Based Medicine. Given the safety profile of PTX-SR and its favourable effects on various aspects of PD (pain, curvature, and plaque volume), studies with different treatment regimens (perhaps higher doses with a longer duration) are warranted

to better elucidate the effects of PTX-SR on PD. In the present study, the improvement in penile curvature, pain and decrease in plaque size correlated significantly with treatment duration.

In conclusion, the present results indicate that improvements in penile curvature and plaque size were better in patients receiving PTX-SR than placebo. We believe that more studies are required to determine the optimal doses and treatment duration.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: PD, Peyronie's disease; PTX(-SR), pentoxifylline (sustained release); ED, erectile dysfunction; US, ultrasonography; Potaba, potassium para-aminobenzoate; EDV, end-diastolic velocity; PSV, peak systolic velocity; RI, resistivity index; IIEF, International Index of Erectile Function; VAS, visual analogue scale; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; GAQ, Global Assessment Question; AI, arterial insufficiency; VOD, veno-occlusive dysfunction.