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Pentoxifylline Associated with Other Antioxidants (Multimodal Therapy) on Patients with Peyronie's Disease. Results of a Controlled Study

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Abstract

Objective: The study was made mainly to investigate the possible benefits of multimodal treatment using Pentoxifylline (PTX) with other antioxidants, in patients with PD enrolled for a conservative medical management. Methods: We carried out a controlled study on 240 patients diagnosed with Peyronie's Disease (PD). We have divided two treatment groups, which differ from each other only for the association with PTX-penile injection. Two groups (A and B) were totally composed by 160 PD patients (80 patients for each group): Group A=PTX injection (penile and peri-lesional) 100 mg, every two weeks for six months + PTX 400 mg /oral/ twice daily + propolis 600 mg / oral / daily + blueberries 160 mg /oral/ daily + Vitamin E 600 mg / oral / daily + topical Diclofenac sodium 4% gel / twice a day, for a period of 6 months. Group B=the same therapy of group A but without PTX penile injection. Patients who refused treatment, for various reasons, were included in the control group=Group C (80 patients). Results: In groups A and B after 6 months of treatment a reduction of penile plaque volume of 50.3% and 25.9% respectively was observed, while in group C a mean increase in plaque volume of 131% was observed. Furthermore, in groups A and B, the mean curvature decrease was -11.07° and -4.4° respectively, while in group C a mean increase of curvature =+14.09° was observed. Conclusion: Our results showed that multimodal treatment with PTX associated with antioxidants and topical Diclofenac is significantly effective in treating PD. Treatment outcomes obtained in the treatment-group A are statistically more significant than those achieved in group B. Pentoxifylline is more effective when the treatment program includes both routes of administration: oral + peri-lesional injection.

Keywords: Pentoxifylline; Antioxidants; Blueberry; Multimodal Therapy; Peyronie's disease; Propolis; Vitamin

Introduction

Peyronie's Disease (PD) is a connective tissue disorder that affects primarily the tunica albuginea with the growth of fibrous inelastic plaques in penile corpora cavernosa. These plaques (also improperly called keloid scars), can obstacle the full and complete penile expansion during erection resulting in a possible penile bending. PD is a relatively common condition, indeed, several studies indicated a prevalence of 3.2 to 13.0 % in adult males [1,2]. The etiology of PD is not fully understood, although in recent years new studies propose the penile trauma as cause of PD [3]. A recent hypothesis suggests that the replicative/tumor-like nature of PD should be regarded as similar to that of keloids [4-8].The disease may occur as a result of traumas or injuries to the penis usually during sexual activity, although the majority of PD-patients do not remember a traumatic event.

Deposition of fibrin determines a secondary inflammatory process and production of phlogistic cytokines (Transforming growth factor beta-TGF-β etc.) associated with collagen overproduction and increase of reactive oxygen species (ROS) [9]. In what follows an activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) with the consequent expression of genes on specific targets (collagen, fibrin, inducible nitric oxide synthase-iNOS, fibroblast growth factor-FGF and TGF-β) [10,11].

Conservative treatment is indicated in early phase of PD and in case of local pain. Surgery is indicated when disease is stabilized [12,13] and in patients with severe penile curvature and/or erectile dysfunction [14]. Nonsurgical treatments include: potaba, Vitamin E, colchicine, tamoxifen, propolis, verapamil, interferons, collagenase, cortisone, pentoxifylline, iloprost, iontophoresi, Extracorporeal Shock Wave Therapy (ESWT) and Capacitive Resistive Energy Transfer (Tcare or TECAR therapy) [15-21]. Since we have already experienced the effectiveness of conservative treatment in the early phase of PD [17,22-24], we implemented a controlled study on patients with PD treated in association with several drugs: Pentoxifylline plus several antioxidants (Vitamin E, blueberries and propolis) and topical Diclofenac.

Materials and Methods

A controlled study was carried out to investigate the possible benefits of multimodal treatment, Pentoxifylline (PTX) associated with other Antioxidants, in patients with PD enrolled for a conservative medical management. This study was carried out by group of Andrologists Medical Researchers (all members of the Italian Society of Andrology - S.I.A.) in different locations of Andrological Operative Units of Italy: Rome, Albano L., Bologna, Pavia, Bari, Monopoli (Bari), Perugia, Prato, Macerata, Alba and Arezzo.

Between May 2, 2012 and October 31, 2013, 298 patients with PD were initially selected and enrolled for this study. All 298 patients had been informed about the possible surgical procedure. However, none

of them wished to undergo surgery and 89 patients refused any treatment (both medical and surgical treatment) for severalmotives: costs of care, hope to heal, fear of the treatment, PD underestimation, distrust in the care, etc.

We have conducted two treatment groups with multimodal therapy, which differ from each other only for the association with PTX-penile injection:

Group A

Pentoxifylline (PTX) injection (penile and perilesional - with needle 30 Gauge) 100 mg, every two weeks (12 total injections - the first injection 50 mg) for six months + PTX 400 mg /oral/ twice daily +propolis 600 mg /oral/ daily (on an empty stomach to facilitate the intestinal absorption) + blueberries 160 mg /oral/ daily + Vitamin E 600 mg / oral / daily + topical Diclofenac sodium 4% gel / twice a day, for a period of 6 months.

(To avoid further penile traumatism, in contrast to other studies, penile injections were not performed directly into the Peyronie's plaque but near the penile plaque: perilesional injection. PTX injection was performed with a very thin needle (30 Gauge) and without use of local anesthetic. Penile PTX injections were performed every 14 days and for a total period of 6 months. All patients of group A were then subjected to 12 total each injection).

Group B

PTX 400 mg /oral/ twice daily + propolis 600 mg /oral/ daily (on an empty stomach) + blueberries 160 mg /oral/ daily + Vitamin E 600 mg /oral/ daily + topical Diclofenac sodium 4% gel/twice a day, for a period of 6 months.

Group C

No treatment was provided to the patients who refused treatment and so all these patients were included in this study as a "control group".

Exclusion criteria (for all patients including control group) were:

- Any medical therapy for sexual dysfunction, before or during the study
- Previous treatments for PD
- Stabilized PD
- Severe penile curvature and/or which prevents sexual intercourse
- Severe erectile dysfunction
- Hypotension (possible transient hypotensive effects by pentoxifylline)
- Patients receiving continued therapy with theophylline (concomitant administration of pentoxifylline and theophylline may increase theophylline levels with possible increase of adverse effects) or potent anticoagulant drugs (dicumarol, etc.)
- Patients with allergy to various substances were used in the present study

From the original 298 patients, 58 cases were excluded from the study because of the following reasons

Three patients with stabilized PD; nineteen patients who have used PDE-5 inhibitors in the 6 months prior to study; five patients who after using Diclofenac-gel had a strong local skin irritation; ten patients who had suffered unpleasant side effects (skin rash, tachycardia, hypotension, dizziness) after initial treatment with oral pentoxifylline and who discontinued quickly the treatment; twenty-one patients that did not guarantee the statistical homogeneity of the three groups for various reasons (plaque echogenicity, type and degree of penile curvature/deformity, plaque volume, calcification size, presence of erectile dysfunction, comorbidity).

Thus, the two treatment groups (Groups A and B) were totally composed by 160 PD patients and each group included 80 patients. The control group (Group C) was composed of 80 untreated PD patients. Nine patients (of the initial 89 cases) were initially excluded from the study because did not guarantee the statistical homogeneity with the other groups (already included in the twenty-one patients excluded - see above). However, also these patients have agreed to be studied and controlled and so these 80 patients were observed evaluating the natural progression of the disease with follow-up after 6 months. The two substances propolis and blueberries, with the same doses used in the study (600 mg and 160 mg respectively) are contained in a tablet of Propolberry-3P® (Brea Srl, Italy).

Main outcome measures

Together with the medical history and the physical examination, initially, all 240 patients were subjected to these tests: dynamic penile ultrasound study, photograph during maximum erection [25], penile pain questionnaire, questionnaire-International Index of Erectile Function (IIEF). Penile pain was evaluated by a conventional 11-point pain-scale (Visual Analogue pain Scale-VAS) [26]. The self-evaluation of the erection was evaluated by all patients using the questionnaire IIEF [27]; the evaluated answers were the questions 1-5 and 15 which specifically refer to penile rigidity (IIEF-EF normal score: 26-30). Patients who had a total score of less than 26 were identified as having erectile dysfunction (ED).

The ultrasound study included an evaluation of the 3 dimensions of the plaque (length, width, and thickness) [28]. The plaque-volume was measured in cm3 using the ellipsoid formula [29-31]. All 240 patients were controlled for a time of 6 months and then underwent the same tests as performed at the start of the study. We performed statistical analysis with software package "Primer of biostatistics" (by Stanton A.Glantz).

Specific informed consent was obtained from all patients. This study was carried out in accordance with the Helsinki Declaration of 1975, and the 1983 revision of the same.

Results

The study included 240 patients (mean age = 53.5 ± 10.9 years; range 22-73 years). In the majority of patients (194/240 cases) there was a penile curvature (80.8%) and the mean curvature was 30.4 degrees (±15.7 SD). Penile pain was present in 162 patients (67.5% of total cases) and the mean pain-score (VAS) was 4.6 (±2.1 SD). ED was present in 95 cases (39, 5% of total 240 cases) and the mean IIEF score was 19.78 (±4.49 SD).

The three groups of this study were sufficiently homogeneous for a statistical analysis of results (patient age, PD duration, plaque size, calcification size, presence and intensity of ED, presence and intensity of penile pain, presence (and degree) of curvature and presence of comorbidities.

Clinical characteristics, basic demographics and comorbidities related to the three groups of PD patients are listed in Table 1.

Evaluation of treatment outcomes

In all cases when calcification was present, it did not exist in the whole area of the plaque, but was only present in small part, confirming that the disease was in the progressive phase (Table 2).

Characteristics	Treated group	Treated group	Treated group	Statistical analysis		
	Group A	Group B	Group C			
	n. 80 cases	n. 80 cases	n. 80 cases	p-Value	p-Value	p-Value
				A versus B	A versus C	B versus C
Mean age (years)+standard deviation	53.42 ± 11.76	53.62 ± 10.16	53.61 ± 11.00	p=0.909 (ANOVA)	p=0.916 (ANOVA)	p=0.995 (ANOVA)
Time since PD onset (months)+standard deviation	11.02 ± 6.47	11.31 ± 6.51	10.96 ± 7.48	p=0.778 (ANOVA)	p=0.957 (ANOVA)	p=0.753 (ANOVA)
Mean plaque volume (cm3)+standard deviation	0.711 ± 0.789	0.718 ± 0.990	0.7 ± 0.641	p=0.961 (ANOVA)	p=0.923 (ANOVA)	p=0.892 (ANOVA)
Cases with calcifications	25	23	24	p=0.971	p=0.903	p=0.885
Cases+%cases/total	31.2	28.7	30	(χ2 test)	(χ2 test)	(χ2 test)
Mean calcification volume (cm3)+standard deviation	0.152 ± 0.372	0.148 ± 0.195	0.142 ± 0.089	p=0.932 (ANOVA)	p=0.815 (ANOVA)	p=0.803 (ANOVA)
Associated erectile dysfunction	31	33	31	p=0.871	p=1.000	p=0.871
Cases+%cases/total	38.7	41.2	38.7	(χ2 test)	(χ2 test)	(χ2 test)
Erectile function index of PD patients with ED mean score+standard deviation	19.6 ± 4.9	19.42 ± 5.12	19.29 ± 3.57	p=0.886 (ANOVA)	p=0.777 (ANOVA)	p=0.907 (ANOVA)
Associated penile pain during	55	54	53	p=0.8653	p=0.8660	p=0.8666
Erection cases+%cases/total	68.7	67.5	66.2	(χ2 test)	(χ2 test)	(χ2 test)
VAS score of PD patients with penile PAIN mean score+standard Deviation	4.727 ± 1.994	4.537 ± 1.829	4.735 ± 2.520	p=0.605 (ANOVA)	p=0.985 (ANOVA)	p=0.642 (ANOVA)
Objective penile curvature	65	64	65	p=0.841	p=1.000	p=0.841
Cases+%cases/total	81.2	80	81.2	(χ2 test)	(χ2 test)	(χ2 test)
Curvature mean degrees°+standard deviation	31° ± 12.6	30.8° ± 14.8	29.2° ± 19.3	p=0.929 (ANOVA)	p=0.535 (ANOVA)	p=0.607 (ANOVA)
Patients with memory of recent	3	2	3	p=0.649	p=1.000	p=0.649
Penile trauma/cases+%cases/total	3.7	2.5	3.7	(χ2 test)	(χ2 test)	(χ2 test)
Comorbidities	n. cases	n. cases	n. cases	p-Value (χ2 test)	p-Value (χ2 test)	p-Value (χ2 test)
Hypertension	21	22	20	p=0.858	p=0.856	p=0.857
Dyslipidemia	15	14	15	p=0.837	p=1.000	p=0.837
Ischaemic heart disease	6	7	7	p=0.772	p=0.772	p=1.000
Diabetes	9	7	8	p=0.792	p=0.797	p=0.786
Hypotestosteronemia	2	2	2	p=1.000	p=1.000	p=1.000
Chronic prostatitis	4	3	4	p=0.699	p=1.000	p=0.699
Dupuytren's contracture	3	3	2	p=1.000	p=0.649	p=0.649

Cigarette smoking	17	16	15	p=0.845	p=0.843	p=0.841
Benign prostatic hyperplasia	8	9	8	p=0.797	p=1.000	p=0.797
Total mixed comorbidities	96	94	91	p=0.909	p=0.650	p=0.820

Table 1: Clinical characteristics and basic demographics of PD patients in the three groups.

Studied patterns	Group A Treated group	Group B Treated group	Group C Control group	Statistical analysis		
				A versus B	A versus C	B versus C
Penile pain disappearance mean rate%/n. patients/total patients	74.54 (41/55)	55.55 (30/54)	7.5 (4/53)	p=0.045 (χ2 test)	P<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Change in VAS-Score in patients with Penile Pain mean score+Standard Deviation	-4.0 ± 1.8	-3.3 ± 1.8	-0.4 ± 2.0	p=0.050 (ANOVA)	p=0.000 (ANOVA)	p=0.000 (ANOVA)
Appearance of penile pain mean rate%/n. patients/total patients	0 (0/25)	0 (0/26)	66.66 (18/27)	p=1.000 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Reduction of plaque size mean rate%/n. patients/total patients	100.0 (80/80)	81.25 (65/80)	0 (0/80)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Change in penile plaque volume mean rate %+Standard Deviation	-50.31 ± 18.76	-25.99 ± 28.12	+ 131.04 ± 258.87	p=0.000 (ANOVA)	p=0.000 (ANOVA)	p=0.000 (ANOVA)
Increase in plaque volume mean rate%/n. patients/total patients	0 (0/80)	5.0 (4/80)	100.0 (80/80)	p=0.120 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Disappearance of the plaque mean rate %/n. patients/total patients	1.25 (1/80)	1.25 (1/80)	0 (0/80)	p=1.000 (χ2 test)	p=0.315 (χ2 test)	p=0.315 (χ2 test)
Reduction of penile calcification size mean rate%/n. patients/total patients	96.0 (24/25)	65.21 (15/23)	4.16 (1/24)	p=0.009 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Change in penile calcification volume mean rate%+standard deviation	-57.07 ± 30.26	-35.94 ± 38.03	+102.12 ± 217.59	p=0.038 (ANOVA)	p=0.001 (ANOVA)	p=0.004 (ANOVA)
Disappearance of the calcification	12.0 (3/25)	8.69 (2/23)	0 (0/24)	p=0.708 (χ2 test)	p=0.234 (χ2 test)	p=0.234 (χ2 test)
Increase in penile calcification volume	4.0 (1/25)	0 (0/23)	75.0 (18/24)	p=1.000 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Appearance of new calcification mean rate %/n. patients/total patients	0.0 (0/55)	0.0 (0/57)	37.5 (21/56)	p=1.000 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Improvement of penile curvature mean rate %/n. patients/total patients	83.07 (54/65)	51.56 (33/64)	4.61 (3/65)	p=0.0002 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Change of curvature angle average - degrees°+standard deviation	-11.07° ± 8.07	-4.4° ± 5.6	+14.09° ± 15.47	p=0.000 (ANOVA)	p=0.000 (ANOVA)	p=0.000 (ANOVA)
Percentage reduction of the penile curvature angle	-36.4 ± 26.3	-19.3 ± 23.4	+74.1 ± 76.7	p=0.000 (ANOVA)	p=0.000 (ANOVA)	p=0.000 (ANOVA)
Penile curvature unchanged mean rate%/n. patients/total patients	16.92 (11/65)	46.87 (30/64)	15.38 (10/65)	p=0.0003 (χ2 test)	p=0.811 (χ2 test)	p=0.0001 (χ2 test)
Disappearance of the curvature mean rate %/n. patients/total patients	6.15 (4/65)	1.5 (1/64)	0 (0/65)	p=0.365 (χ2 test)	p=0.119 (χ2 test)	p=0.496 (χ2 test)
Worsening of penile curvature mean rate %/n. patients/total patients	0 (0/65)	0 (0/64)	46.15 (30/65)	p=1.000 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
appearance of new penile curvature mean rate%/n. patients/total patients	0 (0/15)	0 (0/16)	86.6 (13/15)	p=1.000 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)
Improvement of penile rigidity in patients with Erectile Dysfunction in patients with	96.7 (30/31)	69.6 (23/33)	0 (0/31)	p=0.0062 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)

Erectile Dysfunction mean rate%/n. patients/total patients						
Change in IIEF-Score in patients with Erectile Dysfunction/mean score+standard deviation	61.2 (19/31)+3.7 ± 2.2	18.1 (6/33)+1.2 ± 2.6	0 (0/31)-1.6 ± 1.4	p=0.0007 (χ2 test)	p<0.0001 (χ2 test)	p=0.0246 (χ2 test)
				p=0.000 (ANOVA)	p=0.000 (ANOVA)	p=0.000 (ANOVA)
Appearance of erectile dysfunction mean rate%/n. patients/total patients	0 (0/49)	0 (0/47)	71.42 (35/49)	p=1.000 (χ2 test)	p<0.0001 (χ2 test)	p<0.0001 (χ2 test)

Table 2: Outcomes after 6-month treatment

Intergroup analysis revealed statistically significant differences, in both groups A and B versus group C (control group), in terms of improvement of penile pain, effective plaque size reduction, effective penile calcification size reduction, improvement of penile curvature and effective improvement of erectile function index score.

In group A, after treatment of 6 months, penile pain disappeared in 74.5% of the cases, while in group B and group C pain disappeared in 55.5% (p=0.045) and 7.5% (p<0.0001) of the cases respectively.

In group A and group B, after treatment, a reduction of plaque size occurred in all cases (100%) and 81.2% of the cases respectively (p<0.0001), while group C it never occurred (p<0.0001).

Furthermore, in group A and group B, after therapy, the change in penile plaque size consisted in a reduction of plaque volume of 50.3% and 25.9% respectively (p=0.000), while in group C the change consisted in a mean increase in plaque volume of 131% (p=0.000). In group A and group B, after treatment, a worsening of penile curvature never occurred while in group C this worsening occurred in 46.1% of the cases (p<0.0001).

In group A and group B, after therapy, the improvement of curvature occurred in 83.07% and 51.5% of the cases respectively (p=0.0002), while in group C occurred only in 4.6% of the cases respectively (p<0.0001).

Moreover, in group A and group B, after treatment, the mean curvature decrease was –11.07° and –4.4° respectively (p=0.000), while in group C the change consisted in an increase of penile curvature (mean degrees°) corresponding to +14.09° (p=0.000). Interestingly, in group A and group B, after therapy, in PD patients with ED the restoration of rigid erection occurred in 61.2% and 18.1% respectively (p=0.0007), while in group C it never occurred (p<0.0001 and p=0.02). Otherwise, in group C and in PD patients without ED, at 6 months of follow-up, an erectile deficiency occurred in 71.4% of the cases, while in group A and group B this occurrence never occurred (p<0.0001). Although the treatment results of group A are better than B group, the treatment outcomes of B group versus C group outcomes were also statistically significant.

The tolerance of this multimodal therapy was satisfactory; adverse reactions divided "for each medication" and "for each group" are shown in Table 3 and 4 respectively. Gastro-enteric symptoms, skin rashes, headache and dizziness were the most frequent described effects after PTX treatment. Some of these adverse reactions after oral PTX were transient and disappeared rapidly during the treatment (11.8%). However, ten patients (10/170=5.8%) discontinued the medication (oral PTX treatment) because of unpleasant adverse effects (tachycardia, hypotension, dizziness and skin rashes). After PTX injections, three patients (3, 7%) had small ecchymoses at injection sites. After local use of Diclofenac 4% gel, five patients (3.03%) had a strong local skin irritation and they discontinued the medication. No serious adverse event was recorded.

Adverse events	**PTX oral**	**PTX Injection**	**Propolis+Blueberry/oral**	**Vitamin E oral**	**Diclofenac sodium 4%-gel**
	n. cases% incidence rate (n. cases/total cases)	**n. cases% incidence rate (n. cases/total cases)**	**n. cases% incidence rate (n. cases/total cases)**	**n. cases% incidence rate (n. cases/total cases)**	**n. cases% incidence rate (n. cases/total cases)**
Tachycardia	31.76% (3/170) side effect that caused the suspension of the drug (exclusion from the study)	0	0	0	0
Hypotension	10.58% (1/170) side effect that caused the suspension of the drug (exclusion from the study)	0	0	0	0
Skin rashes	42.35% (4/170) side effect that caused the suspension of	0	0	0	0

	the drug (exclusion from the study)				
Dizziness	21.17% (2/170) side effect that caused the suspension of the drug (exclusion from the study)	0	0	0	0
Headache	21.25% (2/160)	0	0	0	0
Hot flushes	21.25 (2/160)	0	0	0	0
Vomiting	10.62% (1/160)	0	0	0	0
Dyspepsia	42.5% (4/160)	0	0	0	0
Nausea	42.5% (4/160)	0	0	0	0
Meteorism	63.75% (6/160)	0	0	0	0
Strong local skin irritation	0	0	0	0	53.03% (5/165) side effect that caused the suspension of the drug (exclusion from the study)
Hematoma or severe skin ecchymosis	0	0	0	0	0
Small ecchymosis	0	33.75% (3/80)	0	0	0
Significant local pain	0	0	0	0	0
Local swelling	0	0	0	0	0
Total% incidence rate (concerns patients who have completed treatment)	11.8% (19/160)	3.75% (3/80)	0	0	0

Table 3: Adverse events after treatment (for each medication)

Adverse Events	**Group A (with PTX injection)**	**Group B**
Headache	1	1
Hot Flushes	1	1
Vomiting	0	1
Dyspepsia	1	3
Nausea	2	2
Meteorism	3	3
Local Skin Irritation	0	0
Hematoma Or Severe Skin Ecchymosis	0	0
Small Ecchymosis	3	0
Significant Local Pain	0	0
Local swelling	0	0

Incidence rate for each group (n. cases/total)	13.7% (11/80)	13.7% (11/80)
Total incidence rate in in both groups (n. cases/total)	13.7% (22/160)	

Table 4: Adverse events for each treatment group

Although most severe side effects after use of PTX are extremely rare and they never occurred in our study, currently we are investigating the possibility of avoiding the secondary side effects to oral administration of PTX, by associating transdermal PTX iontophoresis (daily) along with PTX penile injection (every two weeks).

Discussion and Conclusions

Pentoxifylline (PTX) reduces ROS production and protects against tissue damage. PTX has antioxidant properties and it exerts antifibrotic and anti-inflammatory activity [29-31]. PTX is a non-specific inhibitor of Phosphodiesterase (PDE); this drug inhibits: TGF-beta-1-stimulated collagen deposition [32,33]; transcriptional activity of NF-kB and TNF-alpha release [34,35]. PTX also inhibits proliferation of Tunica Albuginea-Derived Fibroblasts (TADF) and

attenuates TGF-β1-mediated collagen production in TADF [33]. PTX has inhibitory effects on both elastogenesis and collagen fiber deposition [32]. PTX attenuates the TGF-β1 mediated increase in elastogenesis, possibly by down-regulation of Smad1/5 via an iSmad6 dependent mechanism [33]. SMADs (Small Mother against Decapentaplegic) are intracellular proteins that transduce extracellular signals from TGF-β ligands to the nucleus where they activate downstream gene transcription [36].

Preventing the activity of NF-kB, PTX further contributes to the lower production of collagen. Some studies have indicated that PTX inhibits proliferation and extracellular matrix production and increases collagenase activity [37,38]. Thus PTX plays an important role in PD by inhibiting the TGF-β1-mediated processes leading to further plaque formation [32].

A double-blind placebo-controlled study in patients with PD, has shown that PTX (400 mg/oral/twice daily/6 months) was effective in reducing penile curvature and plaque size [16]. Other studies have confirmed the efficacy of PTX in the treatment of PD [39-42].

Vitamin E was the first oral therapy proposed for the treatment of PD; it is a potent antioxidant that is thought to reduce collagen deposits within the tunica albuginea. Some studies have found that Vitamin E and its metabolites have an anti-inflammatory and anti-COX2 property [43]. In our recent study we evaluated and verified the effectiveness of Vitamin E in the treatment of PD [17].

The components of Propolis, caffeic acid phenethyl ester and terpenoids inhibit the production of interleukins and NF-κB activity [44,45]. Blueberries are flowering plants (Vaccinium spp. Ericaceae) that contain anthocyanins, polyphenols and flavonoids. Blueberry anthocyanins are able to inhibit NF-KB, iNOS and COX-2 expression [46]. Several studies have evaluated the effectiveness of the mentioned antioxidants in the treatment of PD [17,22-24,47-50]. The properties of NSAID's, including the anti-inflammatory activity of Diclofenac, are already known, and it has been already used in the multimodal treatment of PD [17,22,24].

The significant improvements obtained in group A and B concern the basic parameters of the disease: plaque size, degree of penile curvature and penile rigidity (if erectile dysfunction was present). Interestingly and in contrast to the current medical opinion was to observe in group A and B a significant decrease of calcification volume and even the possibility of determining its disappearance in 12.0% and in 8.6% of the cases respectively, after only six months of treatment. In the control group, only few cases where the curvature was improved (4.6% = 3 cases/65 cases with penile curvature) ($p<0.0001$), in reality, the disease, in these cases had progressed as shown by the ultrasound study that found always an increase in plaque volume. In these cases the inflammatory tissue area had progressed locally causing a paradoxical improvement of penile curvature. In group C after 6 months of observation, there was always a statistically significant worsening of the following: penile pain, penile curvature and ED ($p<0.0001$). Furthermore, in all untreated cases always occurred a local progression of disease (increase of plaque size and/or calcification volume).

Our results showed that multimodal treatment with Pentoxifylline associated with Antioxidants and topical Diclofenac is statistically and significantly effective in treating PD.

Pentoxifylline is more effective when the treatment program includes both routes of administration: oral + perilesional injection (group A). In fact, the outcomes obtained in the treatment-group A are statistically more significant than those achieved in group B, and they refer to the main endpoints of the study: modifications of the penile plaque volume ($p<0.0001$), modifications of the penile curvature angle ($p=0.000$) and changes in erectile function ($p=0.000$). Good results were achieved only after 6 months of treatment and this may explain why in other reported studies, using the same drugs but with a shorter time limit of the treatment, showed less satisfactory results. In case the option for conservative therapy exists, as PD is a chronic illness, short-term therapies should therefore be avoided.

Our findings confirm and support that the best approach for treating PD is "multimodal therapy" [41,42,51-56], because it was able to achieve greater results than any single drug alone.

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