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ORIGINAL RESEARCH

Rationale of combination therapy with antioxidants in medical management of Peyronie's disease: results of clinical application

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Abstract: Peyronie's disease (PD) is a connective tissue disorder involving the tunica albuginea of the corpora cavernosa of the penis. We have published several studies describing a "combined therapy" for PD patients, but the present study aims to clearly demonstrate how the association between various antioxidants in PD treatment can significantly increase the likelihood of therapeutic success. We used the following substances: silymarin, *ginkgo biloba*, vitamin E, bilberry, topical diclofenac sodium, and pentoxifylline (PTX). We analyzed the therapeutic impact and possible side effects of one or more antioxidants in patients with early-stage PD. To clearly prove that it is possible to achieve better results when combining more than one agent, we designed this study with five treatment groups, corresponding, respectively, to the administration of a single oral antioxidant; two oral antioxidants; three oral antioxidants; five oral antioxidants + local diclofenac; and five oral antioxidants + local diclofenac + PTX by perilesional injection. One hundred and twenty patients were assigned to five groups of treatment designed according to the abovementioned study aim. Outcomes after 6 months of treatment showed that combined antioxidant therapy is effective in treating PD. Statistical analysis showed significant differences between the treatment groups with regard to: improvement and disappearance of penile pain; percentage of reduction in the volume of penile plaque; reduction in penile curvature; recovery of erectile function in patients with erectile dysfunction; increase in the International Index of Erectile Function score; and reduction of psychosexual impact. Furthermore, we observed that the clinical efficacy of combined therapy is greater when topical use of diclofenac gel and perilesional injection of PTX are added to oral treatment with more than one antioxidant. Although several articles have already been published reporting the effectiveness of combined treatment in PD, this is the first study clearly proving how, as the number of substances used in treatment rises, a proportionally greater therapeutic effect is achieved.

Keywords: Peyronie's disease treatment, combined therapy, penile curvature, penile injections, antioxidant treatment

Introduction

Peyronie's disease (PD) is a connective tissue disorder involving the tunica albuginea of the corpora cavernosa of the penis. It occurs in 3.2%–13% of adult males.[1,2] The disease consists of a thickening of a small area of tissue that gradually turns into an inelastic plaque, which can cause penile deformity (penile curvature, shortening, divot, hourglass deformity, etc), pain during erection, erectile dysfunction [ED], and psychological disorders (psychosexual impact).[3] Although the pathogenesis is not completely understood, most authors recognize that genetic predisposition and penile trauma of various degrees greatly favor the onset of PD.[4–8] There are two stages in the

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disease: an initial active inflammatory remodeling phase, lasting ~12–18 months (actually preceded by a brief, acute posttraumatic period, lasting ~2 weeks wherein powerful recruitment of inflammatory cells occurs), and a second stage in which both tissue damage and deformation stabilize.[9,10] Medical treatment is mainly indicated in the first stage of PD.[11,12] Several options have been suggested, including oral therapy (potaba, colchicine, tamoxifen, vitamin E, carnitine, etc), intralesional injections (verapamil, steroids, interferon, and, recently, collagenase clostridium histolyticum [CCH, Xiaflex]), and physical treatment (iontophoresis, extracorporeal shock wave therapy [ESWT], penile extender).[12–15] Recently, partly as a consequence of several important studies demonstrating the decisive role played by oxidative stress in the pathophysiological mechanisms of PD, several authors have published studies proving the efficacy of antioxidants in the treatment of the disease.[16–40] A tendency to combine various antioxidants and/or therapy modes in treating PD has thus emerged; recently, various studies have been published confirming the effectiveness of a combination therapy.[25,26,34–51] In 1991, Pastorini et al first tested a combination therapy in PD using injectable and oral superoxide dismutase (antioxidant substance) therapy, associated with papaverine intracavernous injection.[52] Combination therapy is a treatment strategy in which a number of oral antioxidants are combined with each other and, sometimes, with other drug agents and/or treatment options (including intralesional and physical therapy) to achieve better results as compared to single-drug or single-mode therapy. Of course, this is not new in the medical field, as combined therapy has already been used – for instance, in the treatment of tuberculosis and in chemotherapy for cancer. Although we have already published several studies describing a combined therapy for treatment of patients suffering from PD, the present study aims to clearly demonstrate how the association between various antioxidants in PD treatment can significantly increase the likelihood of therapeutic success.

Materials and methods

In this study, we analyzed the therapeutic impact and possible side effects of one or more antioxidants in patients suffering from PD in its active stage. To clearly prove that it is possible to achieve better results when combining more than one agent, we designed this study with five treatment groups, corresponding, respectively, to the administration of a single oral antioxidant; two oral antioxidants; three oral antioxidants; five oral antioxidants + local diclofenac; and five oral antioxidants + local diclofenac + pentoxifylline (PTX) by perilesional injection. All patients originally enrolled in this study presented to our andrology clinic, from January 2, 2015, to October 31, 2016, for PD in its active stage. We excluded from the study any patient who met one or more of the following exclusion criteria: coexistence of other treatment(s) for other sexual dysfunction before and during the study; stable disease; significant penile curvature preventing complete sexual intercourse; previous therapies for PD; allergy or intolerance to one or more of the substances used in the study; congestive heart failure, ischemic heart disease, peripheral artery disease, and cerebrovascular diseases; concomitant anticoagulant therapy; recent retinal or cerebral hemorrhage or the mere presence of risk factors for hemorrhage; low blood pressure and/or concomitant theophylline therapy; and allergy to plants and pollen.

We, thus, selected and enrolled in the study 141 patients suffering from PD in its active stage and having none of the abovementioned exclusion criteria. All patients were duly informed of any other types of treatment, including surgery, and had refused the option of surgery, if indicated. Patients were casually assigned to groups of treatment duly designed according to the abovementioned study endpoints:

- Group A: silymarin 200 mg/orally/twice daily, for 6 months;
- Group B: silymarin 200 mg/orally/twice daily + *ginkgo biloba* 250 mg/orally/once daily, for 6 months;
- Group C: silymarin 200 mg/orally/twice daily + *ginkgo biloba* 250 mg/orally/once daily + vitamin E 400 IU/orally/twice daily, for 6 months;
- Group D: silymarin 200 mg/orally/twice daily + *ginkgo biloba* 250 mg/orally/once daily + vitamin E 400 IU/orally/twice daily + propolis 600 mg/orally/once daily + bilberry (*Vaccinium myrtillus* L.) 160 mg/orally/once daily + topical diclofenac sodium 4% spray gel/one application per day (2 pump strokes = 16 mg of diclofenac sodium), for 6 months;
- Group E: silymarin 200 mg/orally/twice daily + *ginkgo biloba* 250 mg/orally/once daily + vitamin E 400 IU/orally/twice daily + propolis 600 mg/orally/per day + bilberry (*Vaccinium myrtillus* L.) 160 mg/orally/once daily + topical diclofenac sodium 4% spray gel /one application per day (2 pump strokes = 16 mg of diclofenac sodium) + PTX 100 mg (perilesional injection) twice a month, a total of 12 penile injections in 6 months.

On analysis and consideration of clinical and demographic characteristics of patients in study subgroups, we had to exclude 21 subjects, despite randomization, because

of their clinical characteristics (degree of penile curvature, plaque volume, presence of ED or penile pain, age, comorbidity, etc), as their presence in the study would have detracted from the necessary statistical homogeneity among the groups. Statistical analysis of various clinical and demographic characteristics of patients in the analysis dataset confirmed substantial statistical homogeneity between the groups.

The study, thus, included 120 cases, equally distributed into five treatment groups, each of which comprised 24 patients. All patients included in the study underwent a physical examination and accurate review of their medical history, as well as the following tests, both prior to treatment and at the 6-month follow-up: penile color Doppler ultrasound, questionnaire for the assessment of erectile function (International Index of Erectile Function [IIEF]), pain assessment questionnaire (Pain Intensity Numeric Rating Scale [PI-NRS]), weight and height assessment for body mass index (BMI) calculation, and evaluation of the disease's psychosexual impact using Peyronie's Disease Questionnaire (PDQ; Symptom Bother Domain).[53]

Besides assessing the plaque's echogenicity, color Doppler analysis included three-dimensional study of the plaque's measurements (length, width, and thickness), with imaging of the penis at maximum erection and photographic poses according to Kelami for goniometric measurement of penile curvature. Plaque volume was measured in cubic centimeters using the ellipsoid formula.[54,55]

In the IIEF, answers specifically pertaining to penile rigidity were taken into consideration – that is, answers to questions 1–5 and 15. The IIEF total score normally ranges between 26 and 30; therefore, patients with a score <26 were considered to be suffering from ED. The pain intensity questionnaire is based on analogical measurement of pain on a scale with 11 degrees, from 0 to 10 (PI-NRS), with 0 = no pain and 10 = worst pain possible. To evaluate psychosexual impact, we used the PDQ/Symptom Bother Domain Questionnaire, which consists of a set of questions (four scored items and two "yes/no" questions) inquiring about the patient's degree of preoccupation and distress; scores go from 0 ("not at all bothered") to 4 ("extremely bothered"); the final score can, therefore, vary from 0 to 16.[53] We then recorded the clinical data and analyzed the following comorbidities and risk factors: high blood pressure, dyslipidemia, diabetes mellitus, obesity, chronic prostatitis, benign prostatic hyperplasia, and habitual cigarette smoking. We considered obesity to be present when the BMI was 30 (kg/m^2) or higher. All 120 subjects signed a specific informed consent. Our study was conducted according to the principles of the Declaration of Helsinki in 1975, 1983, and subsequent revisions. After the approval of the institutional (Italian League Against Cancer [LILT]) ethics committee, specific written informed consents were obtained from all subjects.

The following antioxidants were used in the study: PTX, propolis, bilberry (*Vaccinium myrtillus* L.), vitamin E, silymarin, and *ginkgo biloba*. In addition, in groups D and E, diclofenac – an active substance already widely known for its anti-inflammatory properties – was used topically. PTX was used only via perilesional injection, in consideration of the possibility of side effects secondary to oral therapy.[40]

Statistical analysis

Statistical comparison between baseline and follow-up categorical variables was calculated both cumulatively and individually between the groups by using the chi-square test (χ^2 test). Comparative analysis between baseline and continuous follow-up parameters was undertaken cumulatively using analysis of variance (one-way ANOVA) and individually between the groups using Student's *t*-test. A value of $p < 0.05$ was considered statistically significant. IBM SPSS 22.0 was used for the statistical analysis.

Results

One hundred and twenty patients (median age [SD], 51.2 [±10.2] years; range 27–72 years) participated in the present study.

In 83.3% of cases (100 out of 120), penile curvature varied between 5 and 50 degrees, with an average (SD) of 25.4 (±11.3) degrees. At the beginning of treatment, the mean (SD) time since PD onset was 8.6 (±2.1) months. ED was present in 32.5% of cases (39 out of 120); the IIEF score was between 11 and 25, with an average (SD) of 22.30 (±3.28). Penile pain was present in 50.0% of cases (60 out of 120), and the mean PI-NRS score was 4.6 (±1.9). The psychological impact of the disease, recorded with the PDQ/Symptom Bother Domain questionnaire, had a mean score of 7.9 (±3.64).

In cases where calcification was present (23 out of 120 cases, 19.1% of cases), it was very minimal (mean volume = 0.031± 0.017 cm^3) and situated within the plaque, confirming that PD was in a progressive, active stage in all cases. Table 1 shows the substantial statistical homogeneity of the baseline clinical and demographic characteristics and comorbidities of the groups (with *p*-values between 0.878 and 0.999).

Analysis of results after 6 months of treatment

Statistical analysis revealed statistically significant differences between the treatment groups with regard to: improvement

Table 1 Clinical characteristics and basic demographics of PD patients in the several groups

Clinical features	Group A (n = 24) Silymarin	Group B (n = 24) Silymarin + Ginkgo	Group C (n = 24) Silymarin + Ginkgo + vitamin E	Group D (n = 24) Silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac	Group E (n = 24) Silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac + pentoxifylline injection	Statistical analysis *p*-value
Mean age (years), mean ± SD	51.95 ± 9.80	51.79 ± 6.79	50.95 ± 12.20	51.81 ± 11.06	50.33 ± 11.53	$p = 0.980$ (ANOVA)
Time since PD onset (months), mean ± SD	8.583 ± 2.394	8.708 ± 1.966	8.75 ± 2.558	8.5 ± 2.085	8.625 ± 1.929	$p = 0.995$ (ANOVA)
Plaque volume (cm^3), mean ± SD	0.393 ± 0.320	0.367 ± 0.319	0.382 ± 0.346	0.383 ± 0.387	0.404 ± 0.230	$p = 0.996$ (ANOVA)
Cases with calcifications	4	4	5	5	5	$p = 0.988$
no. cases + % cases / total	16.66	16.66	20.83	20.83	20.83	(χ^2 test)
Calcification volume (cm^3), mean ± SD	0.0297 ± 0.0235	0.0299 ± 0.0142	0.0285 ± 0.0158	0.0321 ± 0.0218	0.0364 ± 0.0167	$p = 0.967$ (ANOVA)
Associated ED	7	8	7	8	9	$p = 0.970$
no. cases + % cases / total	29.16	33.33	29.16	33.33	37.5	(χ^2 test)
Erectile function index of patients with ED, mean score ± SD	22.42 ± 2.37	21.37 ± 5.20	22.57 ± 3.40	22.75 ± 2.54	22.44 ± 2.78	$p = 0.937$ (ANOVA)
Associated penile pain	11	12	11	13	13	$p = 0.955$
no. cases + % cases / total	45.83	50.0	45.83	54.16	54.16	(χ^2 test)
Penile pain intensity (PI-NRS), mean score ± SD	4.27 ± 1.61	4.33 ± 2.18	4.72 ± 1.79	5.0 ± 2.309	4.69 ± 1.79	$p = 0.887$ (ANOVA)
Objective penile curvature	20	19	19	21	21	$p = 0.878$
no. cases + % cases / total	83.33	79.16	79.16	87.5	87.5	(χ^2 test)
Angle of penile curvature, mean degrees ± SD	24.750° ± 11.177	25.263° ± 9.785	25.368° ± 12.419	26.714° ± 11.415	25.238° ± 12.497	$p = 0.987$ (ANOVA)
PDQ score (PD symptom bother/psychosexual impact), mean score ± SD	7.70 ± 3.64	7.91 ± 3.72	8.04 ± 3.88	7.87 ± 3.83	7.95 ± 3.41	$p = 0.999$ (ANOVA)
Comorbidity and potential risk factors	(n)	(n)	(n)	(n)	(n)	*p*-value (χ^2 test)
Hypertension	4	4	4	3	2	$p = 0.894$
Dyslipidemia	3	4	4	3	3	$p = 0.981$
Diabetes	2	2	1	1	2	$p = 0.937$
Obesity	1	2	2	1	1	$p = 0.923$
Chronic prostatitis	3	2	3	2	4	$p = 0.889$
Benign prostatic hyperplasia	2	1	2	2	1	$p = 0.937$
Cigarette smoking	1	2	2	2	3	$p = 0.895$

Abbreviations: ED, erectile dysfunction; SD, standard deviation; PD, Peyronie's disease: PI-NRS, pain intensity numeric rating scale; PDQ, Peyronie's disease questionnaire.

and disappearance of penile pain; percentage of reduction in the volume of penile plaque; reduction in penile curvature; recovery of erectile function in patients with ED; increase in the IIEF score (both in patients with and without ED); and reduction of psychosexual impact (Table 2).

After 6 months of treatment, a reduction in plaque volume was obtained in all treatment groups, although more in-depth statistical analysis made it possible to identify substantial differences between certain therapy groups (Table 3). These results prove that as the number of substances employed grows (combined therapy), the efficacy of treatment grows proportionally. Furthermore, statistical analysis of all other outcomes yields the same conceptual conclusion. Notably, no disease progression took place in any of the treatment groups, and – in particular – none of the following occurred: increase in penile plaque volume; onset of penile pain in

Table 2 Results after 6 months of treatment

	Group A (n = 24) Silymarin	Group B (n = 24) Silymarin + Ginkgo	Group C (n = 24) Silymarin + Ginkgo + vitamin E	Group D (n = 24) Silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac	Group E (n = 24) Silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac + pentoxifylline injection	Statistical analysis Between-group comparisons
Outcome measures	**After 6 months**					***p*-value**
Penile pain						
Pain resolution						
mean rate, %	18.8	33.3	63.6	84.6	84.6	$p = 0.010$
patients/total patients (n/N)	(2/11)	(4/12)	(7/11)	(11/13)	(11/13)	(χ^2 test)
Reduction in pain intensity	−2.181	−3.416	−4.363	−4.692	−4.846	$p = 0.002$
mean PI-NRS score ± SD	± 0.603	± 1.621	± 1.501	± 2.056	± 2.154	(ANOVA)
Appearance of penile pain						
mean rate, %	0	0	0	0	0	$p = 1.000$
patients/total patients (n/N)	(0/13)	(0/12)	(0/13)	(0/11)	(0/11)	(χ^2 test)
Plaque size						
Plaque volume reduction						
mean rate, %	100.0	100.0	100.0	100.0	100.0	$p = 1.000$
patients/total patients (n/N)	(24/24)	(24/24)	(24/24)	(24/24)	(24/24)	(χ^2 test)
Reduction in plaque volume	−23.431	−25.763	−28.435	−32.865	−50.942	$p = 0.000$
mean rate, % ± SD	± 7.322	± 7.343	± 6.281	± 10.468	± 7.827	(ANOVA)
Increase in plaque volume						
mean rate, %	0	0	0	0	0	$p = 1.000$
patients/total patients (n/N)	(0/24)	(0/24)	(0/24)	(0/24)	(0/24)	(χ^2 test)
Penile curvature						
Improvement in penile curvature						
mean rate, %	50.0	52.63	73.68	90.47	90.47	$p = 0.018$
patients/total patients (n/N)	(10/20)	(10/19)	(14/19)	(19/21)	(19/21)	(v2 test)
Decrease in penile curvature angle	−3.30°	−4.73°	−6.0°	−8.52°	−13.09°	$p = 0.000$
mean degrees ± SD	± 4.06	± 5.12	± 4.89	± 6.04	± 6.79	(ANOVA)
Percentage reduction of penile curvature	−15.029	−17.144	−22.342	−30.596	−58.067	$p = 0.000$
mean rate, % ± standard deviation	± 20.570	± 18.362	± 17.449	± 16.171	± 22.871	(ANOVA)
Resolution of penile curvature						
mean rate, %	0	0	0	0	9.5	$p = 0.565$
patients/total patients (n/N)	(0/20)	(0/19)	(0/19)	(0/21)	(2/21)	(χ^2 test)
Worsening in penile curvature						
mean rate, %	0	0	0	0	0	$p = 1.000$
patients/total patients (n/N)	(0/4)	(0/5)	(0/5)	(0/3)	(0/3)	(χ^2 test)
Penile rigidity						
Improvement in penile rigidity in patients with ED						
mean rate, %	57.1	75.0	85.7	100.0	100.0	$p = 0.452$
patients/total patients (n/N)	(4/7)	(6/8)	(6/7)	(8/8)	(9/9)	(χ^2 test)
Recovery of penile rigidity in patients with ED						$p = 0.043$
mean rate, %	28.57	50.0	71.4	100.0	100.0	(χ^2 test)
patients/total patients (n/N)	(2/7)	(4/8)	(5/7)	(8/8)	(9/9)	
Improvement in IIEF-EF score in patients with ED, mean score ± SD	+ 0.8 ± 0.8	+ 2.1 ± 2.6	+ 2.4 ± 2.5	+ 3.2 ± 2.5	+ 4.4 ± 2.4	$p = 0.047$ (ANOVA)
Improvement in IIEF-EF score in patients without ED, mean score ± SD	+ 0.4 ± 0.5	+ 0.6 ± 0.5	+ 0.8 ± 0.6	+ 1.2 ± 0.5	+ 1.4 ± 0.6	$p = 0.000$ (ANOVA)

(*Continued*)

Table 2 (*Continued*)

	Group A (n = 24) Silymarin	**Group B (n = 24) Silymarin + Ginkgo**	**Group C (n = 24) Silymarin + Ginkgo + vitamin E**	**Group D (n = 24) Silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac**	**Group E (n = 24) Silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac + pentoxifylline injection**	**Statistical analysis Between-group** comparisons
Appearance of ED in patients with normal penile rigidity						
mean rate, %	0	0	0	0	0	$p = 1.000$
patients/total patients (n/N)	(0/17)	(0/16)	(0/17)	(0/16)	(0/15)	(χ^2 test)
Symptom bother						
Improvement in PDQ score (PD symptom bother/psychosexual impact) mean score ± SD	−1.37 ± 0.57	−1.79 ± 0.88	−2.08 ± 0.88	−2.50 ± 0.78	−3.41 ± 1.05	$p = 0.000$ (ANOVA)

Abbreviations: ED, erectile dysfunction; SD, standard deviation; PI-NRS, pain intensity numeric rating scale; IIEF-EF, international index of erectile function - erectile function score; PD, Peyronie's disease; PDQ, Peyronie's disease questionnaire.

patients without this symptom; increase in the intensity of penile pain in patients with this symptom; worsening in penile curvature; onset of ED in patients with normal penile rigidity; or increase of psychosexual impact caused by PD.

Evaluation of the tolerability of the substances

Table 4 lists the side effects by the therapy administered. In general, tolerability was satisfactory after individual (silymarin) or multimodal therapy. No side effect occurred after intake of propolis and/or bilberry. For all therapy arms, recorded side effects (Table 4) were mild and transient and disappeared gradually in the course of treatment. In no case was it necessary to suspend treatment. Onset of penile tumescence after perilesional infiltration of PTX occurred in a single patient and at almost every injection (10 times out of 12), without being associated with other side effects. We did not consider this occurrence as an adverse effect, but merely an effect of the well-known non-specific phosphodiesterase (PDE)-inhibiting action of PTX; therefore, we decided not to interrupt the cycle of local injections. This patient (30 years old) was the youngest in group E, his baseline IEEF score was 26 (normal IIEF scores: 26–30), and his score increased to 29 after multimodal treatment. In our study, no marked or severe adverse effect occurred.

Discussion

The properties and mechanism of action of the substances used in this study are already known, but we provide a brief overview of this topic.

PTX is a hemorrheologic agent that was initially used to treat peripheral vascular diseases. PTX has antioxidant, anti-inflammatory, and antifibrotic activity[56–61] and is also a non-specific PDE inhibitor.[62]

Propolis is a plant-based substance, processed by bees (*Apis mellifera L.*), which consists of a mixture of compounds mainly comprising flavonoids (acacetin, apigenin, catechin, chrysin, galangin, kaempferol, luteolin, myricetin, naringenin, pinocembrin, quercetin, and rutin), as well as caffeic acid and caffeic acid phenethyl ester (CAPE). Because of its many components, propolis has antioxidant, anti-inflammatory, and antifibrotic properties.[63–66]

Bilberry (*Vaccinium myrtillus* L.) contains several substances, including anthocyanins (cyanidin, delphinidin, petunidin, malvidin, and peonidin) as well as quercetin, tannins, ellagitannins, catechin, epicatechin, gallocatechin, and epigallocatechin, as well as small quantities of vitamin C. Thanks to its various components, bilberry has antioxidant, anti-inflammatory, and antifibrotic activity.[66–68]

Vitamin E has various properties: it is an antioxidant, anti-inflammatory, and antifibrotic agent, and acts against cell proliferation via a mechanism of protein kinase C (PKC) inhibition.[17,69–71] A recent study by these authors showed the effectiveness of vitamin E when associated with other substances.[72]

Silymarin, from milk thistle, has long been used as a hepatoprotective agent; it also has antifibrotic, anti-inflammatory, and antioxidant properties.[73–75]

Ginkgo biloba, through its extract, has mainly been used to treat memory and concentration problems, but various

Table 3 Between-group comparison of outcomes 6 months of treatment

Outcomes measures	A versus B	A versus C	A versus D	A versus E	B versus C	B versus D	B versus E	C versus D	C versus E	D versus E
Pain resolution	$p = 0.725$ (χ^2 test)	$p = 0.082$ (χ^2 test)	**$p = 0.009$ (χ^2 test)**	**$p = 0.009$ (χ^2 test)**	$p = 0.300$ (χ^2 test)	**$p = 0.027$ (χ^2 test)**	**$p = 0.027$ (χ^2 test)**	$p = 0.478$ (χ^2 test)	$p = 0.478$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Reduction in pain intensity	**$p = 0.027$ (t-test)**	**$p = 0.000$ (t-test)**	**$p = 0.001$ (t-test)**	**$p = 0.001$ (t-test)**	$p = 0.162$ (*t-test*)	$p = 0.052$ (*t-test*)	$p = 0.075$ (*t-test*)	$p = 0.664$ (*t-test*)	$p = 0.538$ (*t-test*)	$p = 0.853$ (*t-test*)
Appearance of penile pain	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Plaque volume reduction	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ **(χ^2 test)**	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Reduction in plaque volume	$p = 0.276$ (*t-test*)	**$p = 0.014$ (t-test)**	**$p = 0.0007$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.182$ (*t-test*)	**$p = 0.009$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.082$ (*t-test*)	**$p < 0.0001$ (t-test)**	**$p < 0.0001$ (t-test)**
Increase in plaque volume	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Improvement in penile curvature	$p = 0.869$ (χ^2 test)	$p = 0.233$ (χ^2 test)	**$p = 0.012$ (χ^2 test)**	**$p = 0.012$ (χ^2 test)**	$p = 0.313$ (χ^2 test)	**$p = 0.020$ (χ^2 test)**	**$p = 0.020$ (χ^2 test)**	$p = 0.327$ (χ^2 test)	$p = 0.327$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Decrease of penile curvature angle	$p = 0.338$ (*t-test*)	$p = 0.068$ (*t-test*)	**$p = 0.002$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.439$ (*t-test*)	**$p = 0.039$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.157$ (*t-test*)	**$p = 0.0006$ (t-test)**	**$p = 0.026$ (t-test)**
Percentage reduction of penile curvature	$p = 0.737$ (*t-test*)	$p = 0.240$ (*t-test*)	**$p = 0.010$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.377$ (*t-test*)	**$p = 0.018$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.128$ (*t-test*)	**$p < 0.0001$ (t-test)**	**$p < 0.0001$ (t-test)**
Resolution of penile curvature	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 0.490$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 0.513$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 0.513$ (χ^2 test)	$p = 0.468$ (χ^2 test)
Worsening in penile curvature	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Improvement in penile rigidity in patients with erectile dysfunction	$p = 0.854$ (χ^2 test)	$p = 0.554$ (χ^2 test)	$p = 0.154$ (χ^2 test)	$p = 0.125$ (χ^2 test)	$p = 0.604$ (χ^2 test)	$p = 0.449$ (χ^2 test)	$p = 0.399$ (χ^2 test)	$p = 0.944$ (χ^2 test)	$p = 0.898$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Recovery of penile rigidity in patients with erectile dysfunction	$p = 0.751$ (χ^2 test)	$p = 0.285$ (χ^2 test)	**$p = 0.017$ (χ^2 test)**	**$p = 0.011$ (χ^2 test)**	$p = 0.751$ (χ^2 test)	$p = 0.083$ (χ^2 test)	$p = 0.063$ (χ^2 test)	$p = 0.388$ (χ^2 test)	$p = 0.340$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Improvement in IIEF-EF score in patients with erectile dysfunction	$p = 0.227$ (*t-test*)	$p = 0.132$ (*t-test*)	**$p = 0.0307$ (t-test)**	**$p = 0.002$ (t-test)**	$p = 0.824$ (*t-test*)	$p = 0.402$ (*t-test*)	$p = 0.077$ (*t-test*)	$p = 0.547$ (*t-test*)	$p = 0.126$ (*t-test*)	$p = 0.328$ (*t-test*)
Improvement in IIEF-EF score in patients without erectile dysfunction	$p = 0.259$ (t-test)	**$p = 0.042$ (t-test)**	**$p < 0.0001$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.307$ (*t-test*)	**$p = 0.002$ (t-test)**	**$p = 0.0004$ (t-test)**	**$p = 0.046$ (t-test)**	**$p = 0.008$ (t-test)**	$p = 0.320$ (*t-test*)
Appearance of erectile dysfunction in patients with normal penile rigidity	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)	$p = 1.000$ (χ^2 test)
Improvement in PDQ score (PD symptom bother/psychosexual impact)	$p = 0.005$ (t-test)	**$p = 0.001$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.259$ (*t-test*)	$p = 0.259$ (*t-test*)	**$p = 0.004$ (t-test)**	**$p < 0.0001$ (t-test)**	$p = 0.086$ (*t-test*)	**$p < 0.0001$ (t-test)**	**$p = 0.001$ (t-test)**

Notes: Data in bold indicates statistical significance. *p*-value (χ^2 test and *t*-test). Treatments in the different groups: group A = silymarin; group B = silymarin + Ginkgo; group C = silymarin + Ginkgo + vitamin E; group D = silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac; and group E = silymarin + Ginkgo + vitamin E + propolis + bilberry + topical diclofenac + pentoxifylline injection.

Abbreviations: IIEF-EF, international index of erectile function - erectile function score; PDQ, Peyronie's disease questionnaire; PD, Peyronie's disease

Table 4 Side effects for each substance

Side effects	Silymarin	Ginkgo	Vitamin E	Propolis	Bilberry	Topical diclofenac	PTX penile injection
Headache	0	1.04% (1/96)	0	0	0	0	0
Hot flushes	0	2.08% (2/96)	0	0	0	0	0
Dyspepsia	0	0	1.3% (1/72)	0	0	0	0
Nausea	0	0	1.3% (1/72)	0	0	0	0
Abdominal tract discomfort/pain	0.8% (1/120)	0	0	0	0	0	0
Constipation	0.8% (1/120)	0	0	0	0	0	0
Meteorism	0	0	1.3% (1/72)	0	0	0	0
Mild local skin irritation	0	0	0	0	0	2.08% (1/48)	0
Penile tumescence	0	0	0	0	0	0	4.1% (1/24)
Incidence rate for each substance	1.6% (2/120)	3.1% (3/96)	4.1% (3/72)	0 (0/48)	0 (0/48)	2.08% (1/48)	4.1% (1/24)

Note: Data presented as % cases / total cases (n/N).

studies have shown it has antioxidant, antifibrotic, and anti-inflammatory properties.[76–80]

Diclofenac has anti-inflammatory, analgesic, and antioxidant activity, but its antifibrotic activity has also been ascertained, as it has been shown to inhibit fibroblast proliferation.[81–84]

As a topical spray gel, diclofenac has excellent penetration capacity. Studies have identified the presence of high concentrations of diclofenac in the synovial tissue of the knee joint after topical administration of diclofenac sodium 4% spray gel.[85] With the proven efficacy of diclofenac in the treatment of large-joint inflammation where the joint-capsule thickness is, on average 1–5 mm thick, and – in particular – in knee-joint inflammation (joint-capsule thickness ~2 mm), it was inferred that topical application of diclofenac in its 4% spray gel formulation could easily allow drug penetration into the corpora cavernosa as the thickness of the tunica albuginea varies from 0.5 to 2 mm.[86] Combining a nonsteroidal anti-inflammatory drug (NSAID) with antioxidants means taking a combined – or multimodal – treatment approach. It is possible to clearly infer from the results of our study that the combination of several active substances in PD treatment leads to a proportionally greater therapeutic effect.[87] The results show that the higher the number of substances used in treatment, the higher the reduction in pain score, and this is also true for all other study endpoints: the number of patients in whom a reduction in the degree of penile curvature was observed was greater when a higher number of treatment substances was used. The same was true with regard to the recovery of normal penile rigidity, for instance. Table 3 shows that, whereas in general there are no statistically significant differences in results between certain contiguous groups (A vs B, B vs C, and C vs D), an extremely relevant statistically significant difference was observed between groups D and E ($p < 0.0001$), proving that perilesional PTX injections significantly improve the global effectiveness of treatment. In group E, the mean reduction in penile plaque volume was 50.9%, versus 30.5% in group D, where no perilesional PTX injection was administered. The same occurred with regard to the degree of penile curvature: in group E, after 6 months of treatment, the degree of penile curvature dropped, on average, by 58%, compared to a 30.5% reduction obtained in group D ($p < 0.0001$), where no perilesional PTX injection was administered. It must be mentioned that total disappearance of penile curvature was observed only in group E, albeit in two patients out of 21.

Another important consideration is that in this study, regardless of the number of substances used, antioxidants always proved capable of arresting disease progression. This is most likely due to the fact that oxidative stress plays an essential role in the pathogenesis of PD.[16–23]

Conclusion

The results of the present study show that combined therapy with antioxidants is effective in treating PD. Furthermore, the study allows us to observe that the clinical efficacy of

combined therapy is greater when topical use of diclofenac gel and perilesional injection of PTX are added to oral treatment with more than one antioxidant. Although several articles have already been published reporting the effectiveness of combined therapy in PD, this is the first study clearly proving how, as the number of substances used in treatment rises, a proportionally greater therapeutic effect is achieved.[25,26,34–52,72,87]

Though the treatment results we achieved in this study are statistically very significant, further randomized controlled trials are necessary to confirm the efficacy of combined therapy with antioxidants in the treatment of PD.

Disclosure

The authors report no conflicts of interest in this work.

Andrea Paulis (Psychologist) is the son of Gianni Paulis. Andrea collaborates in his father's studies as in other past articles.

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