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LETTER TO EDITOR

Treatment with perilesional injections of Pentoxifylline in patients with Peyronie's disease improves the therapeutic effect of oral and topical antioxidant therapy

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To the Editor,

We conducted a retrospective study to demonstrate that it is possible to achieve better therapeutic outcomes through combining perilesional injections of *pentoxifylline* (PTX) with oral antioxidants and the local application of a cream containing antioxidants and a gel containing diclofenac in patients with *Peyronie's disease* (PD). We compared two similar groups of patients with PD using the two treatments mentioned above. The typical symptoms of PD commonly include penile deformity, penile pain, erectile dysfunction, and psychological distress such as anxiety and depression (1, 2).
PTX is a synthetic methylxanthine derivative that has structural similarities to caffeine and theophylline. Originally created as a hemorheological agent, it was first used to treat peripheral vascular diseases, cerebrovascular insufficiency, diabetic neuropathy, sickle cell disease, and various inflammatory and fibrotic conditions. *Brant et al.* (2006) were the pioneers in utilizing PTX for PD. PTX possesses antifibrotic, anticalcific, antioxidant, anti-inflammatory, antiplatelet, and vasorelaxant properties (3). While some guidelines do not recommend the use of antioxidants such as PTX for treating PD, there have been numerous published therapeutic cases involving PTX, either on its own or in combination with other antioxidant and non-antioxidant therapies (3-6). All of these clinical studies in the literature, in which PTX has been used, have demonstrated that this drug is able to counteract PD due to its ability to interfere with the pathogenetic mechanisms of the disease and reduce the most important symptoms of the disease. In our most recent clinical practice we discontinued oral administration of PTX as we observed a high prevalence (15.7%) of side effects that impact the circulatory system, blood pressure, and intestinal system (6). For these reasons, we are now using PTX only through perilesional penile injections. We have not found other studies in the literature where penile injections of PTX have been used to treat PD.
We performed a retrospective analysis of the clinical database of a single uro-andrology clinic. From the database, we extracted 263 patients with active PD (first stage) who had visited our Peyronie's care center between December 2019 and October 2024. In our clinical archive, all clinical information (medical history and physical examination) and diagnostic tests were available, both before and after treatment. Of these 263 patients, 152 had already undergone combined therapy with oral antioxidants + topical therapy, as well as perilesional penile injections with PTX. The remaining 111 patients had undergone the same oral and topical antioxidant therapy but had not received penile injections with PTX. This latter group of patients decided not to undergo penile injections due to a fear of penile pain and/or logistical reasons related to the great distance between their residence and our treatment center. All 263 patients had undergone at least one 6-month treatment cycle and were potentially able to be divided into two treatment groups, as planned for our study. However, after analyzing the data of all these patients, a clear heterogeneity between the two groups was detected. To ensure statistical homogeneity between the two treatment groups and ensure a similar number of participants in these groups, we conducted further selection and excluded another 159 cases from the study. These cases were excluded based on their clinical characteristics, such as the degree of penile curvature, plaque volume, presence of ED or penile pain, age, onset of the disease, and comorbidities. Finally, after this further selection, we included 104 cases in the study, which we divided into two treatment groups (group A and group B), each consisting of 52 cases.
Treatment characteristics for each group were as follows: Group A received a combination of oral antioxidants and topical creams for 6 months, along with peri-lesional penile injections with PTX every 2 weeks. Group B received the same oral and topical treatments as Group A, but without the penile injections with PTX, for 6 months. The detailed characteristics of the treatment for each therapeutic group are shown in the "*legend*" of the Table 1.

This retrospective study was conducted in compliance with the principles contained in the Declaration of Helsinki (*Fortaleza, 2013*); all study subjects were contacted and provided informed consent for study inclusion. All patients were informed that treatment with penile injections of pentoxifylline is an "off-label" therapy. Sensitive data were anonymized to warrant patients' privacy according to Legislative Decree 10 August 2018, n. 101, published in the *Official Gazette of the Italian Republic, General Series, issue 205, 09/04/2018*. All 104 PD patients underwent photographic documentation of penile curvature (according to Kelâmi) and dynamic *Penile dynamic Doppler ultrasound* (PDDU) with plaque and volume measurements and answered the following questionnaires: the *Generalized Anxiety Disorder-7* (GAD-7), the *Patient Health Questionnaire-9* (PHQ-9), the *Visual Analog Scale* (VAS) for penile pain measurements, the *International Index of Erectile Function* (IIEF), and the *Peyronie's Disease Questionnaire* (PDQ, Symptom Bother Domain) for the evaluation of the psychosexual impact of the disease.

Table 1.

Clinical results (related to the reduction and/or the regression of PD symptoms, plaque volume, and its internal calcification) after 6 months of treatment.

Clinical results	Group A n. 52 cases treated with oral and topical antioxidants + PTX injections	Group B n. 52 cases treated only with oral and topical antioxidants without PTX injections	Statistical analysis Group A versus Group B P-value
Decrease in plaque volume Mean rate % ± SD	 - 39.5 ± 11.4	 - 19.5 ± 7.3	P < 0.0001 (t-test)
Decrease in calcification within the plaque Mean rate % ± SD	 - 62.9 ± 19.5	 - 19.2 ± 20.5	P < 0.0001 (t-test)
Decrease of the penile curvature angle Mean decrease (in degrees °) ± SD	 - 8.1 ± 6.5	 - 4.4 ± 4.8	P = 0.002 (t-test)
Mean decrease in the VAS score ± SD	- 3.7 ± 1.3	- 2.1 ± 0.9	P < 0.0001 (t-test)
Mean increase in the IIEF score in patients with ED ± SD	 + 3.3 ± 2.9	 + 1.4 ± 1.2	P = 0.006 (t-test)
Mean decrease in the PDQ-bother score in patients with psychosexual impact by PD ± SD	 - 5.3 ± 1.8	 - 3.6 ± 1.3	P < 0.0001 (t-test)
Mean decrease in the GAD-7 score in patients with anxiety ± SD	 - 6.1 ± 1.6	 - 4.8 ± 1.9	P = 0.001 (t-test)
Mean decrease in the PHQ-9 score in patients with depression ± SD	 - 4.5 ± 1.4	 - 2.7 ± 0.9	P < 0.0001 (t-test)
N. patients with complete plaque regression (%)	0 (out of 52) 0	0 (out of 52) 0	P = 1.000 (χ^2 test)
N. patients with complete regression of the calcification present in the plaque (%)	1 (out of 11) 0.9	0 (out of 10) 0	P = 0.350 (χ^2 test)
N. patients with disappearance of penile curvature (%)	0 (out of 45) 0	0 (out of 47) 0	P = 1.000 (χ^2 test)
N. patients with disappearance of penile pain (%)	26 (out of 27) 96.2	3 (out of 28) 10.7	P < 0.0001 (χ^2 test)
N. patients with disappearance of ED (%)	11 (out of 26) 42.3	2 (out of 25) 8.0	P = 0.01 (χ^2 test)
N. patients with disappearance of psychosexual impact by PD (%)	0 (out of 51) 0	0 (out of 52) 0	P = 1.000 (χ^2 test)
N. patients with disappearance of significant anxiety (%)	35 (out of 46) 76.08	26 (out of 45) 57.7	P = 0.102 (χ^2 test)
N. patients with disappearance of significant depression (%)	27 (out of 33) 81.8	14 (out of 33) 42.4	P = 0.002 (χ^2 test)

Group A: Orally: L-carnitine 1000 mg + propolis 700 mg + Ginkgo biloba 240 mg + bilberry 180 mg + coenzyme Q-10 100 mg + silymarin 400 mg + Boswellia 200 mg + vitamin C 50 mg + vitamin E 48 mg + superoxide dismutase 11,000 IU/g 10 mg daily for 6 months; Topically: cream with propolis and hyaluronic acid 2x daily + diclofenac gel 4% daily for 6 months; Peri-lesional penile injections: PTX 60 mg (with 30 G needle) every 2 weeks for 6 months.

Group B: The same oral antioxidants and topical treatments as Group A for 6 months (without peri-lesional penile injections with PTX).

PD = Peyronie's disease. ED = erectile dysfunction; PTX = Pentoxifylline; SD = standard deviation; $\chi 2$ test = chi-squared test. t-test = Student's t-test.

VAS = Visual analog scale, for pain assessment, score range 0-10. Interpretation of score: mild to moderate pain = 1-5, severe pain = 6-7, very severe pain = 8-10.

IIEF = International Index of Erectile Function, score range 0-30. Interpretation of score: severe ED = 0-10, moderate ED = 11-16, mild to moderate ED = 17-21, mild ED = 22-25, and no ED = 26-30.

PDQ symptom-bother = Peyronie's Disease Questionnaire symptom bother, to evaluate the psychosexual impact, score range 0-16. Interpretation of score: mild bother 1-4, medium bother 5-8, high bother 9-12, severe bother 13-16.

GAD-7 = Generalized Anxiety Disorder-7 questionnaire, for the assessment of anxiety, score range 0-21. Interpretation of score: minimal anxiety = 0-4, mild anxiety = 5-9, moderate anxiety = 10-14, and severe anxiety = 15-21.

Significant anxiety when GAD-7 score > 9.

PHQ-9 = Patient Health Questionnaire-9, for depressive disorder, score range 0-27. Interpretation of score: minimal depression = 0-4, mild depression = 5-9, moderate depression = 10-14, moderately severe depression = 15-19, severe depression = 20-27.

Significant depression present when PHQ-9 score > 9.

P-value: if the p-value is < 0.05, it is judged as significant; if the p-value is > 0.05, it is judged as not significant.

The endpoints of this study were related to the reduction and/or regression of PD symptoms, plaque volume, and its internal calcification.
Our results show that patients in the two treatment groups did not differ in age and most of the associated conditions and comorbidities. At the end of the treatment, we visited all patients again and subjected them to the same diagnostic tests that were performed before treatment.
Statistical analysis of the results after 6 months of treatment highlighted significant differences between the outcomes of the two groups (Group A *versus* Group B), in terms of improvement in penile pain, effective reduction in plaque size, improvement in penile curvature, improvement in IIEF score, and reduction in the psychological impact of PD. Significantly better reduction of PD symptoms, plaque volume, and its internal calcification, was always observed by the addition of perilesional penile injections with PTX (group A) when compared to the oral and topical administration of antioxidants and diclofenac gel alone (group B) (see Table 1). An higher statistically significant regression rate of PD symptoms, plaque, and its internal calcification was observed for Group A (compared to Group B) only for three clinical evaluations: disappearance of penile pain, disappearance of ED, and disappearance of significant depression (see Table 1).
We did not observe any side effects after the use of oral and topical substances.
We only observed in one case a small bruise at the site of PTX injection, which resolved at about 5 days after the injection.
The results of our present study revealed that the combination of periodic perilesional penile injections with PTX significantly increases the therapeutic efficacy, when compared to oral and topical antioxidant therapy alone. Although the therapeutic response to the combination of oral and topical antioxidants (Group B) after 6 months was certainly good, in terms of improvement of all PD symptoms, penile injections with PTX combined with other oral and topical antioxidants (Group A) allowed us to achieve results that were unequivocally superior to those obtained without penile injections (Group B).
The limitations of our study are related to the absence of a control group comprising PD patients not receiving any therapy. As PD is a chronic progressive disease, it would be deemed unethical to withhold treatment, even for the purpose of a research study.
We believe that our therapeutic success in treating PD was mainly due to the addition of penile perilesional injections with PTX to the oral and topical antioxidant therapy. We also consider the following factors to be important: careful selection of antioxidants to use, performing penile ultrasound examination with a modern ultrasound device with an elastography module that allows for very precise measurements of the plaque, and assigning the ultrasound examination to a physician with extensive experience in PD cases.
As we observed high rates of significant anxiety and depression in PD patients, we believe that psychotherapy should be associated with medical treatment for PD patients, in order to improve their quality of life.
Although the treatment results obtained in this study were highly statistically significant, we believe that further randomized and controlled studies with a larger number of cases are needed to confirm the effectiveness of penile injection therapy with PTX.

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Declarations

Ethical approval: *Our study, being a retrospective study, does not require approval from an ethics committee according to current regulations, and in any case it received approval from the Castelfidardo Ethical Commission (protocol code #00243, date of approval 10 September 2024) for studies involving human.*

Availability of data and material: *All inquiries can be directed to the corresponding author (paulisg@libero.it).*

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