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ORIGINAL PAPER

Quality of life of patients with La Peyronie's disease undergoing local iontophoresis therapy: A longitudinal observational study

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Summary ***Objectives: La Peyronie's disease tends to be underdiagnosed and undertreated. In Italy it affects about 7% of the population aged between 50 and 70 years old. The aim of this study is to evaluate the quality of life of patients undergoing iontophoretic therapy with verapamil and treatment outcomes at a two-year interval.***
Materials and methods: This study evaluated 128 patients subjected to treatment cycles over a period of two years. Questionnaires were administered to the patients at the beginning and end of each cycle of iontophoretic therapy in order to monitor the degree of presumed anxiety, depression, pain and the associated quality of life.
Result: This prospective descriptive observational study included 128 patients aged between 42 and 74 years presenting pain during erection and/or coital intercourse, which ceased in 108 cases, diminished in 12 and remained present in 4. Concerning the penile deviation, which was present in all patients (128 cases), it disappeared in 6 cases, regressed in 90 cases, while it remained unchanged in 32 cases. As for the plaque consistency on palpation, in 42 patients the plaque was no longer present, in 50 cases the consistency diminished, while in 36 patients it remained unchanged. None of the cases evidenced an aggravation of the clinical condition. 57% of the evaluated patients had high levels of anxiety in the first cycle of iontophoretic sessions and low levels of depression. Anxiety decreased in 32% of cases. Depression was not related to pain but to sexual dysfunction. About 80 % of the patients assessed had an increase in quality of life at the end of the two-year follow-up.
Conclusions: In conclusion, it can be claimed that iontophoresis combined with verapamil therapy can improve patients' quality of life and offer them psychophysical well-being and an acceptable sexual relationship, thus decreasing anxiety and depression levels.

KEY WORDS: La Peyronie's disease; Penis induration; Iontophoresis; Local therapy; QOL.

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INTRODUCTION

Induratio Penis Plastica, or "*La Peyronie's disease*", is a connective tissue disease involving the tunica albuginea of the corpora cavernosa of the penis and characterized by an inflammatory plaque that becomes progressively more fibrous and inelastic; it often leads to penile deformation (the so-called '*recurvatum penis*') (1). La Peyronie's disease tends to be underdiagnosed and undertreated, and in Italy it affects about 7% of the male population aged between 50 and 70. Several studies indicate a prevalence in adult men between 3.2 and 13.1% and an incidence of 15.9% after radical prostatectomy (2). Two stages of the disease are recognized: the first, the so-called inflammatory stage, characterized by painful erections and the development of fibrous nodules, and the second, the so-called stabilized fibrotic stage, in which the plaques are consistent, hard, fibrotic-calcific and cause deformities (recurvatum) of the penis, sometimes to the extent that coitus becomes difficult if not impossible. The disease is often unruly (3). Spontaneous resolution is rare (3-13%), with most patients either progressing with the disease (30-50%) or stabilizing (45-65%). General factors such as autoimmune diseases, vitamin deficiencies, enzymatic alterations, neurohormonal imbalance, local factors like microtrauma, local vasculitis and predisposing factors including age, family history and collagenopathies have been suggested as causes. The most common risk factors are diabetes, hypertension, smoking, alterations in lipid metabolism and the association with Dupuytren's disease (retraction of the palmar aponeurosis) (4-6). The treatment can be medical or surgical, thus medical treatment is mainly intended for patients in the early stages of the disease, i.e. when pain is present and the plaques are not yet intensely fibrotic or calcified (1). There are many therapeutic options, ranging from the use of oral treatments with drugs belonging to different pharmacological categories (anti-inflammatory drugs, vitamins, potassium paraminobenzoate, tamoxifen, etc.); shock waves; intraplate injections with steroid drugs, collagen, vasodilators, interferons; and iontophoresis (transdermal delivery of polarized drugs by means of a bipolar electric current) (1-3).
Medical therapy with iontophoresis is a non-invasive therapy that enables the drug applied to penetrate inside the corpora cavernosa without using needles or other invasive procedures (7). *Levine and Estrada* in 2003 conclusively demonstrated the efficacy of iontophoresis after measuring Verapamil concentrations (very elevated) in the albuginea of patients operated for PPI and treated precociously with

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iontophoresis (*Verapamil*) (8). The aim of the present study was to assess the quality of life of patients undergoing treatment with iontophoresis and treatment outcomes at a two-year interval. Pain, quality of sexual life, stress and depression disorders were monitored (9, 10). The following questionnaires and scales were used: *Numerical Rating Scale* (NRS) (for pain assessment); GAD -7, *General Anxiety Disorder-7* scale (for the assessment of anxiety); *Beck Depression Inventory* (BDI) (for the assessment of depression) and *QOL Quality of Life Index* questionnaire (for assessment of quality of life). All instruments are described in the following (Materials and Methods) paragraph.

Materials and methods

The study evaluated 128 patients treated as outpatients at the *Città di Alessandria Clinic* and at an outpatient private clinic. The patients underwent cycles of treatment over a two-year period according to the scheme illustrated below. Each cycle included 12 sessions (two sessions per week for about three months). At the end of each cycle the patient suspended treatment for a period of one month.
Assessment scales and a questionnaire were administered before and at the end of each therapy cycle. Iontophoresis is a medical treatment, whereby a drug is released into the body through intact skin (transcutaneous administration) using a low-intensity electric current produced by a special generator.
Essentially, it could be considered a 'needle-free' injection. The advantages of administering drugs in this way are mainly that:

– without systemic administration (oral, intramuscular, intravenous) possible side effects of the drug can be minimized
– applying the drug directly to the disease affected body site, treatment and symptom regression time can be reduced
– enabling the introduction of the active ingredient alone, without the presence of conveyors (excipients), can protect against adverse reactions
– allowing the ions to bind to certain protoplasmic proteins, increasing residence time (half-life) in the anatomical sites concerned, can reduce the quantity of drug implemented for the same disease compared to other administration approaches.
– permitting to hyperpolarize nerve endings.

Having overcome all the drawbacks of taking a drug orally or by infiltration, it is now an advantage to apply the substance directly to the area to be treated, thus reducing the treatment time, with consequent faster symptom regression. The second advantage is the possibility of introducing only the active ingredient of the drug, in an ionic form, without the excipients, which are often the source of variable adverse reactions. The third advantage is that the drug, in an ionic form, binds to specific protoplasmic proteins, increasing the time it spends in the anatomical sites concerned (half-life), which leads to a reduction in the quantities of drug needed for the same condition compared to other administration approaches. The drug used may have either a positive or negative polarity, and in accordance with this, it is placed respectively on the cathode or anode, i.e., on the electrode of the same polarity, while the other electrode will be soaked in water. By applying the electric field, the electricity will carry the drug across the epidermal barrier.
Verapamil is one of the most commonly used drugs. Injected into the plaque, it acts on fibroblasts by inhibiting the formation of extracellular collagen and free radicals. Levine administered to 38 men 4 mg of verapamil every 2 weeks for 24 weeks. All patients were assessed before and after treatment with an echography, rating scales and questionnaires. The results evidenced a remission of pain in 97%, an improvement in sexual function in 72% and a reduction in the curvature in 54% of patients (1, 4, 5).

Local assessment

The parameters used to assess the effectiveness of the treatment were: plaque consistency, penile deviation, and pain during erection and/or coitus.
The development of the condition, both in a regressive as in a progressive sense, was evaluated both clinically and by echography and in some cases also by self-photography.
In terms of the results, an overall assessment was given, distinguishing between:

- unchanged or worsened; if the parameters described above had not undergone any change or had worsened.
- Improved; when there had been a resolution of the pain or an improvement in one of the previously described parameters;
- cured; when, in addition to the absence of pain and plaques, there was also complete resolution of the penile deviation.

Instruments used for evaluation

At the beginning and at the end of each cycle of iontophoretic therapy, the scales and questionnaires listed below were submitted to the patients with the aim of monitoring the level of presumed anxiety, depression and pain and the consequent quality of life.

Numerical Rating Scale - NRS (Downie, 1978; Grossi, 1983)
This is a one-dimensional quantitative 11-point numerical pain rating scale; the scale requires the practitioner to ask the patient to select the number that best describes the intensity of his or her pain, from 0 to 10, at that precise moment.

The Quality of Life Index - QL-Index (Spitzer et al., 1981)
The EuroQol is a generic health questionnaire that includes 5 dimensions: mobility, self-care, usual activities, pain, anxiety/depression. For each dimension the questionnaire investigates whether the subject has severe problems, moderate problems, or no problems at all. The questionnaire also includes a visual analogical scale from 0 to 100 to indicate the perceived level of health status of the respondent. The EQ-5D is a widely used instrument in many countries. It is also recommended for use in studies evaluating the cost-effectiveness of interventions.

Generalized Anxiety Disorder Scale (GAD-7)
The GAD-7 (*Spitzer et al*., 2006) is a self-completed 7-question questionnaire (Likert scale 0 to 3) for the assessment of the anxiety condition (cut-off ≥ 8). The *Beck Depression*

Inventory (BDI) is a self-assessment tool consisting of 21 multiple-choice items. According to Beck, depressed patients are characterized by a negative triad, i.e. negative representations of themselves, the Present and the Future.

Statistical analysis

Since this is an exploratory observational study, the scales used to measure the quality of life of patients have been analyzed with descriptive methods. As a bivariate correlation coefficient the Pearson correlation coefficient r was calculated. Descriptive statistics were used for all variables using SPSS version 25.

Table 1.
Clinical results.

Clinical Parameters	Patients N	Disappeared F	%	Regressed F	%	Unchanged F	%	Worsened F	%
Pain during erection and/or coitus	124	108	87.1	12	9.7	4	3.2	0	0.0
Penile deviation	128	6	4.7	90	70.3	32	25.0	0	0.0
Plaque consistency	128	42	32.8	50	39.1	36	28.1	0	0.0

Table 2.
Results of the scale GAD 7 (anxiety).

GAD 7 0/3	I cycle		II cycle		III cycle		IV cycle	
Anxiety	3 months		3 months		3 months		3 months	
Total score	Mean value	Std dev	Mean value	Std dev	Mean value	Std dev	Mean value	Std dev
First year	10.53	4.17	8.21	3.11	8.42	3.04	8.55	3.07
Second year	8.38	3.11	8.52	3.18	8.37	3.25	8.11	3.02

Table 3.
Results BDI (depression).

BDI: 0/3	I cycle		II cycle		III cycle		IV cycle	
Depression	3 months		3 months		3 months		3 months	
Total score	Mean value	Std dev	Mean value	Std dev	Mean value	Std dev	Mean value	Std dev
First year	15.34	5.42	15.47	4.92	17.63	5.71	18.44	6.17
Second year	14.92	6.55	14.47	5.40	14.23	5.30	13.98	5.15

Results

This is a prospective observational study. A total of 128 patients aged between 42 and 74 years were assessed. Twenty-four of these patients had never undergone any treatment before, while the remaining (104) had undergone one or more treatments both systemically and locally. The total dosage in milligrams of the drug used is 4 mg per session. In no case was it necessary to suspend the treatment due to complications.

Considering the various parameters, pain in erection and/or coitus disappeared in 108 (87.1%) cases while it regressed in 12 and remained present in 4 patients. There were no cases of worsening (Table 1). Pain variations along the two years of treatment are presented in Figure 1. Regarding penile deviation, which was present in 128 cases, it disappeared in 6 cases, regressed in 90 cases, while it remained unchanged in 32 cases and worsened in 0 cases. Finally, as far as the consistency of the plaque is concerned, in 42 patients the plaque disappeared, in 50 cases the consistency of the plaque regressed, while in 36 patients it remained unchanged. There were no cases of worsening (Figure 2).

Regarding the levels of anxiety and depression we can state that about 57% of patients evaluated had high levels of anxiety (average 2 on the individual items of the scale) in the first cycle of iontophoretic sessions and low levels of depression (average 15). Anxiety decreased in 32% of cases even though the treatment did not bring immediate benefits (Table 2). In the following months depression scores averaged 18 by the end of the first year and averaged 14 (no depression) in the second year of treatment. Depression was not related to pain but to sexual dysfunction (Table 3).

The EQ-5 questionnaire in the examined population (128 patients) did not reveal any problems in the areas of: ability to move, personal care, habitual activities.

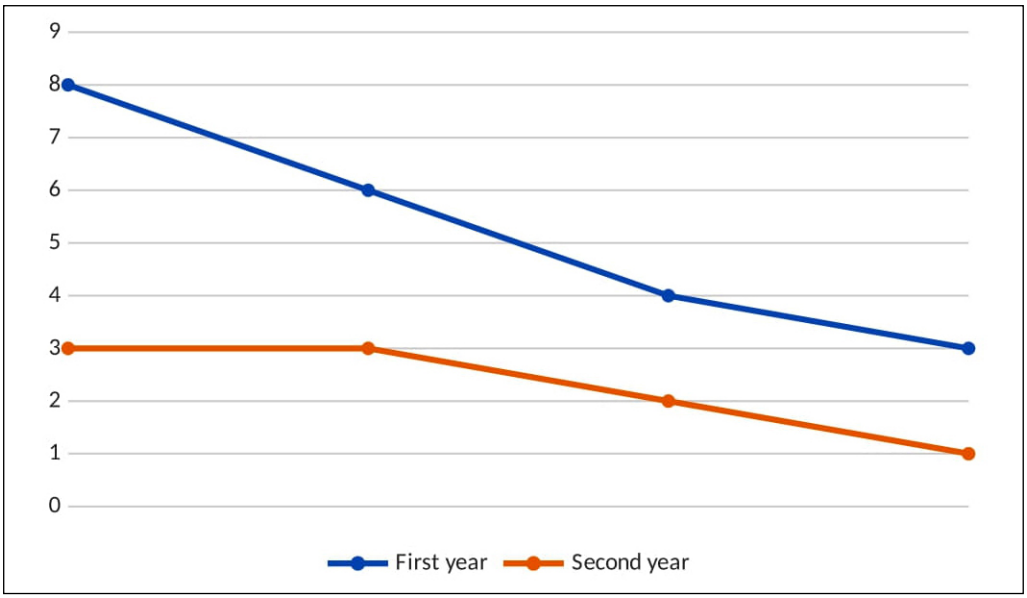

Figure 1.
Graphical representation of pain variation along the two years of treatment.

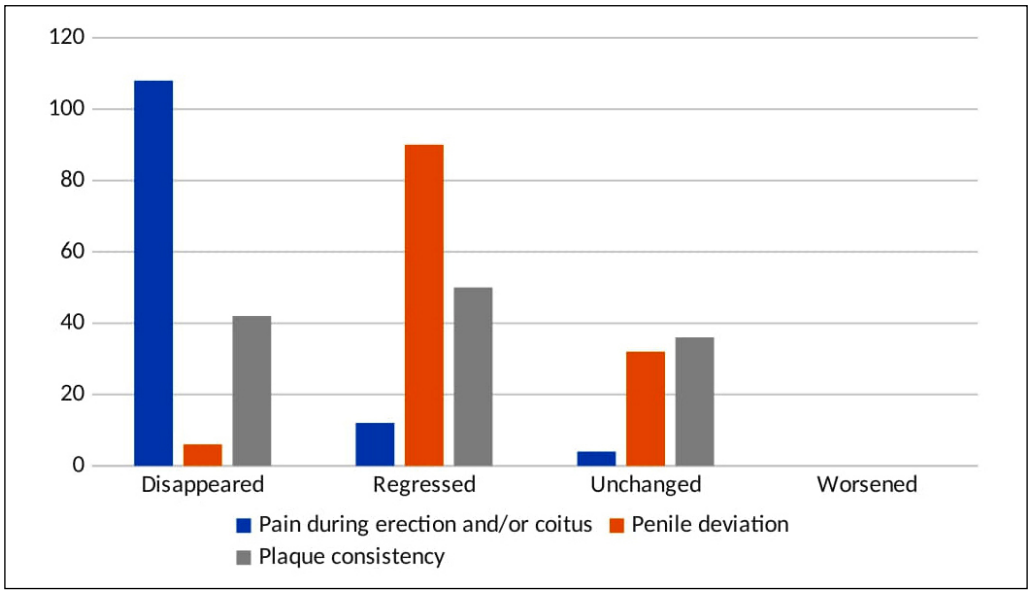

Figure 2.
Clinical results (graphics).

Table 4.
Results of the scale EQ (quality of life).

Patients n = 128 EQ 1/3	I cycle		II cycle		III cycle		IV cycle	
generic health	3 months		3 months		3 months		3 months	
First year	**Mean value**	**Std dev**	**Mean value**	**Std dev**	**Mean value**	**Std dev**	**Mean value**	**Std dev**
mobility	1.43	0.61	1.31	0.59	1.27	0.52	1.31	0.59
salf-care	1.22	0.42	1.18	0.39	1.14	0.35	1.18	0.39
usual activities	1.25	0.45	1.23	0.44	1.20	0.42	1.23	0.44
pain	2.75	0.43	2.72	0.53	2.70	0.55	2.71	0.53
anxiety/depression	2.88	0.32	2.90	0.30	2.87	0.36	2.88	0.32
EQ: VAS scale 0/100								
perceived level of health status	36.41	16.11	38.24	15.39	40.91	16.92	41	18.32
Second year								
mobility	1.22	0.50	1.20	0.47	1.16	0.39	1.05	0.21
salf-care	1.13	0.34	1.07	0.26	1.06	0.24	1.02	0.12
usual activities	1.16	0.36	1.13	0.33	1.12	0.32	1.06	0.24
pain	2.53	0.59	2.41	0.69	2.41	0.69	2.23	0.81
anxiety/depression	2.52	0.57	2.49	0.58	2.42	0.60	2.20	0.60
EQ: VAS scale 0/100								
perceived level of health status	60.86	18.37	65.47	20.49	66.25	21.05	71.27	19.43

Critical issues emerged in the areas of pain and discomfort, anxiety, or depression.
In these domains the levels were almost always at a maximum for the first year of assessment and this resulted in low levels of quality of life. The most frequently reported value (according to a score between 0 and 100) was between 30 and 50 in the first year of treatment and between 60 and 80 in the second year of treatment. At the end of the two years of treatment, quality of life improved and levels of anxiety and depression decreased in 68% of cases (Table 4).

Discussion

Based on the above results, it can be observed that the most relevant data is that on the symptom of erection and/or coital pain. In fact, this pain disappeared or regressed in a high percentage of cases (120 patients, i.e., 97%). As far as penile deviation is concerned, the results were extremely encouraging, since in 90 cases (94%) there was regression and in 42 patients (70%) this also led to the disappearance of the plaque ($p < 0.001$). Regarding the plaque, the results seem positive, particularly in cases where therapy was started at an early stage, where the plaque was single with a fibrous consistency and its diameter was less than 2 cm.
However, the reported results are difficult to compare with the case histories and experience of others because they are not perfectly homogeneous, and under certain aspects, due to difficulty in objectively quantifying the plaques. In our opinion, in fact, the diagnostic tool, rather than being useful for the morphological evaluation and/or for the extension of the plaque, it may help to monitor over time disease progression or to evaluate the therapeutic efficacy.
As to the questionnaire and scales submission, from the analysis of the relative data it is evident that pain diminished from the third session of the first iontophoresis cycle. Mean values are reported in the Table 5.

NRS (0/10) pain	I cycle 3 months		II cycle 3 months		III cycle 3 months		IV cycle 3 months	
	Mean value	**Std dev**	**Mean value**	**Std dev**	**Mean value**	**Std dev**	**Mean value**	**Std dev**
First year	7.73	2.08	6.38	2.42	4.27	1.95	3.43	2.03
Second year	3.28	1.94	3.04	1.85	2.40	1.68	1.13	1.07

Table 5.
Mean values of Numerical Rate Scale (pain) along the follow up of patients.

As illustrated in the table and in the graph, pain had a linear regression trend throughout the two-year period in patients who underwent regular cycles.
The levels of anxiety and depression were variable, since patients associated many times the result of the therapy with the effectiveness of sexual performance, which unfortunately did not always improve with the disappearance of the plaques and there is a lack of patient awareness of other factors, which might influence their quality of life. There are no recent studies, that have examined the levels of anxiety and depression in patients suffering from this condition, so a monitoring over time and the involvement of other centres at a national level would be worthwhile.
Another value of considerable importance emerged from the submission of the QOL 5. The data showed that about 80 % of the patients assessed had an increase in quality of life at the end of the two-year follow-up.
The importance of including QOL among the parameters for assessing the quality of care is effectively underlined by the *American College of Physicians*, which states: "*Assessment of the patient's physical, psychological, and social functioning is an essential part of clinical diagnosis, a crucial determinant of treatment choices, a measure of their effectiveness, and a guide for long-term care planning*".
In measuring health-related quality of life, there is broad consensus regarding its subjective, multidimensional nature and the aspects that are most likely to be affected by disease and should therefore always be considered. These aspects can be summarized in three main dimensions: physical, psychological, and social. The data analysis revealed that as pain decreased, the value of quality of life increased: cycle 1/year 1 r = -0.3 ($p < 0.001$ IC = 95%), cycle 1/year 2 r = -0.7 ($p < 0.001$ IC = 95%), cycle 4/year 2 r = -0.8 ($p < 0.001$ IC = 95%). In summary, we can affirm that therapy with iontophoresis gives good results from the first applications, i.e. in the inflammatory phase. It is therefore important to act in the phase preceding the formation of sclerotic plaques that is prior to the so-called degenerative phase.

Conclusions

Depression and anxiety disorders occur in up to 25% of patients with medical conditions. About 85% of patients with depression have significant anxiety, and 90% of patients with an anxiety disorder have depression.
The symptoms may initially seem vague and non-specific. A careful anamnesis and screening with appropriate tests should be used to make the diagnosis. Once the diagnosis has been made, rating scales can identify the severity of the condition and help monitor the progress of treatment. Both a depressive disorder and a specific anxiety disorder require appropriate treatment. For these reasons, in the case of a patient with Peyronie's disease, it is essential to monitor the progress of treatment from the very beginning of patient care.
In conclusion, it can be asserted that iontophoresis combined with verapamil therapy can improve the patients' quality of life and offer them psychophysical well-being with an acceptable sexual relationship, thus decreasing the levels of anxiety and depression. The improvement in the patients' quality of life induces them to continue therapy cycles with regularity and determination.
Further national and international studies are required to strengthen the results obtained.

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