Actas Urol Esp. 2019;43(4):182–189

Actas Urológicas Españolas

www.elsevier.es/actasuro

ORIGINAL ARTICLE

Ten-year experience with multimodal treatment for acute phase Peyronie's disease: A real life clinical report☆

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Received 30 June 2018; accepted 27 August 2018
Available online 7 April 2019

KEYWORDS
Peyronie's disease;
Multimodal therapy;
Intralesional verapamil injections;
L-arginine;
Pentoxifylline;
Penile traction therapy

Abstract

Objectives: To present our experience with multimodal therapy for Peyronie's disease.
Methods: Retrospective data were collected since 2008–2017. The following features were evaluated at baseline and after treatment: age, duration of disease, erectile function, erected penile curvature, and stretched penile length. All patients were offered the same protocol including: 12 intralesional verapamil injections, oral therapy (OT) – L-arginine 2 g once and pentoxifylline 400 mg 3 times a day for 6 months – and penile traction therapy. The adherence to each of the 3 components of multimodal treatment was evaluated.
Results: One hundred and seventy-seven individuals were considered. Depending on the grade of adherence our survey was divided into 3 groups. Group 1: patients who only completed OT; group 2: men who accomplished OT and intralesional verapamil injections; group 3: patients who completed the entire protocol. Seventy-six, 45 and 56 men were assigned to group 1, 2 and 3 respectively. The mean age at the diagnosis was 59 ± 8.4, 59.1 ± 5.9 and 54.2 ± 4.8 years, while the mean duration of the disease was 6.3 ± 3.4, 4.8 ± 2.9 and 3.9 ± 3.1 months in group 1, 2 and 3. The erected penile curvature before and after treatment was 24.2 ± 9 and $23.7 \pm 8.9^{\circ}$ in group 1 ($p < 0.36$); 25.4 ± 16.8 and $24.1 \pm 13.6^{\circ}$ in group 2 ($p < 0.34$), and 34.3 ± 17.9 and $26.1 \pm 17.2^{\circ}$ in group 3 ($p < 0.001$).
Conclusions: OT alone was successful to block the progression of the disease. The add of intralesional verapamil injections to OT brought only mild improvements. The complete protocol significantly reduced erected penile curvature and improved erectile function.

☆ Please cite this article as: Gallo L, Sarnacchiaro P. Diez años de experiencia con el tratamiento multimodal de la fase aguda de la enfermedad de Peyronie: reporte médico de la vida real. Actas Urol Esp. 2019;43:182–189.

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PALABRAS CLAVE
Enfermedad de Peyronie;
Terapia multimodal;
Inyecciones intralesionales de verapamilo;
L-arginina;
Pentoxifilina;
Terapia de tracción del pene

Diez años de experiencia con el tratamiento multimodal de la fase aguda de la enfermedad de Peyronie: reporte médico de la vida real

Resumen
Objetivos: Presentar nuestra experiencia con la terapia multimodal para la enfermedad de Peyronie.
Métodos: Los datos retrospectivos se recopilaron entre 2008 y 2017. Las siguientes características fueron evaluadas al inicio y al final del tratamiento: edad, duración de la enfermedad, función eréctil, curvatura del pene erecto y longitud del pene flácido. Todos los pacientes fueron tratados bajo el siguiente protocolo: 12 inyecciones intralesionales de verapamilo, terapia oral (TO) – L-arginina 2 g una vez al día y pentoxifilina 400 mg 3 veces al día durante 6 meses – y terapia de tracción del pene. Se evaluó la adherencia de los pacientes a cada uno de los 3 componentes del tratamiento multimodal.
Resultados: Fueron evaluados 177 pacientes. Nuestro estudio se dividió en 3 grupos, de acuerdo con el grado de adherencia al tratamiento. Grupo 1: pacientes que solo completaron TO; grupo 2: pacientes que completaron el tratamiento con TO e inyecciones intralesionales de verapamilo; grupo 3: pacientes que llevaron a cabo todo el protocolo. Setenta y seis, 45 y 56 hombres fueron asignados a los grupos 1, 2 y 3, respectivamente. La media de edad al realizar el diagnóstico fue de de $59 \pm 8{,}4$, $59{,}1 \pm 5{,}9$ y $54{,}2 \pm 4{,}8$ años, mientras que la duración media de la enfermedad fue de $6{,}3 \pm 3{,}4$, $4{,}8 \pm 2{,}9$ y $3{,}9 \pm 3{,}1$ meses en los grupos 1, 2 y 3. La curvatura del pene erecto pre y postratamiento fue de $24{,}2 \pm 9$ y $23{,}7 \pm 8{,}9^{\circ}$ en el grupo 1 ($p < 0{,}36$); de $25{,}4 \pm 16{,}8$ y $24{,}1 \pm 13{,}6^{\circ}$ en el grupo 2 ($p < 0{,}34$), y de $34{,}3 \pm 17{,}9$ y $26{,}1 \pm 17$, 2° en el grupo 3 ($p < 0{,}001$).
Conclusiones: La TO en exclusiva bloqueó la progresión de la enfermedad. La combinación de inyecciones intralesionales de verapamilo + TO demostró mejoras leves. El protocolo completo redujo significativamente la curvatura del pene erecto y mejoró la función eréctil.

Introduction

Peyronie's disease (PD) is a fibrotic penile wound-healing disorder of the tunica albuginea that can result in various symptoms and penile deformities including pain, erectile dysfunction, penile length loss, curvature and hourglass narrowing.[1] PD has a documented incidence of 3–10% in the general population.[2] Usually patients request for a urology appointment within the first 6 months since symptoms arise.[3] Studies describing the natural evolution of PD have clearly demonstrated that this pathology does not have a spontaneous resolution: if untreated, it may lead to penile deformities deterioration in up to 48% of cases.[4] Although a myriad of nonsurgical treatments was proposed, none of these showed a significant effectiveness supported by strong scientific evidences. However, the body of literature suggests that several therapies can reduce deformity, improve sexual function, reduce pain, and stabilize the disease process, especially when initiated as early as possible in the acute phase.[5] Even if nonsurgical approaches failed to show significant results when administered as monotherapy, the revolutionary concept of a multimodal approach that integrates the synergistic effects of various treatments has arisen.[6] Some protocols were published providing the evidence that combination between oral agents, injections and mechanical forces (traction therapy) achieved the best nonsurgical opportunity for successful management of PD.[7–12] However, all these studies had the limitations to have been performed prospectively on very selected cohorts including motivated patients, which did not reflect the real-life of daily urologic clinical practice.

The objective of the present study is to expose our ten-year experience with multimodal therapy for the conservative management of PD in acute phase. This study is not only focused in its functional results. It has even analyzed the rate of adherence to each component of the multimodal approach.

Materials and methods

We collected the retrospective data from patients who underwent multimodal treatment for PD between 2008 and 2017 at our center. At first consultation they went through a meticulous evaluation that included complete medical and sexual history, physical examination and penile ultrasound. A nonsurgical therapeutic protocol with a multimodal approach was offered to all patients diagnosed with a PD in the acute inflammatory phase according to the following diagnostic criteria:

- disease onset in previous 12 months
- presence of at least one penile plaque and/or soft nodule at physical examination
- penile curvature

The following features were collected from our charts at baseline and after the completion of the treatment:

- Age at diagnosis (years);
- Time since onset of disease (months);
- Erectile function (EF) (IIEF 5 score);
- Nature and severity of erected penile curvature (EPC) were assessed by a single investigator (LG) using a goniometer from the auto-photographs taken (before and after treatment) by the patient in full erection on craniocaudal, lateral, and anteroposterior projection. In case of a concomitant ED (IIEF $5 \leq 20$) the penis photographs were taken at consultation, after intracavernosal injection of alprostadil. The predominant type of curvature was considered (dorsal, ventral, lateral).
- Stretched penile length (SPL) was measured dorsally from pubis to corona by the same investigator (LG).
- Severity of painful erection was assessed by the VAS (Visual Analog Scale), ranging from 0 (no pain) to 10 (severe pain).

The exclusion criteria were: presence of a completely calcified plaque with posterior acoustic shadowing, time since disease onset greater than 12 months, congenital penile curvature, previous penile surgery, concomitant oral and/or intralesional treatments for PD and use of any other adjuvant traction device for PD.

All patients were offered the same multimodal treatment that included:

a) Oral therapy (OT): 2 g of oral L-arginine every morning for 6 months and 400 mg oral pentoxifylline three times per day for 6 months
b) Intralesional verapamil injections (IVIs): 12 injections using a 26-gauge needle attached to a 5 ml syringe. 10 mg of verapamil dissolved in 4 ml of saline solution were injected always by the same main investigator (LG) into the main plaque using a single-puncture approach. IVIs were executed without local anesthesia every other week for a total of 12 injections in a period of 22 weeks. Furthermore, in order to prevent cavernosal fibrosis and to promote tissue healing, the side of the injection was always alternated, starting always with the right side. Injections were carefully delivered into the plaque avoiding accidental damages to the dorsal neurovascular bundle and to the urethra. Moreover, by moving carefully the syringe with an ''inside–outside'' movement, a gentle pressure was applied with the aim of disrupting the plaque with the mechanical force exerted by the needle.
c) Penile traction therapy (PTT): employment of a penile extender device for 6 months. Men who elected PTT, bought the penile extender Andropenis® online. Patients were instructed on proper application and were advised to wear the device from 2 to 8 hours during the 6 months of our protocol.

All patients who accepted to receive our therapeutic protocol signed a special written consent.

Complications, compliance to therapy and drop-out incidence were collected and reported.

To conclude the protocol, a follow-up consultation was carried out one month after the last IVI, in which the characteristics evaluated at the beginning were measured once more, with the same methodology and carried out by the same researcher (LG). With respect to the curvature, treatment response was defined as a reduction of at least 10° in the curvature of the penis. No progression and/or a stable curvature were also satisfactory outcome criteria. An increase of at least 10° was considered as a worsened curvature.

Patients' adherence to each of the three components of the multimodal treatment was analyzed according to the following criteria:

- Adherence to OT: taking both oral compounds for 6 months;
- Adherence to IVIs: completion of the entire cycle of 12 IVIs;
- Adherence to PTT: use of the penile extender for at least 2 hour per day for 6 months.

Finally, the main reasons to reject or abandon one or more components of the protocol were evaluated specifically for each individual.

A descriptive analysis of the variables of the study population was performed. The mean differences between the three groups at baseline were compared using unpaired *t*-test with the significance level at 0.05. The differences of mean values of each group before and after treatment in terms of EF, severity of curvature and SPL were analyzed using the same test. When the assumption of uniform variance was violated, we used the Satterthwaite approximation based on *t* distribution. The data analysis was conducted using IBM SPSS STATISTICS V.22.

Results

All charts regarding PD patients at our center from 2008 to 2017 were reviewed from our database. A total of 177 individuals met the inclusion criteria and were considered in the present analysis. Patients were invited to accept and complete the entire protocol, but not all of them accepted and/or were able to accomplish the combined therapy. Our survey was divided into three groups according to the grade of adherence to each component of multimodal therapy:

- Group one: patients who only completed OT;
- Group two: men who accomplished OT and IVIs;
- Group three: patients who completed the entire protocol.

Based on these criteria, 76 (42,9%),45 (25.4%) and 56 (31.6%) patients were assigned to group one, two and three respectively.

Results are reported as mean (±standard deviation). The mean age at diagnosis was 59 (±8.4), 59.1 (±5.9) and 54.2 (±4.8) years, while the mean duration of the disease was 6.3 (±3.4), 4.8 (±2.9) and 3.9 (±3.1) months in group one, two and three respectively (Fig. 1).

The grade of EPC before and after treatment was 24.2° (±9) and 23.7° (±8.9) in group one (OT alone) ($p = 0.36$); 25.4° (±16.8) and 24.1° (±13.6) in group two (OT + IVIs) ($p = 0.34$), 34.3° (±17.9) and 26.1° (±17.2) in group three (entire protocol) ($p = 0.006$) (Fig. 2). We reported the following rates of EPC reduction of at least 10 degrees for the three groups: 0% in group one, 17.8% in group two and 50% in group three. The percentage of stable curvature was 94.7%,

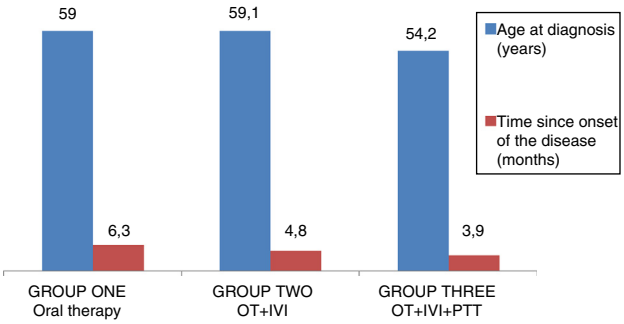

Figure 1 Age and time since onset of the disease at baseline.

73.4% and 42.9% in group one, two and three respectively. The percentage of worsened curvature was 5.3%, in group one, 8.8% in group two and 7.1% in group three (Fig. 3).

Mean EF, determined using the IIEF 5 score, went from 17.7 (±4.5) at baseline to 18.5 (±4.3) after treatment in group one ($p = 0.12$), from 20.4 (±3.7) to 21.6 (±2.3) in group two ($p = 0.066$) and from 20 (±2.2) to 22.4 (±1.6) in group three ($p < 0.0001$) (Fig. 4).

The mean SPL pre- and after therapy was 10.5 (±1.9) cm and 10.4 (±2) cm in group one ($p = 0.33$), 10.7 (±2.4) cm and 10.6 (±2.2) cm in group two ($p = 0.37$), 10.3 (±2) cm and 11 (±2.3) cm in group three ($p = 0.1$) (Fig. 5). Pain after treatment was never reported by any patient. Results are shown in Table 1.

All 177 men included in our survey accepted and completed OT. 42.9% did not complete IVIs. Among them, 26.3% refused and 73.7% dropped-out from this therapy. Causes for IVI refusal were: fear of injections in 5 cases, poor motivation in 5 and lack of time in 8 men. The main reasons for IVIs drop-out were: skepticism about results in 25 men, stable curvature in 26 and worsened curvature in 5 cases. 68.3% of our patients did not complete PTT. Among this percentage 89.2% refused and 10.8% dropped-out. Ten men refuse PTT because they were unable and/or skeptical about purchasing on the internet, 84 were poorly motivated and 14 were doubtful about the effectiveness of this device.

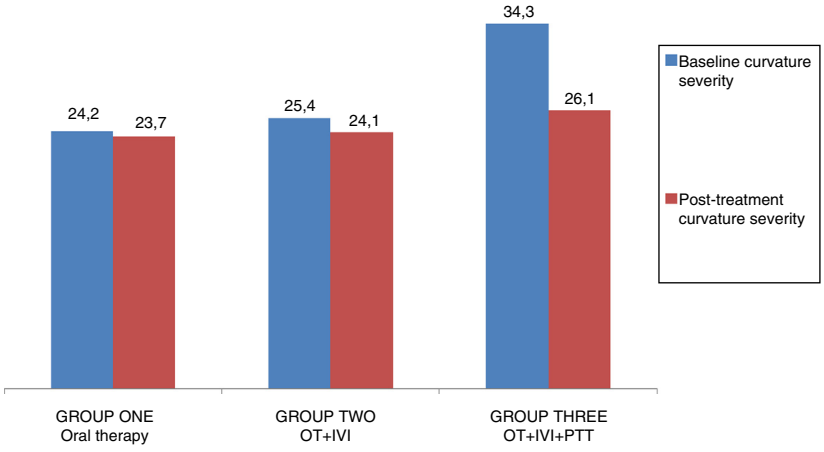

Figure 2 Severity of erected penile curvature before and after treatment.

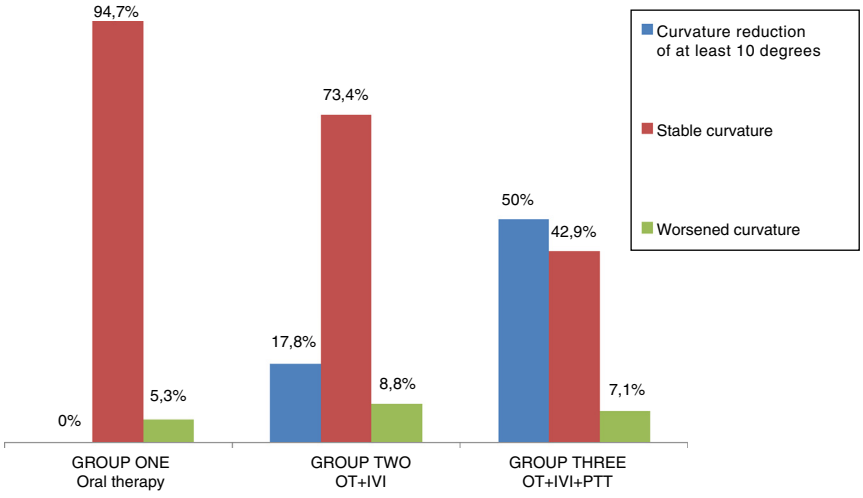

Figure 3 Penile curvature alteration rates.

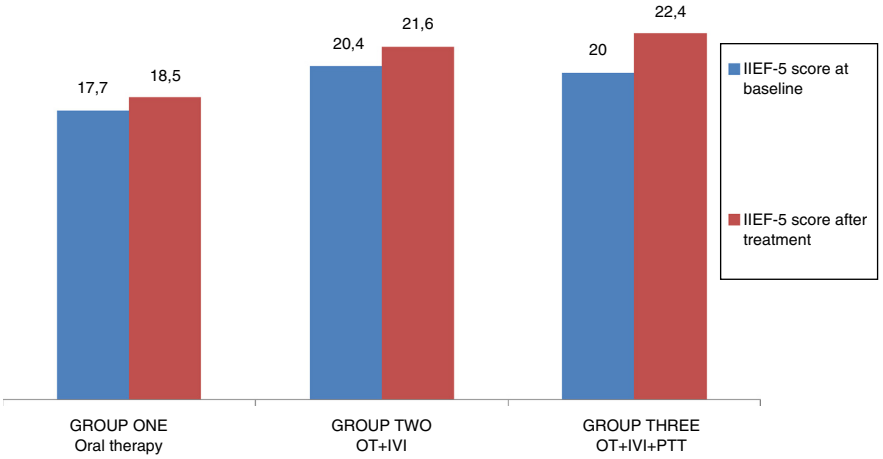

Figure 4 Erectile function (IIEF 5 score) before and after treatment.

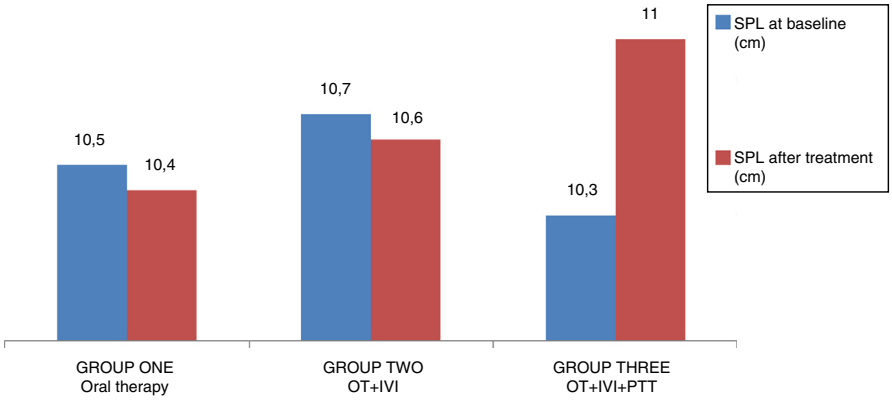

Figure 5 Stretched penile length (SPL) before and after treatment.

39% bought and tried to use the andropenis. Among those, 13 men (18.9%) were not able to complete PTT: four individuals complained about lack of time, six patients had problems applying the device and three presented pain. No major side effects were reported with PTT use.

Discussion

Our interest for multimodal treatment for PD came after studying a review by the group from Chicago led by Dr. Levine published in 2008.[13] We were immediately very intrigued by this revolutionary approach. It seemed logical to us and was provided with good scientific evidence. In fact, the effectiveness of each element of multimodal therapy in treating PD was already known in 2008, and other articles were subsequently published.

Pentoxifylline (PTX) is a derivative of xanthine acting as a nonspecific phosphodiesterase inhibitor. Its employment in early PD is based on its properties for prevention of the tunica albuginea fibroblasts proliferation, and reduction of deposition of collagen.[14,15] It has been demonstrated that PTX improves penile curvature, reduces plaque volume and stabilizes or reduces the calcium content in PD plaques.[16,17]

L-arginine is an amino acid stimulating the nitric oxide synthase expression and a nitric oxide precursor. In a rat model of Peyronie's plaque, L-arginine significantly reduced the plaque size and decreased the expression of type I collagen.[18]

Verapamil is a calcium channel blocker. Its employ for PD is justified by its actions demonstrated in vitro: inhibition of fibroblasts production of local extracellular matrix, reduction of fibroblasts proliferation and increase of local collagenase activity.[19,20] In 1994, the Levine group was the first to introduce IVIs for PD.[21] Subsequently, this agent was used in several human trials proving its beneficial effects.[22]

PTT provides a remodeling of the plaque through a process called ''mechanotransduction''. PTT has been proposed for PD to stop the progression of scarring, to recover penile length and to reduce the curvature.[23,24]

In that same year (2008) we started to prescribe the same protocol proposed by Levine et al. consisting on IVIs, oral arginine and pentoxifylline and PTT. We only slightly modified the injection technique: in the first place we did not use local anesthesia for IVIs as described later by Wolff et al.; secondly we enter the plaque with the needle with the intent to break it in a mechanical way associating the chemical action of the verapamil with the mechanic power of the needle.[25] We started to propose multimodal treatment

Table 1 Summary of results.

	Group one OT	Group two OT + IVIs	Group three OT + IVIs + PTT
Number of patients	76	45	56
Age at diagnosis (years)	59	59.1	54.2
Time since onset of disease (months)	6.3	4.8	3.9
Dorsal curvature (*n*)	48	29	36
Lateral curvature (*n*)	24	12	16
Ventral curvature (*n*)	4	4	4
Erectile function at baseline (IIEF − 5 score)	17.7	20.4	20
Erectile function after treatment (IIEF − 5 score)	18.5	21.6	22.4
p	0.12	0.066	<0.0001
Curvature severity at baseline (degrees)	24.2	25.4	34.3
Curvature severity after treatment (degrees)	23.7	24.1	26.1
p	0.36	0.34	0.006
Curvature reduction of at least 10 degrees (%)	0	17.8	50
Stable curvature (%)	94.7	73.4	42.9
Worsened curvature (%)	5.3	8.8	7.1
Stretched penile length at baseline (cm)	10.5	10.7	10.3
Stretched penile length after treatment (cm)	10.4	10.6	11
p	0.33	0.37	0.1
Severity of painful erection at baseline (VAS score 0–10)	0.5	0.9	0.9
Severity of painful erection after treatment (VAS score 0–10)	0	0	0

because many of our patients were diagnosed in the acute phase and were willing to undergo a conservative treatment. In 2012 this group from Chicago published a prospective trial showing optimal results with the same multimodal treatment protocol. In this study 74 patients were treated with IVIs + OT + optional PTT. Statistically significant reductions in EPC were observed in both groups, but patients in the group that included PTT had a major reduction of curvature and gained SPL.[7] Later, more groups published their experience with synergistic combined therapy for PD showing positive results.[8–12] However, all these studies present the limitation of having been performed in a prospective way in very selected and motivated patients, which does not reflect the real-life of daily urologic clinical practice. The present article reports our ten-year experience with multimodal treatment for acute phase PD in 177 patients. In our opinion this study is pioneer as it is the first retrospective analysis about this topic and gives a realistic report of daily urology practice.

At baseline, men who were able to accomplish the entire protocol (group three) presented the following significant variables: younger, with more recent onset of disease, with more severe curvature and a better EF than the ones included in group one ($p < 0.0001$). Analyzing patient features at baseline, significant differences were also found in terms of age and EPC between group three and two and when comparing duration of the disease and EF between group one and two ($p < 0.0001$).

We found a tendency in curvature reduction in group one and two, but it was not statistically significant: from 24.2° to 23.7° in group one ($p = 0.36$) and from 25.4° to 24.1° ($p = 0.34$) in group two. As demonstrated in previous clinical trials, even the present study showed that OT was successful to block the progression of the disease and can be easily prescribed in poorly motivated patients.[10,17,18] Since all 177 men included in our survey accepted and completed it, we can affirm that OT is safe, inexpensive, simple and well tolerated. The optional addition of IVIs to OT brought just a mild improvement in terms of curvature reduction that was not provided with statistical significance. Our results are not comparable with the ones reported by other published studies concerning IVIs[7,21,26] and appear consistent with other trials showing no major effects in terms of curvature reduction.[27,28] Likely, a potential determining factor could be the technique of injection: inserting the needle in the plaque and trying to disrupt it could be beneficial if associated with the synergistic remodeling action of the PTT. Instead, if performed alone, IVIs with plaque needle breaking could exacerbate the inflammatory cascade and be counterproductive. However, in many patients who underwent IVIs, it was possible to appreciate a mild plaque reduction and softening that was even subjectively referred by patients. However, this feature was very difficult to determine, and it was not evaluated in the present analysis since, as previously demonstrated, reduction in the plaque size has not been associated with a reduction in deformity.[6] Further studies are required to show if plaque reduction/softening could be a useful achievement for surgical correction and/or for subsequent collagenase injections.

We report a statistically significant improvement in EF in patients who completed the entire multimodal protocol ($p < 0.001$) and a curvature reduction of 34.3° at baseline and 26.1° after treatment ($p = 0.006$) consisting on a decrease of 23.9%. Our outcomes are in general less successful than the ones published by Abern et al. who reported a curvature reduction of 41.2% (from 36.6° baseline to 21.5° after treatment) using the same protocol.[7] This difference could be explained by a different use of the penile extender device, since it is not possible for the researcher to determine the precise tension placed on the penis by each patient. In

other cases, it could have been underutilized, compromising the potential benefit of the combined treatment. Furthermore, we defined adherence to PTT as the use of the penile extender for at least 2 hour per day whereas other studies showed that best results were achieved when men used the device for at least three hours per day.[7,12] Patients in group three even presented an increased SPL. However, this was not significant ($p = 0.1$), whereas men in the other two groups revealed a tendency toward penile shortening.

IVIs have shown high drop-out rates of 73.7%. Motivations depended on the different expectations and personal emotional approach: some patients dropped-out from IVIs because they felt satisfied with stable curvature, while others, more pretentious, were expecting an improvement in curvature reduction. Regarding this aspect, we must highlight the importance of communication between physicians and patients: they (professional) should explain that a stable curvature is a favorable outcome (about the 50% of the patients affected by PD experienced a worsening in penile deformities).[4] We have seen that IVIs can be performed without anesthesia, as none of the patients presented pain when receiving them.

Only 31.6% of cases in our survey accomplished PTT with strong motivations since all of them completed the entire protocol. This rate of adherence to PTT was consistently lower than those reported in previous prospective trials by Martinez Salamanca (57.3%) and Abern (52.7%) and is very similar to that referred by Yafi (31%) in a retrospective review about 112 patients treated with interferon injection and potential add of PTT.[7,12,24] In another study led by Nikoobakt concerning the use of penile extender for another indication, short penis syndrome, the rate of acceptance was even lower (23%).[29] 121 men did not complete PTT and 108 of them (89.2%) did not even buy the device because of skepticism or poor motivation. Interestingly, from a total of 69 individuals, 56 (81.1%) initiated and completed PTT, while the remaining 13 (18.9%) were not able to use it for lack of time, difficulties applying the device and pain. This information confirms that highly motivated patients who try PTT can accomplish it without mayor side effects.

Interestingly, 0 patients in our survey completed oral and traction therapy but accomplished the IVIs treatment. Probably that occurred because the PTT required a higher grade of motivation than IVIs, that's why who was able to complete IVIs cycle accomplished PTT as well.

We admit that the results of the present article were limited due certain grade of contamination because some patients classified in one group partially accomplished another group's treatment. Finally, we believe that positive results could come from further studies evaluating the association between oral and traction therapy without IVIs.

Conclusions

With our ten-year experience on 177 patients with multimodal treatment for acute phase PD we can draw the following conclusions:

OT alone is a safe, inexpensive and simple approach. It was successful to block the progression of the disease and can be easily prescribed in poorly motivated patients.

Supplementary IVIs to OT can produce only mild improvements in terms of curvature reduction.

The only conservative approach that was successful in EPC reduction was the simultaneous employment of OT, IVIs and PTT. However, only 31.6% of our surveyed patients accomplished the entire protocol. Particularly, a young age, an earlier disease onset, a more severe curvature and a better EF were demonstrated to be positive factors for adherence to multimodal treatment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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