Original Article

Prospective study to evaluate the clinical outcome of intralesional interferon-α2b in the management of Peyronie's disease

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Abstract

Context: Interferon (IFN)-α2b in Peyronie's disease (PD).

Aims: This study aims to evaluate clinical efficacy of the IFN-α2b in both subjective and objective manner for the treatment of PD and compared with previously used intralesional verapamil in terms of cost-benefit analysis.

Settings and Design: Prospective study.

Materials and Methods: A prospective study conducted from January 2013 to July 2016 in the Department of Urology, Government Medical College, Kota, Rajasthan, India. We included patients with identifiable Peyronie's plaque with or without pain, curvature ranging between 30 and 90 degrees. We excluded patients with a calcified plaque and the ventral location of the plaque, any infective foci over the penis, erectile dysfunction due to other etiologies and patients who had received previous intralesional therapy. Patients were evaluated by clinical history, physical examination including plaque location, size, consistency, and penile curvature. Patients received intralesional IFN-α2b in a dose of 3×10^6 IU. Patients completed the visual analogue pain (VAS) score for pain, and International Index of Erectile Function-5 (IIEF-5) questionnaire at first visit as well as at follow-up of 1 month and 3 months.

Statistical Analysis Used: Comparisons were performed using the paired Student's *t*-test and Chi-square tests as appropriate. Patient's objective and subjective clinical characteristics were described as a means (standard deviation).

Results: We included 86 patients in this study. Patients had a mean age of 48.6 years, mean plaque volume 256 mm^3, and disease duration of 15.2 years. After 1 month of treatment, there was a significant change in plaque volume 256–60.8 mm^3; $P < 0.01$) and penile curvature 34.8–24.6°; $P < 0.01$). The patients reported significant improvement in pain score VAS and IIEF-5.

Conclusions: IFN-α2b, as minimal invasive (intralesional) options for the treatment of PD, demonstrated significant improvement in plaque volume, penile curvature with minimal complications. Patients subjectively reported significant improvement in pain on erection and sexual activities. IFN-α2b and verapamil had an almost similar clinical outcome, but verapamil at much lower cost.

Keywords: Erectile function, interferon-α2b, penile curvature, Peyronie's disease, verapamil

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Received: 24.04.2017, **Accepted:** 01.07.2017

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_65_17

How to cite this article: Sokhal AK, Jain NK, Jhanwar A, Singh K, Saini DK. Prospective study to evaluate the clinical outcome of intralesional interferon-α2b in the management of Peyronie's disease. Urol Ann 2018;10:154-8.

INTRODUCTION

Peyronie's disease (PD) was first described by Francois Gigot de la Peyronie in his first clinical series about penile curvature in 1743. PD, described by de la Peyronie as "induratio penis plastica," is a fibrotic disorder of tunica albuginea resulting in penile curvature.[1,2] PD has significant physical and psychological impact on men's sexual health. PD presents as a symptom complex of penile deformity with pain on erection, unsatisfactory sexual intercourse, even inability, to penetrate the vagina, loss of self-esteem, depression, and poor quality of life.[3,4] The prevalence of PD has been estimated to range from 0.39% to 13.1% among different ethnic groups.[5] Since longtime PD has remained in the discussion, but still exact pathophysiology and etiology is obscure. PD is a multifactorial disease characterized by an abnormal fibrous plaque in the tunica albuginea with fibroblastic proliferation and altered elastin substructure.[6] PD is proposed as an abnormal healing response to repetitive penile microtrauma occurring during intercourse. It remained unclear that PD develops in a few individuals, while penile microtrauma occurred in all sexually active men. Other studied contributing factors in the pathogenesis of PD include genetic profile, hypogonadism, smoking, and inflammatory conditions of genital tract.[7-9]

Management spectrum of PD includes proper counseling, medical therapy, minimal invasive and surgical treatment. Spontaneous resolution of the plaque has been reported in 13%–40% of PD patients,[6] so effective counseling required about the natural history of disease, curvature correction, pain relief, recovery of erectile function, and available treatment options and their efficacy. Various oral medications had been described, none with proven benefits. Oral therapy includes vitamin E, tamoxifen, colchicine, potaba (potassium aminobenzoate), coenzyme Q10, omega-3 fatty acid, and many more.[10,11] Many nonpharmacological, nonsurgical measures as extracorporeal shock wave, hyperthermia therapy, penile traction therapy, and radiotherapy had been attempted. Intralesional delivery of hypo-proliferating agents, including collagenase, verapamil, steroids, interferon (IFN)-α2b, orgotein, onabotulinumtoxinA, and many under evaluation.[11,12] Intralesional collagenase *Clostridium histolyticum* has been a recently added only the United States Food and Drug Administration approved agent for PD.[13] Surgical intervention depends on patient's virtue on erectile function, penile deformity, plaque characteristics, and surgeon's choice.

Despite the availability of numerous treatment options, there is a lack of good quality research for making definitive consensus. European Association of Urology guidelines for the treatment of PD considered intralesional IFN-α2b as a potential option.[13] The AUA guidelines also mentioned IFN-α2b as a potential treatment option (evidence Grade C). Intralesional verapamil administration has been described as an effective therapy, but its use has been decreased recently. Intralesional verapamil has the advantages of low cost, better availability, and without risk of flu-like symptoms.

Therefore, we conducted a prospective study to evaluate the clinical efficacy of the IFN-α2b in both subjective and objective manner for the treatment of PD and compared with previously used intralesional verapamil in terms of cost-benefit analysis.

Objective

The objective of this study is to evaluate clinical efficacy of the IFN-α2b in both subjective and objective manner for the treatment of PD and compared with previously used intralesional verapamil in terms of cost-benefit analysis.

MATERIALS AND METHODS

After obtaining ethical approval from the institutional research committee, we conducted a prospective study from January 2013 to July 2016. After informed consent, we enrolled patients of PD, who referred to the Department of Urology, Government Medical College, Kota, Rajasthan, India. We included patients with identifiable Peyronie's plaque (dorsal, lateral, and dorsolateral) with or without pain, curvature ranging between 30° and 90°. We excluded patients with calcified plaque and ventral location of plaque and any infective foci over the penis. Ventral plaques were excluded due to the fear of urethral injury. Patients with erectile dysfunction due to another etiology and patients who had received previous intralesional therapy were also excluded. Enrolled patients were evaluated by detailed clinical history, including degree of curvature, pain and sexual disability, physical examination including plaque location, size, consistency, and penile curvature. Patients were investigated by complete blood count, serum chemistry, and penile ultrasonography for assessing plaque characteristics. Curvature assessment was performed after artificial penile erection. We used papaverine (24 mg/dl) and phentolamine (1 mg/ml) diluted with normal saline for penile erection. We measured penile curvature using goniometer in two different planes. Curvature assessment at the first visit and follow-up visit was done by one of the available providers (DKS, KS), who was blinded to the patient characteristics and treatment provided. Patients

completed visual analogue pain (VAS) score for pain, and International Index of Erectile Function (IIEF-5) Questionnaire at first visit as well as at follow-up of 1 month and 3 months.

Treatment technique

After penile block, the patient received intralesional IFN-α2b (Intalfa 3MIU) in a dose of 3×10^6 IU, available as prefilled syringe. After stabilizing plaque, we injected IFN by multiple punctures throughout the plaque. We administered IFN every week for 12 weeks [Figure 1].

Statistical analysis

Comparisons were performed using the paired Student's *t*-test and Chi-square tests as appropriate. Patient's objective and subjective clinical characteristics were described as a means (standard deviation). Patients without complete data for each respective injection were excluded from analysis. We performed statistical analysis using SPSS Software, version 16.0.0, SPSS Inc. Chicago, IL, USA. All reported *P* values were 2-sided, with $P < 0.05$ considered statistically significant.

RESULTS

We assessed 94 patients, among them, 86 patients were included in the study. Four patients did not give written consent, and four patients drop out from the study due to various reasons. The patient characteristics are shown in Table 1. Patients had a mean age of 48.6 years, mean plaque volume 256 mm^3, and disease duration of 15.2 years.

After 1 month of treatment, there was a significant change in plaque volume 256–60.8 mm^3; ($P < 0.01$) and penile curvature 34.8 to 24.6 degrees; $P < 0.01$). The patients reported significant improvement in pain score VAS and IIEF-5 [Table 2].

Figure 1: Technique of intralesional interferon-α2b in Peyronie's plaque

At 3-month follow-up, a significant improvement in objective and subjective disease characteristics was found [Table 2 and Figure 2].

DISCUSSION

PD is a fibrotic deformity of penis having a triple impact on male sexuality by causing pain on erection, penile curvature leading difficulty in vaginal penetration, and subsequent impaired overall sexual ability which resulted in depression, shame, and poor quality of patient as well as life partner. Treating urologist can have a basket full of treatment agents, but get frustrated by the results and also by the patient's expectations for treatment results. Etiopathogenesis of PD always remained under research for more than 260 years, but still, exact mechanism remained obscure. Most agreed mechanism is repeated mechanical microtrauma to tunica albuginea and its septal fibers. Repeated trauma incites microvascular injury and tissue damage and triggers a cascade of inflammatory reaction. Resulted excessive

Table 1: Baseline patient demographics and disease characteristics

Variables	Subjects (*n*=86)
Age (mean±SD)	48.6±12.2
Comorbidities	
Diabetes	12
Hypertension	20
Disease duration (%)	
<1 years	38 (44.2)
1-2 years	26 (30.2)
>2 years	22 (25.6)
Associated pain	
Yes	68
No	18
Plaque location (%)	
Pure dorsal	38 (44.2)
Pure lateral	16 (18.6)
Dorsolateral	32 (37.2)
Penile curvature (mean±SD)	34.8±11.4
<30° (%)	48 (55.8)
30°-60° (%)	26 (30.2)
60°-90° (%)	12 (14)
Cost of treatment (INR/patient)	7236

INR: Indian Rupee, SD: Standard deviation

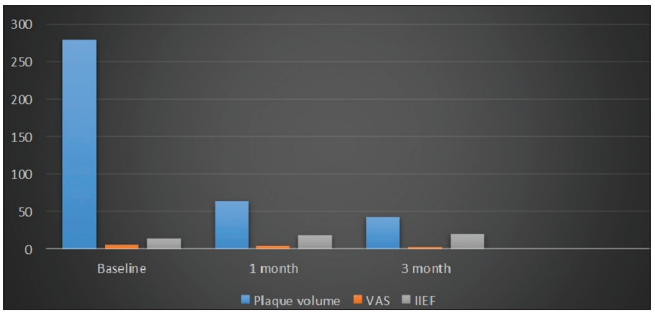

Figure 2: Graphic depiction of comparison of plaque volume, visual analog scale and International Index of Erectile Function-5 at baseline, 1- and 3-month follow-up

Table 2: Comparison of outcome parameters at 1- and 3-month follow-up

Variables	Time	Mean±SD	*P* (baseline vs. 3 months)
Plaque length (mm)	Before	12.9±4.1	0.0001
	1 month	8.2±2.8	
	3 months	4.3±2.8	
Plaque width (mm)	Before	6.2±2.2	0.0001
	1 month	4.1±2.1	
	3 months	2.4±1.6	
Plaque volume (mm)	Before	256±52.4	0.0001
	1 month	60.8±18.4	
	3 months	31.4±10.9	
Penile curvature (°)	Before	34.8±11.4	0.0001
	1 month	24.6±4.1	
	3 months	18.6±3.6	
VAS	Before	5.1±3.6	0.0001
	1 month	3.6±1.4	
	3 months	1.8±1.2	
IIEF-5	Before	13.8±4.2	0.0001
	1 month	19.3±3.6	
	3 months	21.2±2.7	

IIEF: International Index of Erectile Function, VAP: Visual analog pain, SD: Standard deviation

extracellular collagen deposition in the tunica albuginea by fibroblast activation and proliferation.[1,2]

IFNs, a natural, low molecular weight protein, displayed an integral role in immune modulation. Three types of IFNs such as alpha, beta, and gamma were used clinically for different indications-hepatitis B, hepatitis C, Kaposi's sarcoma.[7] *In vitro* studies on PD derived human fibroblast model and corpora cavernosa-derived myofibroblasts model, demonstrated IFN-α2b effective in inhibiting collagen production, and increasing collagenase activity.[8,9] Thereafter, IFN-α2b was introduced as therapy for many fibrotic conditions such as PD, keloid scars, and scleroderma.[10]

Calcium channel blockers have demonstrated anti-fibroblastic activity in many *in vivo* and *in vitro* studies. Verapamil was administered intralesional to suppress and degrade collagen fibrosis because dose to induce this effect was beyond serum safe limit.

We conducted this prospective study to evaluate intralesional efficacy of IFN-α2b for the treatment of PD by both subjective and objective assessments and compared it with existing literature of intralesional verapamil. In our study, a total of 86 patients completed 3-month follow-up after treatment and included in the final analysis. Mean age (range) of our study population was 48.6 years (range = 34–58 years). Mean age described in many studies range between 52 and 57 years.[11,12] The early age of presentation in our study may be due to early marriage custom and hence early intercourse and repeated penile microtrauma.

Intralesional verapamil injection had been used in PD for many years. It had demonstrated significant efficacy in reducing plaque volume, penile curvature and improvement in pain, and sexual function in many studies.[13-15] Alizadeh *et al*. in 2004 compared the efficacy of verapamil with pentoxifylline and reported 36.7% curvature reduction, 33.3% plaque size reduction, 66.7% improvement in erectile function, and 76.6% pain reduction.[16] In a non-randomized study, Levine *et al*. (2002) reported a decrease in curvature in 60%, pain reduction in 84%, and overall sexual function improvement in 71% patients.[17]

IFN-α2b has been evaluated as a potential agent in PD treatment in multiple studies.[18,19] In 1999, Ahuja *et al*. administered intralesional IFN-α2b in 10 patients and reported a decrease in plaque size in 85% patients, 65% patients had significant curvature correction, and 90% resolution of pain.[20] Hellstorm *et al*. conducted a single-blind, multicenter, placebo-controlled study in 2006, including 117 patients and documented statistically significant improvement in plaque size, penile curvature, phallalgia, and sexual quality of life as compared to controls.[21] In this study, 86 patients completed 3-month follow-up after IFN-α2b administration. We objectively found 87% decrease in plaque volume and 47% improvement in penile curvature in our study, which subjectively improved sexual function in 87% and pain relief in 83% patients. The results of intralesional IFN-α2b were promising with significant impact on male sexual quality of life.

In literature, very low rate of complications described with intralesional IFN-α2b injection therapy. In our study, minor complications reported which resolve spontaneously or with supportive treatment. We reported nausea in six patients, weakness in 8, low-grade fever in 4, and skin rashes in two patients.

In recent years, intralesional verapamil therapy is being lagged behind in spite of having an almost equal objective and subjective improvement in PD. Both verapamil and IFN-α2b had demonstrated similar pathways of fibroblast inhibition, collagen synthesis inhibition, and collagenase activation in many *in vivo* and *in vitro* studies.[22-24] In our study, we calculated the cost of the injections and compared it from injection verapamil, which was found a significant difference (INR 7236 vs. 120). A number of visits to the clinic were also more with IFN-α2b injection therapy as compared to the Verapamil therapy (Twelve vs. six visits). The overall intralesional verapamil therapy was found much cost effective, which is a significant concern for the patients of developing country like India, where bearing

of medical expenses matters a lot. Probably due to low cost, verapamil therapy is not getting the support of drug manufacturing companies, which makes this treatment of PD quite difficult.

Our study is strengthened as being a prospective study with a reasonable follow-up period. We evaluated the clinical impact of intralesional IFN-α2b injection therapy and compared it with intralesional verapamil therapy which was popular a decade ago. Our study enriches the literature showing significant clinical results with IFN-α2b but also highlighted that was feasible at much lesser cost with verapamil. However, further studies with standardized objective and subjective parameters with validated questionnaires with large number of patients with longer follow-up are required to label the treatment benefits. The limitations of our study include a small number of patients.

CONCLUSIONS

PD continues as an age-old enigma known for anatomical and functional impact on men's sexual health with significant psychological detrimental effects on the patient and his sexual partner.

Intralesional IFN-α2b demonstrated significant improvement in plaque volume, penile curvature with minimal complications. Patients subjectively reported significant improvement in pain on erection and sexual activities. IFN-α2b and verapamil had an almost similar clinical outcome, but verapamil at much lower cost.

Acknowledgments

We would like to acknowledge the cooperation of residents of Department of Urology, Government Medical College, Kota, Rajasthan, India who participated in data collection and evaluation of the patient. We also appreciate the commitment and compliance of the patients who reported the required data.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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