Intralesional Injection of Hyaluronic Acid in Patients Affected With Peyronie's Disease: Preliminary Results From a Prospective, Multicenter, Pilot Study

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ABSTRACT

Introduction: Hyaluronic acid has been shown to be efficacious in decreasing scar formation, inflammation, and oxidative stress.

Aim: To assess the efficacy of intralesional injection of hyaluronic acid in patients affected by Peyronie's disease.

Methods: In this prospective, single-arm, self-controlled, interventional, multicenter pilot study, 65 patients underwent a 10-week cycle of weekly intraplaque injections with hyaluronic acid (0.8% highly purified sodium salt hyaluronic acid 16 mg/2 mL; Sinovial, IBSA, Lodi, Italy). Patients were re-evaluated 2 months after the end of therapy.

Main Outcome Measures: Plaque size (millimeters), penile curvature (degrees), International Index of Erectile Function (IIEF-5) score, visual analog scale (VAS) score for sexual satisfaction, and Patient's Global Impressions of Improvement (PGI-I) score.

Results: Median age was 57 years (range = 23−70). At baseline, mean plaque size was 10 mm (range = 3−30 mm), mean penile curvature was 30° (range = 0°−50°), and mean IIEF-5 score was 20 (range = 0−25), with slight to moderate erectile dysfunction (IIEF score < 21) in 36 of 65 patients (55%). A median VAS score of 6 (range = 2−10) was found. Mean follow-up was 12 months (range = 6−24 months). Statistically significant post-treatment improvements were detected for plaque size (before treatment = 10 mm [3−30 mm], after treatment = 8 mm [1−30 mm], $P < .0001$), penile curvature (before treatment = 30° [0°−50°], after treatment = 20° [0°−40°], $P < .0001$), IIEF-5 score (before treatment = 20 [11−25], after treatment = 21 [15−25], $P < .0001$), and VAS score (before treatment = 6 [2−10], after treatment 8 [2−10], $P < .0001$). After treatment, the rate of patients with an IIEF score lower than 21 decreased from 55% (36 patients) to 40% (25 patients). Overall improvement on the PGI-I questionnaire was 69%.

Conclusion: Intralesional treatment with hyaluronic acid can improve plaque size, penile curvature, and overall sexual satisfaction and seems preferably indicated in the early (active) phase of the disease. Furthermore, it is easy to perform and well tolerated.

Key Words: Hyaluronic Acid; Intralesional Therapy; Penile Curvature; Peyronie's Disease

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INTRODUCTION

Peyronie's disease (PD) is an acquired, localized fibrotic disorder characterized by the deposition of collagen and fibrin in the form of plaque on the tunica albuginea of the penis. Its pathophysiology is unknown and frequently results in penile deformity, penile pain, and erectile dysfunction,[1] leading to a significant negative impact on patient quality of life, with associated rates of significant depression up to 48%.[2] Recent prevalence estimates vary from 3.2% to 8.9%.[3,4]

The etiology of PD is largely unknown. According to current popular theories, a single traumatic event or repeated microtraumas during sexual activity can lead to a low-level autoimmune response arising from a prolonged and complex inflammatory reaction of the tunica albuginea fibers,[5] which leads to plaque formation.[6–9]

From a historical point of view, it is worth highlighting that the first descriptions of a penile condition that could refer to PD probably date to the 13th century, and the first accurate description of PD was reported by the Italian anatomist Gabriele Falloppio in the 16th century. In 1743, Francois Gigot de la Peyronie's wrote a landmark article on PD, and his name was associated with the disease. Despite this long history, there are no medical or surgical therapies[10] and there is a paucity of knowledge on the natural history of PD, although deformity stabilization and improvements in specific subsets of men with untreated PD have recently been reported.[11]

The European Association of Urology and the American Association of Urology have released clinical practice guidelines for the diagnosis, evaluation, treatment, and follow-up of patients with PD.[12,13] Conservative treatment of PD is focused primarily on patients in the early (acute inflammatory) stage, and surgical remediation is used to correct curvature, allow for satisfactory intercourse, and is reserved for patients who have stable disease for at least 12 months.[12]

Several options have been suggested for non-operative PD treatment, including oral pharmacotherapy, intralesional injection therapy, and other topical treatments. Of these, injection of pharmacologically active agents directly into penile plaques represents the most valid treatment option, because current evidence discourages the use of oral and topical agents. In particular, current American Association of Urology clinical practice guidelines suggest intralesional administration of *Clostridium histolyticum* collagenase (CHC) in combination with modeling or intralesional interferon alfa-2b or verapamil.[14] However, these compounds have been found to produce the potential occurrence of mild to severe adverse events, including penile ecchymosis, swelling, pain, and corporal rupture with collagenase; sinusitis, flulike symptoms, and minor penile swelling with interferon alfa-2b; and penile bruising, dizziness, nausea, and pain at the injection site with verapamil.[14] In addition, therapy with collagenase is limited by the high cost of the compound. Based on currently available scientific evidence, the intralesional agent presenting the optimal benefit-risk ratio is far from determined, and further research of novel intralesional agents is strongly needed.

Hyaluronic acid has been shown to be efficacious in decreasing scar formation and blocking the effects of substances that generate inflammation and oxidative stress. For this reason, it is used widely in numerous medical applications, including cosmetic surgery (for treatment of wrinkles and scar) and orthopedics (intra-articular therapy for osteoarthritis) because of its consolidated therapeutic efficacy and treatment-cycle feasibility.[15,16]

The present study investigated whether intralesional use of hyaluronic acid could provide a positive effect on the pathogenesis of PD by its interference with inflammatory and pro-fibrotic processes. Therefore, the aim of this prospective, single-arm, self-controlled, interventional, multicenter pilot study was to assess the efficacy of intralesional injections of hyaluronic acid to decrease plaque size, decrease penile curvature, and increase sexual satisfaction in patients affected by PD.

METHODS

This is a single-arm, self-controlled, interventional study. Patients were enrolled from 10 Italian andrology centers and pretreatment clinical evaluations were carried out by urologists experienced with PD management.

Sexually active men older than 18 years affected by PD were eligible for this study. Study criteria included (i) a palpable nodule or plaque in the tunica of the penis and (ii) pain in the flaccid state or during painful erections. Exclusion criteria were (i) calcified plaques or hourglass deformity as defined at duplex Doppler ultrasonography, (ii) previous PD therapy with oral agents or intralesional injections, and (iii) severe concomitant erectile dysfunction (International Index of Erectile Function [IIEF-5] score < 7).

After the preliminary evaluation for eligibility, including medical and sexual histories, physical examination, and self-administration of IIEF-5 questionnaires, enrolled patients were invited to undergo a 10-week cycle of weekly intraplaque injections with hyaluronic acid (0.8% highly purified sodium salt hyaluronic acid 16 mg/2 mL,; Sinovial, IBSA, Lodi, Italy).

All patients provided written informed consent and the study was approved by the institutional review board (ethics committee of Perugia University, Perugia, Italy).

Pretreatment Workup

All patients underwent Duplex Doppler ultrasonography in the basal condition and after the induction of penile erection with the assistance of an intracavernous injection of a tri-mix (papaverine 30 mg/mL, phentolamine 1 mg/mL, alprostadil 10 μg/mL). Repeat dosing was administered to a maximum of three doses until full erectile rigidity was achieved. All procedures were performed by the same experienced operator at each center. Plaque position and size (the longest diameter was considered when evaluating the results) were carefully assessed. Penile