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ORIGINAL ARTICLE

Male Health

Intraplaque injections of hyaluronic acid for the treatment of stable-phase Peyronie's disease: a retrospective single-center experience

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Peyronie's disease (PD) is a condition of penile connective tissue affecting up to 10% of men worldwide. In the complexity of its management, nonsurgical treatments, such as intraplaque injections, are gaining attention. The current literature shows data on the efficacy of intraplaque injections of hyaluronic acid (HA) mainly in acute-phase PD. However, data on injections of HA in stable-phase PD are lacking. Data for this retrospective study were derived from a prospectively maintained database of private patients presenting at a private medical practice affiliated to the University of Naples "Federico II" (Naples, Italy) with stable-phase PD between January 2020 and March 2023. Patients underwent a standard protocol of three injections, each administered at a two-week interval. During the intervals, patients performed vacuum device therapy, penile stretching, and modeling exercises. All patients compiled the Peyronie's Disease Questionnaire (PDQ) and Global Assessment of Peyronie's Disease (GAPD) at baseline and 2 weeks after the third injection. A penile Doppler ultrasound was performed 2 weeks after the last injection to record the final curvature. Overall, we recruited 62 patients with stable-phase PD and a mean (±standard deviation [s.d.]) curvature of 52.7° (±9.7°). After 6 weeks, eight (12.9%) patients did not experience any curvature improvement. The remaining 54 patients had a final mean (±s.d.) curvature of 40.3° (±9.1°) with $P < 0.001$, compared to that before treatment. We found improvement in all PDQ domains (all $P \leq 0.01$), and 50 (80.6%) patients reported subjective improvement of the penile curvature according to the GAPD. In conclusion, we demonstrated that after three injections of HA administered according to the adopted protocol, patients with stable-phase PD could experience significant improvements in penile curvature, and physical and psychological consequences of the disease without significantly relevant side effects.

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INTRODUCTION

Peyronie's disease (PD) is a condition of connective tissue affecting up to 10% of men worldwide, with incidence peaking between 45 years and 60 years old.[1] Particularly, PD is characterized by the formation of fibrous plaques in the tunica albuginea of the penis, leading to penile deformity, curvature, shortening, and penile discomfort or pain during erections. Although the precise etiology of PD is unknown, genetic, vascular, and mechanical factors are believed to be involved.[2] Classical evolution of the disease recognizes an acute phase of PD, characterized by penile pain and curvature worsening, and a chronic phase with pain resolving and curvature stabilization.[3]

Regardless of the etiology, scientific research is far away from defining a definitive cure for PD. Indeed, the available treatment options are limited and not devoid of adverse effects.[2] Among all, surgical interventions are typically deemed as last resort for patients with severe curvature, functional impairment, or geometrical difficulties in penetrative intercourses.[4] Nonsurgical remedies for PD include oral antioxidant therapies and intralesional injections.

The rationale behind the use of oral antioxidants is based on the reduction of inflammation and oxidative stress which contributes to plaque formation and progression with curvature worsening.[5] However, data from available literature are contrasting regarding the effectiveness of oral antioxidants in PD treatment.[6] One of the most effective nonsurgical options for PD is identified by intraplaque injections of collagenase of clostridium histolyticum (CCH) which have acquired popularity in the last decade.[7] CCH is an enzyme degrading collagen, the protein accountable for the formation of fibrous lesions in PD. It is injected directly into the plaque and previous clinical trials showed its efficacy in enhancing penile curvature and reducing PD-related symptoms.[6,7] However, CCH therapy can also cause side

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effects such as penile hematoma, penile edema, and discoloration.[8] Moreover, CCH injections have become difficult to find beyond the USA. Due to the limitations in the use of CCH, several other intraplaque agents have been tested.[2] Among all, hyaluronic acid (HA) has emerged in recent years as a novel therapy for PD due to its ability to modulate inflammation, promote tissue repair, and restore extracellular matrix (ECM) homeostasis.[9] HA is a naturally occurring glycosaminoglycan found in numerous body tissues, including the penis, with a crucial role in maintaining the structural integrity and function of the ECM and is involved in modulating cell proliferation, differentiation, and migration.[9] The potential benefits of HA, with low rates of adverse effects, have encouraged andrologists to use this substance in several procedures such as in penile girth and glans augmentation.[10,11] Moreover, several previous studies demonstrated the anti-inflammatory, antioxidant, and analgesic properties of HA in various tissues, which may be advantageous in the treatment of PD.[12–14]

Despite the potential benefits of HA in PD treatment, the current evidence regarding its efficacy and safety is equivocal and limited. Previous preclinical and clinical studies on the use of HA in PD have created new perspectives for the nonsurgical treatment of acute-phase PD.[15] However, according to a recent review by Schifano *et al*.,[16] although some studies have shown promising results with HA for PD, the overall quality of the evidence is low, and more high-quality studies are required to establish its efficacy.

Consequently, considering the limitation of evidence published in the current literature, the present retrospective study aims at analyzing the efficacy of intraplaque injections of HA in a cohort of men presenting with stable-phase PD.

PATIENTS AND METHODS

Study design

In the present study, a retrospective analysis of a prospectively maintained database was performed from January 2020 to March 2023. Data for this study were obtained from a prospectively maintained database of private patients presenting at a private medical practice affiliated to the University of Naples "Federico II" (Naples, Italy) with stable-phase PD. All patients were naïve to any treatment for PD and were seen and treated in outpatient clinics and underwent intraplaque injections of HA. The analysis included all patients who received an intraplaque injection of HA. The adopted protocol was inspired by previous studies on CCH injections.[8] The standard protocol involved a cycle of three injections, with each injection administered at a two-week interval. During the interval between injections, patients performed vacuum device therapy, penile stretching, and modeling exercises.

All patients underwent physical examination and penile Doppler ultrasound using intracavernosal injections of 10 μg of alprostadil (Pfizer Italia S.r.l., Milan, Italy). During the examination, the point of maximal curvature (PMC) was marked and the distance from the corona was measured and recorded.

The injections were performed using a ring-block technique with 10 ml of 7.5% ropivacaine (B.Braun S.p.a., Milan, Italy) as a local anesthetic. Subsequently, a 1 ml solution of sodium salt of HA titrated to 0.8% concentration was injected (IBSA Italia, Institut Biochimique SA, Lodi, Italy). The molecular weight of the injected HA was similar to the endogenous form, reaching one million Daltons. The injections were administered at the site of maximum curvature. Patients were not required to wear semi-compressive dressings and were advised to use nonsteroidal anti-inflammatory drugs in case of pain. The database excluded patients with ventral curvatures or completely calcified plaques, accordingly with IMPRESS I and II trials.[17] Routine questionnaire completion was performed by all patients, including the International Index of Erectile Function (IIEF), Peyronie's Disease Questionnaire (PDQ), and Global Assessment of Peyronie's Disease (GAPD), to assess erectile function and evaluate the overall impact of the disease.

Every patient fulfills questionnaires before undergoing the first injections and 2 weeks after the third injection. A new penile Doppler ultrasound with artificial erection is performed 2 weeks after the last injection to record the curvature at the end of the cycle.

Data collection followed the principles outlined in the Declaration of Helsinki; all patients had signed informed consent agreeing to deliver their own anonymous information for future studies. The study was approved by the Ethics Committee of University of Naples "Federico II" (Approval No. 454/15).

Statistical analyses

Each variable distribution has been tested with the Shapiro–Wilk normality test and a Q–Q plot. The normally distributed variables have been compared using a paired *t*-test. All tests were two-sided with a significance level set as $P < 0.05$. For the statistical analyses, the IBM Statistical Package for the Social Sciences (SPSS® version 25.0; IBM Corp., Armonk, NY, USA) was utilized.

RESULTS

Sixty-two patients completed a cycle of three HA injections (**Table 1**). Each patient received one HA injection every 2 weeks for 6 weeks. The mean (± standard deviation [s.d.]) age of the patients was 58.6 (± 10.6) years. The mean (±s.d.) baseline SPL was 12.6 (± 1.7) cm. At the baseline, the mean (±s.d.) penile curvature was 52.7° (± 9.7°). The most frequent direction of the curvature was pure dorsal in 29 patients (46.8%), whereas 27 patients (43.5%) had dorsal and left curvature and 3 patients (4.8%) had dorsal and right curvature. Only 1 patient (1.6%) and 2 patients (3.2%) had pure left and pure right curvature, respectively.

Of the 62 patients in the study, eight (12.9%) did not experience any curvature improvement. The mean improvement of penile curvature was 12.4° (range: 5°–30°) or 23% of the initial curvature (range: 7.7%–46.1%). After 3 HA injections in combination with the use of vacuum device, and penile modeling and stretching, the final mean (±s.d.) curvature was 40.3° (± 9.1°; $P < 0.001$). None of the curvature directions was predictive of success. Patients with partial calcifications of the plaque did not experience significant change of the curvature improvement compared with the ones without calcifications ($P = 0.847$).

A statistically significant improvement in all different domains of the PDQ questionnaire was found. In particular, the mean (±s.d.) improvement in the physical and psychological domain was 1.3 (±3.7; $P = 0.01$), in the pain and bother domains were

Table 1: Descriptive statistics and questionnaire scores of 62 patients as segregated according to three treatments with hyaluronic acid, vacuum device, and penile stretching

Variable	*Before treatments*	*After treatments*	*P*
Curvature angle (°)	52.7 (±9.7)	40.3 (±9.1)	<0.001
PDQ			
Psychological and physical symptoms	12.2 (±6.2)	10.9 (±6.6)	0.01
Penile pain	7.4 (±7.3)	4.0 (±4.1)	<0.001
Symptom bother	8.6 (±3.9)	7.2 (±3.2)	<0.001

Data are expressed in mean (±s.d.). PDQ: Peyronie's Disease Questionnaire; s.d.: standard deviation

3.4 (±3.5; $P < 0.001$) and 1.5 (±3.0; $P < 0.001$), respectively. Regarding the GAPD questionnaire, 50 patients (80.6%) reported subjective improvement of the penile curvature. Among those, 13 patients (21.0%) reported a "small but important" improvement, 12 patients (19.4%) reported a "moderate" improvement, and 25 (40.3%) patients reported a "huge" improvement.

No long-lasting local adverse effects were recorded in the database. In one patient (1.6%), a transient palpable lump appeared after the injection and disappeared at the 3-month follow-up visit. No systemic side effects were recorded in the database.

DISCUSSION

PD is still given much attention today, especially taking into consideration minimally invasive treatments.[18] One of the therapeutic approaches, which is always taken into great consideration, is based on the injections of pharmacologically active substances right into penile plaques. This approach could enable the localized administration of a specific agent delivering high-concentration medication directly into the plaque. However, it might be challenging to guarantee that the chosen compound will reach the target location, especially in the case of a solid or calcified plaque. This is one of the reasons why patients with stable-phase PD are included by most of the studies focusing on proving the efficacy of new and more effective intralesional injections of pharmacologically active substances.[19,20]

Nowadays, the only medications approved for the intralesional treatment of PD are CCH and interferon (IFN)-2b, whereas intraplaque injections of HA may be taken into consideration only in ethical approved clinical trials. This statement is reflected by the European Association of Urology guidelines on Sexual and Reproductive Health, based on literature findings of clinical trials on HA excluding patients with chronic-phase PD or with calcified plaques.[3]

The possible rationale behind the use of HA in stable-phase PD lies in different aspects. First, it has been demonstrated that high molecular weight-HA (HMW-HA) has anti-inflammatory and immunosuppressive effects.[21] This is the main reason why it has been used and proved efficient in the acute phase of the disease. Second, the ECM contains HA and is crucial for tissue regeneration and repair. In this context, HA injections into the plaque may aid in modulating the ECM's composition, which may help in the remodeling of fibrotic tissue and enhance the flexibility and regular structure of the penile tissue. Lastly, HA is able in maintaining hydration for space filling by improving lubrication. Thus, the expanding ability due to the HMW-HA may interfere with the traction forces applied by the plaque to the tunica albuginea during erection.

In the present retrospective study, 62 patients received 3 intraplaque injections, administrated within two weeks of each other, followed by a protocol of modeling, stretching, and use of a vacuum device. Overall, with respect to baseline curvature, patients had a median improvement of 12.4° and almost half of them had reported a "huge" improvement according to the GAPD questionnaire. Moreover, the analysis of the PDQ revealed improvements in all three domains.

Current literature data show contrasting results regarding the utility of HA injections in improving penile curvature in patients with acute-phase PD. Indeed, Gennaro *et al.*,[22] in a case–control study involving 83 patients with PD treated with HA injections and 81 patients who refused the same injections, did not find significant improvement in penile curvature after 30 injections of 20 mg of HA over 6 months. Contrary, Zucchi *et al.*,[23] in a prospective, single-arm, interventional, multi-center study, involving 65 patients with acute-phase PD treated with intralesional injections of HA, found a median improvement of penile curvature of 10° after a 10-week cycle of weekly intraplaque injections of HA. The findings from our analysis support previous data on the utility of administrating HA intraplaque injections with improvements in penile curvature after 3 injections administrated every two weeks. Moreover, we are here to demonstrate improvements in penile curvature in patients with stable-phase PD.

PD is a sexual dysfunction recognized for the great impact on men and couples' mental health.[24] According to a literature review of 2016 by Terrier and Nelson,[25] almost half of the men affected by PD suffer from depressive mood, and described themselves as "abnormal", "ugly", "disgusting", "like a cripple", and a "half man". Moreover, previous authors demonstrated that the perception of greater penile curvature degrees increases the psychological consequences of PD, with an overall higher symptomatic burden as scored with the PDQ.[26] In this context, along with improvements in penile curvature thanks to direct injections of HA, in our study, we found a statistically significant improvement also in all the PDQ domains after the 6-week adopted protocol. Indeed, patients reported improvements in penile pain and the physical and psychological impact of the disease. This result is also confirmed by the analysis of the GAPD questionnaire which showed that more than 80% of involved patients reported subjective improvement of penile curvature referred to as "huge" by patients.

Finally, accordingly with evidence emerged since the first study concerning HA intraplaque injection,[23] no significant systemic side effects were recorded in the involved population of our study. Indeed, just one patient presented a local transient palpable lump which completely disappeared after 3 months, thus confirming the overall safety of this approach in the administration of HA and also in the stable-phase PD.

Our study is certainly not devoid of limitations. First, the retrospective nature of the study may cause biases due to missing data. Second, we did not use a number of questionnaires potentially useful in this specific setting, thus including for instance the self-esteem and relationship questionnaire, which could have suggested further relevant clinical findings. Third, the study was not randomized and did not include control groups treated with placebo or other therapies, thus, larger studies are needed to confirm results from the current study. However, despite limitations, here, we define the effectiveness and safety of a 6-week protocol based on HA intraplaque injections every two weeks, followed by vacuum device therapy, penile stretching, and modeling exercises, in patients with stable-phase PD.

In conclusion, HA injections are gaining attention in the treatment of PD. We demonstrated that after 3 injections of HA administered every 2 weeks, patients with stable-phase PD could experience with significant improvements in penile curvature and perception of physical and psychological consequences of the disease without any significantly relevant side effects.

AUTHOR CONTRIBUTIONS

SC, M Capece, RLR, G Celentano, GIR, and MF provided the conception and design of the study. SC, M Capece, C Marino, and MR contributed to data acquisition. SC, M Capece, AM, and M Creta analyzed and interpreted data. CM, G Califano, and CC drafted the manuscript. RLR, GIR, AM, and MF provided style revision. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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