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Comparison of Intralesional Hyaluronic Acid *vs*. Verapamil for the Treatment of Acute Phase Peyronie's Disease: A Prospective, Open-Label Non-Randomized Clinical Study

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Purpose: To compare the efficacy and safety of intralesional hyaluronic acid (HA) as compared with verapamil injection in patients with Peyronie's disease (PD).

Materials and Methods: Between January 2015 and December 2018, men in PD acute phase were prospectively recruited. This open-label, prospective study included 2 different protocols. Group A: 8-week cycle of weekly intraplaque injections with HA; Group B: 8-week cycle of weekly intraplaque injections with verapamil. Penile curvature, plaque size, International Index of Erectile Function (IIEF)-15 score and visual analogue scale (VAS) were assessed at baseline and after 3 months.

Results: Two-hundred forty-four patients were enrolled. Of these, 125 received intralesional HA (Group A), 119 received intralesional verapamil (Group B). At enrollment, median age was 56.0 years (interquartile range [IQR]=47.0–63.0 years), median curvature 35.0° (IQR=25.0°–45.0°), median IIEF-15 score 19.0 (IQR=16.0–23.0), median VAS 4.0 (IQR=4.0–5.0). Median difference for IIEF-15 was 1.0 (95% confidence interval [CI]=1.12–1.94) in Group A and 0.0 (95% CI=-0.04–0.14) in Group B ($p<0.05$) and median difference for VAS score was -4.0 (95% CI=-4.11–-3.65) in Group A and -1.0 (95% CI=-0.50–2.01) in Group B ($p<0.05$). Plaque size decreased by -1.50 mm (IQR=1.60–2.10 mm) in Group A and -1.20 in Group B ($p=0.10$), while penile curvature decreased by -9.50° (IQR=4.50°–13.00°) in group A and -4.50 (IQR=2.50–7.50) in Group B ($p<0.01$).

Conclusions: Intralesional HA injections could represent a reliable treatment option for the conservative management of patients with acute phase of PD.

Keywords: Hyaluronic acid; Penile induration; Penile curvature; Peyronie disease; Verapamil

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INTRODUCTION

Peyronie's disease (PD) is defined as a chronic benign condition characterised by the formation of localized fibrous inelastic scars at the level of the tunica albuginea of the penis. This condition can lead to penile curvature, painful erections and erectile dysfunction (ED). PD is believed to affect 3% to 9% of the male population, with a higher prevalence among patients suffering from ED, diabetes and cardiovascular disease [1-4]. PD presents 2 different phases: active or acute and stable or chronic. It is paramount to distinguish between acute and chronic phase of the condition, since management is different in the 2 phases. Plaque formation and calcification generally take place during the acute phase [5,6], which can last for up to 18 months [7]. In the chronic phase, penile pain will be reduced, and penile deformity stabilized. Transition to the chronic phase is defined when curvature remains stable for at least 3 months [8].

Treatment of PD includes both medical and surgical approaches and the management is tailored to the phase of the disease, the degree of deformity, the quality of the erections and patient's choice [4,9,10]. Currently, intralesional injections of corticosteroids and verapamil represent the most common treatments offered for the management of acute phase of PD [10,11]. Hyaluronic acid (HA) seems to be effective in interfering with scar formation and counteracting the negative effects of inflammation and oxidative stress mediators [12]. In particular, in the early stage of PD, oxidative stress seems to play a key role in the pathogenesis of PD as it induces overexpression of fibrogenic cytokines and increases collagen synthesis.

The aim of the present study is to investigate whether intralesional injections of HA in the acute phase could reduce the progression of PD thanks to its interference with inflammatory and pro-fibrotic processes. Therefore, a prospective, longitudinal, open-label, non-randomized clinical study, has been designed to evaluate and compare the efficacy and safety of intralesional HA as compared with the use verapamil injection in patients during the acute phase of PD.

MATERIALS AND METHODS

1. Patient population

The analyses were based on prospectively collected data of a cohort of 244 patients who were treated with intralesional HA or verapamil for PD between January 2015 and December 2018.

The study was carried out after the realization of a specific informed consent, with the internatl approval of Donatello Private Hospital Committee (MED-2019-VD). Sexually active men older than 18 years and 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) progressive penile curvature >15° and/or penile pain in the flaccid state or at erection in the last 12 months. Patients with ventral curvature, hourglass deformity, initial curvature less than 15° and calcified penile plaques were excluded. Congenital penile curvature, history of previous penile surgery, concomitant oral treatment for PD, intralesional therapy or use of any traction device, clinically stable disease and history of symptomatic disease longer than 12 months were also considered criteria of exclusion.

2. Study design

A prospective, controlled study on men suffering from acute phase of PD was conducted. The 2 treatment arms included:

- Group A: 8-week cycle of weekly intraplaque injections with HA (0.8% highly purified sodium salt HA 16 mg/2 mL);
- Group B: 8-week cycle of weekly intraplaque injections with verapamil (10 mg in 5 mL of normal saline water).

Assessment visits were scheduled at screening visit on day 0 and 3 months after completion of therapy.

3. Outcome measures

After the preliminary evaluation for eligibility, including medical and sexual history, patients were asked to complete self-administered questionnaires, such as the International Index of Erectile Function (IIEF-15) [13]. The IIEF-15 scale analyses the degree of ED, classified as follows: severe (IIEF-15≤10), moderate (IIEF-15 between 11 and 16), and mild (IIEF-15 between 17 and 25). Penile curvature was assessed using a goniometer at maximum penile rigidity. Self-assessment of penile pain was measured using a visual analogue scale (VAS) ranging from 0 to 10.

4. Statistical analysis

Descriptive statistics were obtained reporting me-

Table 1. Baseline characteristics of the patients

Characteristic	Group A (hyaluronic acid)	Group B (verapamil)	p-value
Patient	125 (51.2)	119 (48.8)	
Age (y)	55.0 (46.0–61.0)	57.0 (47.0–63.0)	0.21
BMI (kg/m^2)	24.0 (22.0–26.0)	25.0 (22.0–27.0)	0.65
Hypertension	53 (42.4)	54 (45.4)	0.32
Cardiovascular disease	28 (22.4)	24 (20.2)	0.42
Diabetes	30 (24.0)	33 (27.7)	0.27
Duration of the disease (mo)	2.0 (1.5–3.0)	2.5 (1.8–3.5)	0.28
Penile curvature (°)	35.0 (25.0–45.0)	35.0 (27.0–48.0)	0.35
Plaque size (mm)	10.40 (7.50–13.4)	11.20 (8.50–14.30)	0.38
IIEF-15 score	20.0 (18.0–22.0)	19.0 (16.0–23.0)	0.56
VAS score	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.8

Values are presented as number (%) or median (interquartile range).
BMI: body mass index, IIEF: International Index of Erectile Function, VAS: visual analogue scale.

dians (and interquartile ranges, IQR) for continuous variables, and frequencies and proportions for categorical variables, as appropriate. Continuous variables were compared by the Student t or the Mann–Whitney U-test based on their normal or not-normal distribution, respectively (normality of variables' distribution was tested by the Kolmogorov–Smirnov test). Categorical variables were tested with the chi-square test. Differences between median penile curvature changes observed in the different groups were compared using one-way ANOVA test. All statistical analyses were completed using Stata software ver. 14 (Stata Corp., College Station, TX, USA). For all statistical comparisons, a significance level of $p<0.05$ was considered to show differences between the groups.

RESULTS

Overall, 244 patients with acute phase of PD were screened. Of these, 125 patients (51.2%) received intralesional HA (Group A), while 119 (48.8%) received intralesional verapamil (Group B). Table 1 reports the demographics and clinical data of the study groups. Overall, median age was 56.0 years (IQR=47.0–63.0), median curvature was 35.0° (IQR=25.0°–45.0°), median IIEF-15 score was 19.0 (IQR=16.0–23.0), and median VAS was 4.0 (IQR=4.0–5.0). No differences between the groups were found according to baseline characteristics of the patients. All subjects completed the treatment cycle and attended the 3-month follow-up visit. No injection-site ecchymosis or hematomas were observed.

No local or systemic drug reactions were recorded.

At 3-month follow-up, plaque size decreased by -1.50 mm (IQR=1.60–2.10 mm) in Group A and -1.20 mm in Group B, showing no statistically significant differences between the 2 treatment schedules (p=0.10). As regards penile curvature, it decreased by -9.50° (IQR=4.50°–13.00°) in group A and -4.50° (IQR=2.50°–7.50°) in Group B (p<0.01). The median difference between pre- and post-treatment IIEF-15 was 1.0 (95% confidence interval [CI]=1.12–1.94) in Group A and 0.0 (95% CI=-0.04–0.14) in Group B (p<0.05), while the zmedian difference for VAS score was -4.0 (95% CI=-4.11–-3.65) in Group A and -1.0 (95% CI=-0.50–2.01) in Group B (p<0.05) (Table 2).

Table 2. Mean changes of primary outcomes between groups from baseline to final follow-up

	Group A (hyaluronic acid)	Group B (verapamil)	p-value
Plaque size (mm)[a]	-1.50 (1.60–2.10)	-1.20 (0.80–1.30)	0.10
Penile curvature (°)[a]	-9.50 (4.50–13.00)	-4.50 (2.50–7.50)	<0.01
IIEF-15 score[b]	1.0 (1.12–1.94)	0.0 (-0.04–0.14)	<0.05
VAS score[b]	- 4.0 (-4.11–-3.65)	-1.0 (-0.50–2.01)	<0.05

IIEF: International Index of Erectile Function, VAS: visual analogue scale.
[a]Values are presented as median (interquartile range). [b]Values are presented as median (95% confidence interval).

DISCUSSION

PD is a disorder characterized by a pathological collagen deposition at the level of the tunica albuginea of the penis, leading to the formation of fibrous and inelastic plaques that can cause penile shortening and deformity and worsen the quality of erections. To date, there is not unanimous consent over the ideal management of the acute phase of PD.

Although surgery remains the gold standard treatment option for patients with stable PD, it is not recommended for men in the active phase. On the other hand, collagenase *clostridium histolyticum* (CCH) represents the only licensed drug for the minimally invasive treatment of PD [14,15], however the acute phase of PD is not currently an indication for CCH therapy [3,16,17]. Four studies [18-21] demonstrated significant improvements in penile curvature after 10 or 15 mg intralesional verapamil, although the protocols varied widely, ranging from 6 to 12 injections. Heidari et al [19] also

demonstrated improvements in erectile function after intralesional injection of verapamil 10 mg. However, current available data concerning intralesional therapy with verapamil show significant heterogeneity, due to the use of various treatment schemes. Furthermore, the absence of placebo groups undermines the reliability of the results, limiting their capability to provide robust evidence.

In light of these considerations, the current study evaluates the safety and efficacy of intralesional HA as compared with the use verapamil injection in patients in the acute phase of PD. Intralesional HA showed an excellent safety profile, since no injection-site ecchymosis or hematomas were observed and no adverse drug reactions were recorded, resulting in an optimal compliance to the treatment. At 3-month follow-up, HA injection therapy was associated with a better outcome in term of VAS score reduction, as compared with intralesional verapamil. IIEF-5 improved as well in HA group, while no difference between pre and post treatment was found in the verapamil group. Furthermore, we observed a greater meaningful reduction in terms of penile curvature in the HA group, while HA injection therapy was associated with better outcome in terms of plaque size reduction, as compared with intralesional verapamil, although difference did not reach statistical significance.

HA represents the predominant glycosaminoglycan found in in the extracellular matrix. It is composed of glucuronic acid and N-acetylglucosamine, kept together by β-glycosidic bonds. High levels of HA are present in the tunica albuginea and regulate the distribution of bio elements in the connective tissue. In the early stages of PD, oxidative stress provokes overexpression of fibrogenic cytokines and increases collagen deposition. To this regard, HA has shown to counteract the effect of inflammatory cytokines, thus limiting plaque generation and progression. In a prospective, single arm multicentric study, Zucchi et al [12] showed that intralesional HA reduced plaque size and penile curvature and improved IIEF. Similar findings were reported by Gennaro et al [22] in another study including 83 patients undergoing intralesional treatment with HA *vs.* 81 subjects in the control group. Furthermore, a recent multicentric, prospective, randomized study by Favilla et al [23] compared intralesional verapamil *vs.* HA in patients with early of PD. In line with the findings of the current study, Favilla et al [23] demonstrated greater efficacy of HA in terms of patients' satisfaction compared to calcium-antagonists. However, Favilla et al [23] also found a statistically impact of HA injections on penile curvature, which differs from what the findings of the current study. Although HA is more expensive than verapamil, the cost of HA is certainly lower than other intralesional agents, such as CCH [24]. Moreover, the use of intralesional HA showed no significant drug related adverse events and excellent level of patients' compliance. Therefore, intralesional HA injections could represent a reliable therapeutic option for the management of the acute phase of PD.

The main limitations of the current series are the lack of a control group treated with placebo and the short follow-up, which might have limited interpretation of data. Furthermore, the lack of randomization might have added statistical bias, undermining the reliability of the findings. Despite of these limitations, the findings of the current series provide a robust foundation to assess efficacy and safety of different intralesional therapies during the acute phase of PD. Further prospective, randomized, placebo-controlled studies with larger cohorts and longer follow-up will be needed to confirm the findings of the current series and to establish the real impact of intralesional HA as a therapeutic option for early-stage PD.

CONCLUSIONS

HA injections seem to provide an effective minimally invasive option in the acute phase of PD and might have the potential to lower penile pain and ameliorate IIEF, as compared with other intralesional agents. Further prospective studies with higher statistical power and larger cohorts will be required to confirm our preliminary findings.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: AC, FDM, GC. Data curation: AC, FDM, GC, GIR. Formal analysis: PV, NL, RC, AM, MDM, MF. Supervision: GG, AM, GIR. Validation: AC, AM, GIR. Visualization: AC, GC, GG, AM, GIR. Writing – original draft: AC, FDM, GC. Writing – review & editing: AM, GIR.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time due to technical and time limitations.

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