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ORIGINAL RESEARCH ARTICLE

Efficacy of Collagenase *Clostridium histolyticum* (Xiapex®) in Patients with the Acute Phase of Peyronie's Disease

Andrea Cocci[1] · Fabrizio Di Maida[1] · Giorgio Ivan Russo[2] · Paolo Capogrosso[3] · Lotti Francesco[4] · Michele Rizzo[5] · Marina Di Mauro[2] · Andrea Salonia[3] · Gianmartin Cito[1] · Marco Falcone[6] · Andrea Romano[1] · Gaia Polloni[7] · Juan Ignacio Martinez-Salamanca[8] · Esaù Fernández-Pascual[8] · Andrea Minervini[1] · Nicola Mondaini[9]

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Abstract

Background and Objective Plaque formation ordinarily takes place in the acute phase of Peyronie's disease. There is no unanimous consent regarding the management of the acute phase of Peyronie's disease. The objective of this study was to evaluate the advantages of using a single intralesional injection of collagenase *Clostridium histolyticum* in patients with the active phase of Peyronie's disease and to assess its effect on disease progression by reducing penile curvature and ameliorating pain during sexual intercourse.

Methods Sexually active men aged older than 18 years with the acute phase of Peyronie's disease were enrolled. All patients received treatment with a single intralesional injection of collagenase *Clostridium histolyticum*. The primary outcome of the study was the change in penile curvature after treatment while secondary outcomes were the change in sexual function (International Index of Erectile Function [IIEF-5]) and in the Peyronie Disease Questionnaire (PDQ) and its sub-scores, PDQ-PS (psychological symptoms), PDQ-PP (penile pain) and PDQ-BD (bother disease).

Results Overall, 74 patients were enrolled. Mean penile curvature at baseline was 41.1° ± 12.2°. The mean changes before and at the 3-month evaluation in terms of penile curvature, Visual Analog Scale score at rest, and Visual Analog Scale score during intercourse were − 19.3 ± 8.4 ($p < 0.0001$), − 0.8 ± 1.1 ($p < 0.0001$) and − 3.8 ± 0.9 ($p < 0.0001$) with the benefit persisting also after 6 months. Moreover, improvements of mean IIEF-5 score (1.1 ± 0.9, $p = 0.03$; 0.9 ± 0.5, $p = 0.02$), PDQ-PS (− 2.7 ± 2.2; − 2.5 ± 2.0, $p = 0.01$), PDQ-PP (− 1.2 ± 1.6; − 1.1 ± 1.2, $p = 0.02$) and PDQ-BD (− 3.8 ± 3.4; − 3.5 ± 3.1, $p = 0.001$) were observed 3 and 6 months after the end of treatment, respectively. At the multivariable regression analysis, the time since disease onset (modelled with non-linear terms) and baseline curvature were independently associated with the degree of curvature improvement (coefficient: 0.30; 95% confidence interval 0.16–0.44) after a single intralesional injection (all $p < 0.03$).

Conclusions Although intralesional therapy with collagenase *Clostridium histolyticum* is not yet indicated for the acute phase of Peyronie's disease, these preliminary results suggest the effectiveness of this minimally invasive option by improving penile curvature and IIEF-5 and PDQ scores.

1 Introduction

Peyronie's disease (PD) presents with the onset of confined fibrous inelastic plaques in the tunica albuginea of the penis, usually leading to penile deformity, painful erections and, finally, erectile dysfunction. The pathophysiology of PD remains the subject of great discussion. Some authors have suggested there might be a disturbance of the healing cascade at the level of the tunica albuginea, seemingly secondary to microtraumas during sexual intercourse [1, 2].

Key Points

To date, the ideal management of the acute phase of Peyronie's disease remains open to discussion.

A single collagenase *Clostridium histolyticum* injection during the acute phase might represent an effective, minimally invasive treatment option by improving penile curvature and pain during sexual intercourse, especially when collagenase *Clostridium histolyticum* is administered within the first 3 months of disease onset.

✉ Fabrizio Di Maida
fabrizio.dimaida@unifi.it

Extended author information available on the last page of the article

However, as the primary inflammation process persists, the disorder can progress to the formation of fibrous plaques, which are responsible for the widely known penile unnatural curvature and shortening [3, 4]. Peyronie's disease is typically characterised by the onset of an acute and a chronic phase. It is critical to distinguish the two phases, as treatment choices can vary depending on the different stages of the disorder. Indeed, plaque formation ordinarily takes place in the acute phase [5, 6], while during the chronic phase, the pain will commonly be reduced and penile curvature stabilised. The watchful waiting approach of the acute phase could be dangerous for patients because of the possible worsening of the curvature and contextual shortening.

To date, there is no unanimous consent regarding the management of the acute phase of PD. Indeed, although surgery still embodies the most common treatment alternative for patients presenting with stable PD, it is not recommended for men in the active phase. However, even though collagenase *Clostridium histolyticum* (CCH) represents the only licensed drug for the conservative management of PD [7, 8], the acute phase has not been recognised as an indication for intralesional therapy with CCH [9–11]. Until a unanimous consensus on the definitions of acute and stable phase PD is reached, the use of CCH in the early stage of the disease might be an option. Therefore, the assessment of the efficacy of the CCH intralesional injection in patients in the acute phase of PD currently represents a clinical unmet need.

To this regard, the present prospective, single-arm, clinical study was designed to investigate whether a single intralesional injection of CCH during the acute phase of PD could limit the progression of the disorder by reducing penile curvature and ameliorating penile pain during sexual intercourse.

2 Patients and Methods

2.1 Patient Population and Assessment

Between January 2018 and January 2019, we prospectively gathered demographic and clinical data of a cohort of 74 patients treated with intralesional CCH for the acute phase of PD. Every subject filled out a written fully informed consent before enrolment. The study was conducted in accordance with Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. Sexually active men aged older than 18 years and presenting with an acute phase of PD were considered eligible for the present study. Main inclusion criteria at baseline were (1) presence of a palpable plaque at the level of tunica albuginea of the penis and (2) penile curvature > 15° and/or penile pain either in a flaccid state or during erection in the previous 3 months.

Penile curvature was calculated using a goniometer at maximum erection. Baseline curvature was also assessed using the Ruler Web App, as a further quality control. To this regard, patients were asked to take a preliminary photograph of their penis during erection. Moreover, a preliminary evaluation was performed by ambulatory ultrasonography to identify possible non-palpable lesions and to assess the extent of penile fibrosis. Detection of calcifications within the plaque suggested stabilisation of the disease and, thus, those patients were excluded from the final analyses. Similarly, patients showing penile ventral curvature were excluded.

All eligible patients received treatment with a single intralesional injection of CCH (CCH-Xiapex®, Swedish Orphan Biovitrum (Sobi), Stockholm, Sweden) 0.9 mg diluted in 0.25 mL of saline solution. The injections were administered without local penile anaesthesia. After the initial screening visit, patients were requested to fill in self-administered questionnaires such as the International Index of Erectile Function (IIEF-5) and the Peyronie's Disease Questionnaire (PDQ). Self-assessment of penile pain was evaluated by a Visual Analog Scale (VAS) with a range from 0 to 10. The results were evaluated at baseline and at 3 and 6 months after treatment.

After the CCH injection, subjects were instructed to perform a combination of modelling and stretching to mechanically stretch the fibrous plaque. Starting 48 h after the CCH injection, home modelling was performed with patients attempting to gently straighten the erect penis. Stretching exercises involved a gradual stretch of the flaccid penis for 60 s. All patients were advised on the importance of adhering to the home stretching exercises.

2.2 Statistical Analysis

Data were reported as means ± standard deviation. Continuous variables were compared by the Student *t* test or the Mann–Whitney *U* test depending on their normal or not-normal distribution, respectively. Normality of variables' distribution was tested by the Kolmogorov–Smirnov test. Differences between pre- and post-treatment variables were assessed using the paired *t* test. Locally weighted regression methods were used to explore the relationship between clinical characteristics and the degree of curvature improvement after treatment. A quadratic regression analysis was applied to test for the non-linear association between time since disease onset and the investigated outcome. A multivariable regression model tested the predictor of the degree of curvature improvement after a single CCH intralesional injection. All statistical analyses

were performed using Stata statistical software, version 14 (2015, Release 14; StataCorp LP, College Station, TX, USA). A significance level of $p < 0.05$ was set for all tests.

3 Results

Overall, 74 patients with an acute phase of PD were eligible for the present study. Table 1 reports the demographics and clinical data of the whole cohort. The mean age in the whole cohort was 48.4 ± 1.7 years. The mean time since disease onset was 4 ± 1.2 months, while mean penile curvature at baseline was 41.1° ± 12.2°. Table 2 reports baseline and post-treatment clinical parameters: mean penile curvature significantly improved after a single intralesional injection of CCH, with a mean difference between baseline and the 3 month-evaluation curvature of − 19.3 (standard deviation [SD]: 8.4; 95% CI 17.4–21.3, $p < 0.0001$), with the improvement reducing to − 18.9 ± 7.4 ($p < 0.0001$) after 6 months. The mean differences (SD) of the VAS score at rest and of the VAS score during intercourse between baseline and after a single injection of CCH were − 0.8 (SD: 1.1; 95% CI 0.5–1.0; $p < 0.0001$) and − 3.8 (SD: 0.9; 95% CI 3.6–4.1; $p < 0.0001$), respectively, with the benefit persisting at the 6-month evaluation. Furthermore, at the first follow-up visit, we observed an improvement of the post-treatment IIEF-5 score (mean difference − 1.1; SD: 0.9; 95% CI 0.9–1.3; $p = 0.03$), PDQ-PS (mean difference − 2.7; SD: 2.2; 95% CI 1.9–3.5; $p = 0.01$), PDQ-PP (mean difference − 1.2; SD: 1.6; 95% CI 0.6–1.8; $p = 0.02$) and PDQ-BD (mean difference − 3.8; SD: 3.4; 95% CI 2.7–4.5; $p = 0.001$). After 6 months, post-treatment mean changes slightly reduced in terms of IIEF-5 score (mean difference 0.9; SD: 0.5; $p = 0.02$), PDQ-PS (mean difference − 2.5; SD: 2.0; $p = 0.01$), PDQ-PP (mean difference − 1.1; SD: 1.2; $p = 0.03$) and PDQ–BD (mean difference − 3.5; SD: 3.1; $p = 0.001$). No injection-site ecchymosis or hematomas were observed. No local or systemic drug reactions were recorded.

Table 3 shows the results of a multivariable regression analysis predicting the degree of curvature improvement. We observed a non-linear significant association ($p = 0.03$) between time of disease onset and the degree of curvature reduction: patients with a disease lasting for more than 3 months appeared less likely to have a clinically significant improvement after a CCH injection (Fig. 1). Moreover, patients with a greater baseline curvature appeared to improve more after treatment (coefficient 0.3; 95% CI 0.16–0.44; $p < 0.0001$).

Table 1 Patients' baseline characteristics ($N = 74$)

Baseline characteristic	Value (mean ± SD)
Age (years)	48.4 ± 1.7
Partner age (years)	46.8 ± 1.5
Time since disease onset (months)	4 ± 1.21
Curvature (°)	41.1 ± 12.2
VAS score at rest	0.8 ± 1.1
VAS score during intercourses	4.3 ± 0.8
IIEF-5 at baseline	20.1 ± 1.8
PDQ–PS at baseline	9.1 ± 3.7
PDQ–PP at baseline	3.8 ± 1.9
PDQ–BD at baseline	13.5 ± 5.8

BD bother domain, *IIEF* International Index of Erectile Function, *PDQ* Peyronie's Disease Questionnaire, *PP* penile pain, *PS* physical symptom, *SD* standard deviation, *VAS* Visual Analogue Scale

Table 2 Descriptive statistics of efficacy parameters at the follow-up assessment and mean changes in values from baseline to the 3-month evaluation for penile curvature, International Index of Erectile Function (IIEF-5) and Peyronie's Disease Questionnaire (PDQ) sub-domains

Parameter	Baseline	After single intralesional injection	Post-treatment (3 months) difference	95% CI	*p* value[a]	Post-treatment (6 months) difference	*p* value[a]
Curvature (°)	41.1 (12.2)	21.1 (11.2)	− 19.3 (8.4)	17.4–21.3	< 0.0001	− 18.9 (7.4)	< 0.0001
VAS score at rest	0.8 (1.1)	0.05 (0.2)	− 0.8 (1.1)	0.5–1.0	< 0.0001	− 0.8 (1.1)	< 0.0001
VAS score during sexual intercourses	4.3 (0.8)	0.5 (0.8)	− 3.8 (0.9)	3.6–4.1	< 0.0001	− 3.4 (0.8)	< 0.0001
IIEF-5	20.1 (1.8)	21.3 (1.5)	1.1 (0.9)	0.9–1.3	0.03	0.9 (0.5)	0.02
PDQ–PS	9.1 (3.7)	6.3 (2.9)	− 2.7 (2.2)	1.9–3.5	0.01	− 2.5 (2.0)	0.01
PDQ–PP	3.8 (1.9)	2.6 (2.1)	− 1.2 (1.6)	0.6–1.8	0.03	− 1.1 (1.2)	0.03
PDQ–BD	13.5 (3.8)	9.6 (4.2)	− 3.8 (3.4)	2.7–4.5	0.001	− 3.5 (3.1)	0.001

All variables are expressed as mean (standard deviation)

VAS Visual Analogue Scale, *BD* bother domain, *CI* confidence interval, *PP* penile pain, *PS* physical symptom

[a]Paired *t* test

Table 3 Multivariable regression analysis predicting the degree of curvature improvement

Parameter	OR	95% CI	*p* value
Age	0.11	0.26–0.50	0.1
Time since disease onset	–	–	0.03[a]
Baseline curvature	0.30	0.16–0.44	< 0.0001

CI confidence interval, *OR* odds ratio

[a]Modelled with non-linear terms

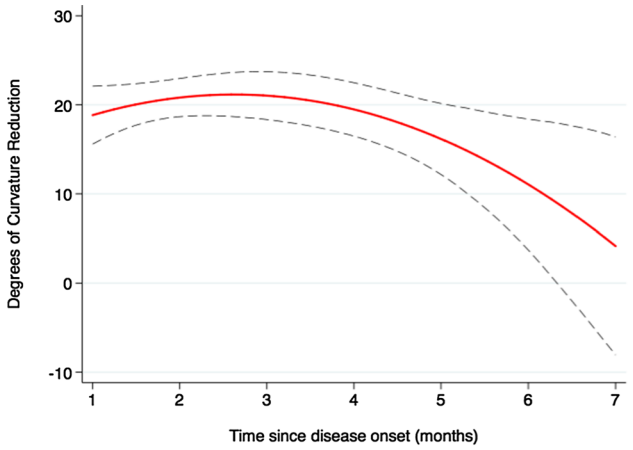

Fig. 1 Curvature reduction after a single intralesional injection according to the time since disease onset (the dashed lines represent the 95% confidence interval)

4 Discussion

To date, the ideal management of the acute phase of PD remains open to discussion [12–14]. On the one hand, most studies in the currently available literature assessing CCH efficacy enrolled only subjects with stable disease. On the other hand, we must point out that delaying treatment until penile curvature is stabilised can be unsatisfying for patients as the acute phase can last up to 12–18 months. Being unable to engage in sexual intercourse for long periods can have an adverse psychological effect. As a result, although international guidelines still do not recommend CCH therapy until penile plaque and curvature are stabilized [15], recently, post-approval studies started to include patients who also meet the acute-phase criteria.

In light of these considerations, the current study aimed to assess the safety and efficacy of a single intralesional CCH injection in patients in the acute phase of PD. Intralesional CCH showed an excellent safety profile with no major injection-site or systemic drug-related adverse events recorded, ending in an optimal compliance to the therapy. Notably, after a single CCH intralesional injection, a meaningful improvement was observed with regard to penile curvature, VAS score, IIEF-5 and PDQ scores, with the benefits slightly reducing at the 6 month-evaluation but still maintaining a statistically significant difference as compared with baseline. Most of all, we observed that curvature reduction was related to time since disease onset, being significantly greater when intralesional CCH had been administered within the first 3 months.

Only a few reports are available in the literature regarding the use of CCH therapy for the early stages of PD. Yang and Bennett [16] first reported a mean curvature decrease of 20° with intralesional CCH in 12 patients in the acute phase. Despite the limited sample size, this study was pivotal in proving that CCH may be able to modify the course of PD even if an intervention takes place during the acute phase. Moreover, we hypothesised that the CCH intraplaque injection during the acute phase could be more beneficial in terms of penile curvature improvement as compared with treatment in the stable phase. Similarly, Anaissie et al. [17] in a recent retrospective study found that patients in the acute phase of PD had a median decrease in penile curvature comparable to that observed in patients presenting with the stable phase. Of note, while this study failed to demonstrate superiority over stable-phase intervention, it provided a robust foundation to further support CCH intralesional injections during the acute phase.

The effectiveness of early intervention with CCH in the acute phase of PD can be partially explained by the prevention of plaque development. The pathophysiology of PD is still the subject of great discussion; however, it is widely believed that fibroblasts may play a significant role in plaque formation by depositing collagen in response to several cytokines such as transforming growth factor (TGF)-β1 [18–21]. In particular, TGF-β1 has been recently implicated also in plaque calcification through osteoblast differentiation. Indeed, TGF-β1 represents one pivotal paracrine modulator able to stimulate the conversion of fibroblasts into myofibroblasts and promote osteogenesis [22, 23]. In this light, by interfering with TGF-β production and, thus, collagen deposition in the tunica albuginea, CCH administration during the acute phase might in fact preclude the onset of calcified plaques that will eventually become harder to treat [10, 11].

However, some would argue that CCH intralesional therapy can be burdened by higher costs as compared with the most common therapeutic agents for the treatment of early stages of PD, such as verapamil and calcium antagonists. Indeed, although effective, CCH use during the acute phase of PD is not currently listed as an indication for CCH administration and, as such, is not reimbursable from healthcare systems or insurance providers. Nevertheless, it must be said

that in the current paper, unlike previous works, we demonstrated that even a single intralesional CCH injection can be effective in ameliorating related symptoms and penile curvature, thus significantly reducing related treatment costs. However, whether the repetition of another CCH injection would be able to provide even better outcomes and its timing still remain clinical unmet needs.

The main limitations of the current paper are the lack of any placebo control group and the relatively low sample size and short follow-up, which might have weakened the evidence reported. Despite these limitations, the findings of the current series provide further evidence to deepen the knowledge on alternative treatment options for early stages of PD. Our findings are promising for subjects who desire to start treatment in the acute phase of the disorder. Indeed, our results suggest that even a single CCH injection can be used earlier to potentially obtain an overall better response. Further prospective randomised studies with larger cohorts and a longer follow-up are needed to confirm our preliminary results and to better clarify the real potential employment of a single CCH injection as an effective therapeutic alternative for the acute phase of PD.

5 Conclusions

Although the acute phase of PD has not been recognised as an indication for intralesional therapy with CCH, preliminary results suggest that a single CCH injection during this phase might represent an effective, minimally invasive treatment option by ameliorating penile curvature and improving IIEF scores, especially when patients are treated within the first 3 months of disease onset. Further prospective studies with larger cohorts are needed to validate our findings.

Compliance with Ethical Standards

Funding No sources of funding were received for the conduct of this study or the preparation of this article.

Conflict of interest Andrea Cocci, Fabrizio Di Maida, Giorgio Ivan Russo, Paolo Capogrosso, Lotti Francesco, Michele Rizzo, Marina Di Mauro, Andrea Salonia, Gianmartin Cito, Marco Falcone, Andrea Romano, Gaia Polloni, Juan Ignacio Martinez-Salamanca, Esaù Fernández-Pascual, Andrea Minervini and Nicola Mondaini have no conflicts of interest that are directly relevant to the content of this study.

Ethics approval The study was approved by the Donatello Private Hospital Committee (MED-2019-VD) and conducted in accordance with Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

Informed consent All patients provided written informed consent to participate in the study.

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Affiliations

Andrea Cocci[1] · Fabrizio Di Maida[1] · Giorgio Ivan Russo[2] · Paolo Capogrosso[3] · Lotti Francesco[4] · Michele Rizzo[5] · Marina Di Mauro[2] · Andrea Salonia[3] · Gianmartin Cito[1] · Marco Falcone[6] · Andrea Romano[1] · Gaia Polloni[7] · Juan Ignacio Martinez-Salamanca[8] · Esaù Fernández-Pascual[8] · Andrea Minervini[1] · Nicola Mondaini[9]

1 Department of Urology, Careggi Hospital, University of Florence, Viale S. Luca, 50134 Florence, FI, Italy

2 Urology Section, Department of Surgery, University of Catania, Catania, Italy

3 Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy

4 Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

5 Department of Urology, University of Trieste, Trieste, Italy

6 Urology Clinic, A.O.U. Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy

7 Psychosexuologist, Como, Italy

8 Department of Urology, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

9 Andrology Center, Villa Donatello Hospital, Florence, Italy