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Intralesional collagenase *Clostridium histolyticum* for acute phase Peyronie's disease: a single-center, retrospective cohort study

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Background: Peyronie's disease (PD) can be subdivided into acute and chronic phases. Intralesional collagenase *Clostridium histolyticum* has been shown to improve curvature in the chronic phase. Initial clinical trials excluded patients in the acute phase from treatment. Recent studies show comparable results among men in the acute phase. The definition of acute phase varies among existing studies, but it is generally understood to last 12–18 months and is accompanied by penile pain and progression of deformity. We sought to evaluate the safety and efficacy of intralesional collagenase injection therapy during the acute phase of PD using multiple definitions of the acute phase.

Methods: All men receiving intralesional collagenase for PD from October 2015 through December 2020 at a single academic institution were retrospectively assessed for patient demographics and comorbidities, pre- and post-treatment curvature, and adverse events. Two definitions of acute phase were used: (I) acute phase duration ≤6 months, chronic phase duration >6 months; and (II) acute phase duration ≤12 months with penile pain, chronic phase duration >12 or no penile pain.

Results: Of 330 patients identified, 229 underwent intralesional collagenase treatment with pre- and post-treatment erect penile goniometry. 65 (28%) met criteria for definition 1 of acute phase, 37 (16%) met criteria for definition 2, and 76 (33%) met criteria for either. Percent change in penile curvature was not significantly different between acute and chronic phases using definition 1 (16.0% *vs.* 16.6%, P=0.89), definition 2 (19.9% *vs.* 15.7%, P=0.43), or either (16.5% *vs.* 16.3%, P=0.96). The rates of development of bruising, swelling, hematoma, or corporal rupture were not significantly different between the acute and chronic phases under either definition (all P>0.05).

Conclusions: This single-center, retrospective cohort analysis suggests that intralesional collagenase is both safe and effective for the treatment of men with acute phase PD. Limitations exist inherent to retrospective review, since many men did not return for post-treatment goniometry, possibly skewing our cohort toward incomplete responders. Prospective, randomized studies will be required to confirm these findings.

Keywords: Peyronie's disease (PD); acute phase; collagenase *Clostridium histolyticum*

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Introduction

Peyronie's disease (PD) is a penile condition characterized by fibrotic plaque formation within the tunica albuginea, causing pain and deformity. It affects an estimated 3.2–12% of men in the United States, and up to 20.3% of men with metabolic comorbidities (1-3). PD presents with concomitant erectile dysfunction (ED) in 40–50% of men. The physical manifestations of PD contribute to the development of emotional distress and relationship problems (4-12).

The natural history of PD can be divided into the acute (active) phase and the chronic (stable) phase. The acute phase is typified by progressive changes in penile morphology and the presence of erectile pain. The chronic phase is generally defined by stability in penile morphology for at least three months, as well as absence of erectile discomfort (13,14). The duration of the acute phase varies in the literature, although it is commonly accepted to last up to 12–18 months (15-18). Surgical treatment for PD is most definitive but is reserved for those with stable disease. For patients with acute phase PD, some non-surgical and minimally invasive treatment options include L-citrulline, pentoxifylline, vitamin E, and intralesional interferon-α2b, verapamil, or hyaluronic acid (15,18-23).

Intralesional injectable collagenase *Clostridium histolyticum* (trade name Xiaflex, Endo, Malvern, PA) works by cleaving the irregular amalgamations of collagen in PD plaques and is the only United States Food and Drug Administration (FDA) approved treatment for PD (24). The IMPRESS (Investigation of Maximal Peyronie's Reduction and Safety Studies) trials showed that intralesional collagenase with penile modeling significantly reduced curvature 32.4% and 34% with an acceptable safety profile (25,26). Those studies excluded patients in the acute phase of PD. Small studies have examined intralesional collagenase use in the acute phase (27-29). Nguyen *et al.* was the first to explicitly compare the acute and chronic phases in a single- and recently multi-institutional study, demonstrating no difference in efficacy and safety profile of collagenase between groups using a 12-month (with pain) cut-off and a 6-month cut-off respectively (30,31). However, more research in collagenase for acute phase PD is needed. Our study aims to retrospectively evaluate our institutional use of collagenase for acute phase patients as defined by those two definitions and to determine whether treatment with intralesional collagenase in the acute phase in our large patient cohort is safe and effective. We present the following article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-188/rc).

Methods

Patient population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board (IRB # 17-001594) at the University of California Los Angeles and individual consent for this retrospective analysis was waived. We obtained a database of all men undergoing intralesional injection of collagenase *Clostridium histolyticum* for the treatment of PD at our andrology clinic. We retrospectively analyzed the medical records of all patients in the database from October 2015 through December 2020 to evaluate curvature outcomes and adverse events. Patients at our clinic were considered candidates for treatment if they had a pre-treatment curvature of >30° and a palpable plaque. Patients with hourglass deformity and ventral curvature were considered candidates despite exclusion from the IMPRESS trials based on clinical judgement. Penile duplex ultrasonography was evaluated before and after treatment to determine presence and location of plaque and whether there was calcification within plaque. If the plaque had calcification, then the patient was counseled on surgical options for Peyronie's disease rather than intralesional collagenase.

Patients were categorized as experiencing the acute phase of PD at time of initiation of intralesional collagenase treatment based on the two following definitions:

- Definition 1: acute phase is defined by PD symptom duration ≤6 months.
- Definition 2: acute phase is defined by PD symptom duration ≤12 months with penile pain.

These two definitions were employed in separate analyses to address the variable use of the term "acute phase" in prior studies in the PD literature.

Intralesional injection protocol

Completion of pre-treatment and post-treatment erect penile goniometry was required for inclusion in analysis. Penile goniometry was performed at the point of maximal curvature after medication-induced erection (Trimix) at the time of duplex ultrasonography. Curvature degree for

primary and secondary curvatures were measured separately if present. Palpable plaque size was evaluated and noted at time of initial ultrasonography if not recorded during the initial consultation. Individual treatment cycles consisted of two injections of 0.58 mg collagenase *Clostridium histolyticum* (Endo Pharmaceuticals, Malvern, PA, USA) separated by 48–72 hours. A full course of therapy consisted of four treatment cycles, separated by six weeks, totaling 8 injections. Injections were performed using a previously described technique (32), followed by temporary application of a compressive wrap. Patients were instructed to perform flaccid penile modeling daily and abstain from sexual activity for 2 weeks after each cycle.

Outcome measures

The primary outcome measure for efficacy was percent change in primary penile curvature after a course of intralesional collagenase treatment. A secondary outcome measure was the identification of predictors of change in curvature. The primary endpoint for safety was the frequency of treatment-related adverse events (TRAE). Adverse events were recorded at each follow-up clinic visit and were categorized into minor and major events. Minor adverse events were defined as injection-site swelling or bruising (non-palpable discoloration), and major events were defined as hematoma formation [ecchymosis with palpable collection based on prior definition (32)] or penile corporal rupture.

Statistical analysis

We used descriptive statistics to assess the study population. All continuous variables were visually assessed for normality. Normally distributed variables were tabulated with means and standard deviations, whereas non-normal distributions were tabulated with medians and interquartile ranges. Student's *t*-test was used to compare percent change in curvature among patients with acute phase versus chronic phase PD. Multivariable linear regression was used to assess the independent association between phase of PD and percent change in curvature. Confounding variables and potential effect modifiers were selected *a priori* and based on previous literature (4,7,31,33-36). These included patient characteristics such as age; race/ethnicity; history of diabetes; smoking status; history of genitourinary surgery or Dupuytren's contracture; and disease characteristics such as concomitant ED, initial degree of curvature, primary curvature direction, size of palpable plaque, presence of two palpable plaques, and history of collagenase injections with an outside urologist prior to initial consultation within our system. The model was repeated with the application of both definitions of acute phase PD. Pearson chi-squared tests were used to compare the prevalence of complications between acute phase versus chronic phase PD. All tests were two-sided, and P values less than 0.05 were considered statistically significant. Statistical analysis was performed with Stata version 13 (StataCorp, College Station, TX, USA).

Results

We identified 330 patients who received intralesional collagenase injections for PD from October 2015 through December 2020. Of these patients, 229 had both pre-treatment and post-treatment erect penile goniometry, with a mean follow up time of 10.5±4.2 months between measurements, and were therefore included for analysis. Ten (4%) patients had at least one collagenase injection with an outside urologist before presenting for initial consultation at our institution. Two hundred twenty-three patients (97%) completed a full course of 8 injections, with six patients terminating therapy early due to dissatisfaction, hematoma formation, or to pursue surgical treatment.

Separate analyses were performed under Definition 1 and Definition 2 of acute and chronic phase PD. Under Definition 1, 65 patients (28%) met criteria for acute phase PD and 164 (72%) met criteria for chronic phase PD. Under Definition 2, 37 (16%) met criteria for acute phase PD and 192 (84%) for chronic phase PD. Using either definition, 76 (33%) met criteria for acute phase PD and 153 (67%) for chronic phase PD.

Mean age of the patient cohort was 60±11.4 years. Fifty-two patients (23%) had penile pain at time of initial consultation, and 134 (59%) presented with concurrent ED. Total median symptom duration was 12 months (IQR 6–36). Patients with acute phase PD had shorter median symptom duration [Definition 1: 4 months (IQR 2–6), Definition 2: 6 months (IQR 4–9), Either: 5 months (IQR 3–6)] compared to patients with chronic phase PD [Definition 1: 24 months (IQR 12–48), Definition 2: 18 months (IQR 8–43), Either: 24 months (IQR 12–60)]. Mean initial curvature was 45.3°±15.5°. Complete demographic and medical characteristics are summarized in *Table 1*, while presenting characteristics of PD are summarized in *Table 2*.

There was no difference in initial curvature whether

Table 1 Demographic and medical characteristics of patients who received intralesional collagenase *Clostridium histolyticum* injections for Peyronie's disease

Characteristics	Patients (n=229)
Age, mean (SD)	60.0 (11.4)
Race, n [%]	
American Indian or Alaska Native	1 [0.4]
Asian	2 [1]
Black	4 [2]
Other	16 [7]
White	172 [75]
Refused/unknown	34 [15]
Ethnicity, n [%]	
Hispanic/Latino	15 [7]
Diabetes mellitus, n [%]	22 [10]
Hypertension, n [%]	52 [23]
Hyperlipidemia, n [%]	53 [23]
BMI category, n [%]	
Normal	127 [55]
Overweight	65 [28]
Obese	37 [16]
Current alcohol use, n [%]	117 [51]
Smoking history, n [%]	
Never smoker	161 [70]
Former smoker	61 [27]
Current smoker	7 [3]
History of Dupuytren's disease, n [%]	9 [4]
Any genitourinary surgery, n [%]	40 [17]

BMI, body mass index.

Table 2 Disease characteristics of patients who received intralesional collagenase *Clostridium histolyticum* injections for Peyronie's disease

Characteristics	Patients (n=229)
Penile pain upon presentation, n [%]	52 [23]
Concurrent ED, n [%]	134 [59]
Hourglass deformity, n [%]	40 [17]
Curvature, n [%]	
Ventral	22 [10]
Dorsal	127 [55]
Left lateral	53 [23]
Right lateral	27 [12]
Secondary curvature, n [%]*	
Ventral	1 [4]
Dorsal	8 [31]
Left lateral	12 [46]
Right lateral	5 [19]
Initial degree of curvature, mean (SD)	45.3 (15.5)
Palpable plaque size, mean (SD) cm^2	3.7 (2.5)
Two palpable plaques, n [%]	6 [3]
Symptom duration, median [IQR] months	12 [6–36]
Injections before presentation, n [%]	10 [4]

*, Direction of secondary curvature if present in addition to the primary curvature measured. ED, erectile dysfunction.

Definition 1 or Definition 2 of the acute phase was used. There was also no significant difference in curvature outcomes using either Definition 1 or 2. Using Definition 1, patients in the acute phase had an improvement in curvature after treatment of 16.0% while patients in the chronic phase had an improvement of 16.6% (P=0.89). Using Definition 2, acute phase patients had a decrease in curvature of 19.9% while chronic phase patients had a decrease in curvature of 15.7% (P=0.43). Furthermore, patients who we classified into the acute phase using either definition had a post-treatment change of 16.5% compared to 16.3% in the chronic phase (P=0.96). Complete curvature data is presented in *Table 3*.

On univariable analysis, neither the acute phase Definition 1, Definition 2, nor combination of either definition had a significant effect on the outcome of percent change in penile curvature. This remained true when adjusting for patient and disease characteristics that could confound or modify the results as displayed in *Table 4*. On univariate analysis of the selected confounding variables or effect modifiers, initial degree of curvature was the only variable that was found to significantly affect outcomes. For every 1° increase in initial curvature, there was a 0.38% increase in percent change in curvature with treatment (P=0.002).

With respect to minor TRAE, 118 (52%) of all patients experienced bruising at least once during treatment with

Table 3 Change in curvature after treatment with intralesional collagenase *Clostridium histolyticum*

Curvature	Acute	Chronic	P value
Definition 1	Patients (n=65)	Patients (n=164)	
Initial curvature, mean (SD)	45.2 (15.3)	44.7 (15.2)	0.80
Follow-up curvature, mean (SD)	37.9 (17.5)	36.6 (14.2)	0.56
Percent change, mean (SD)	16.0 (31.2)	16.6 (28.8)	0.89
Definition 2	Patients (n=37)	Patients (n=192)	
Initial curvature, mean (SD)	41.4 (16.4)	45.4 (15.0)	0.10
Follow-up curvature, mean (SD)	33.6 (16.8)	37.6 (14.8)	0.15
Percent change, mean (SD)	19.9 (33.5)	15.7 (28.7)	0.43
Either definition	Patients (n=76)	Patients (n=153)	
Initial curvature, mean (SD)	44.3 (15.5)	45.0 (15.1)	0.70
Follow-up curvature, mean (SD)	37.0 (16.8)	36.9 (14.3)	0.99
Percent change, mean (SD)	16.5 (29.7)	16.3 (29.4)	0.96

Table 4 Univariable and multivariable analysis of acute phase Peyronie's disease on change in curvature

Definition	Percent change (β, 95% CI)	P value
Univariable analysis		
Acute definition 1	−0.6 (−9.1, 12.0)	0.89
Acute definition 2	+4.2 (−6.2, 14.6)	0.43
Either definition	+0.2 (−8.0, 8.4)	0.96
Multivariable analysis*		
Acute definition 1	−0.2 (−8.8, 8.5)	0.97
Acute definition 2	+6.5 (−4.1, 17.1)	0.23
Either definition	+1.1 (−7.2, 9.4)	0.80

*, Adjusted for age, diabetes (yes/no), any genitourinary surgery (yes/no), history of Dupuytren's (yes/no), smoking (never, former, current), concomitant erectile dysfunction (yes/no), initial degree of curvature, primary curvature direction, size of palpable plaque, presence of two palpable plaques (yes/no), and history of injections prior to initial consult (yes/no).

collagenase, while 43 (19%) experienced swelling. Major TRAE were rare: 2 (0.9%) patients developed the most severe and dreaded complication of penile corporal rupture, which is a rupture in the tunica albuginea, typically as a result of rigid erection and sometimes combined with vigorous sexual activity. Both patients were able to be managed non-operatively. 14 (6%) developed a hematoma based on a prior definition of hematoma (32). There were no statistically significant differences in number of TRAE between the acute and chronic phase groups using either definition (*Table 5*).

Forty (17%) patients in our cohort presented with hourglass deformity at the time of initial consultation. Patients with hourglass deformity presented with smaller degree of curvature compared to those without hourglass deformity at the time of pre-treatment (mean 38.3°±13.0° *vs.* mean 46.8°±15.6° respectively, P=0.0015) and post-treatment evaluation (mean 30.0°±16.9° *vs.* mean 38.4°±14.4° respectively, P=0.001). However, percent change in curvature was not significantly different between the patients with and without hourglass deformity (21.5% *vs.* 15.3% respectively, P=0.23).

Discussion

We present the second largest series to date comparing the use of intralesional collagenase in patients in the acute and chronic phases of PD. We found no difference in safety or efficacy of intralesional collagenase for PD between the acute and chronic phases on retrospective evaluation of a large cohort of patients undergoing treatment. To the best of our knowledge, this is the first study to analyze outcomes using varying definitions of the acute phase. Intralesional collagenase is FDA-approved for use in Peyronie's disease due to the IMPRESS trials, though its use has generally been limited to the chronic phase of

Table 5 Frequency of minor and major treatment-related adverse events with intralesional injection of collagenase *Clostridium histolyticum* during acute phase or chronic phase treatment

Event	Acute	Chronic	P value
Definition 1	Patients (n=65)	Patients (n=164)	
Bruising, n (%)	36 (55.38)	82 (50.00)	0.46
Swelling, n (%)	16 (24.62)	27 (16.46)	0.15
Corporal rupture, n (%)	0 (0.00)	2 (1.23)	0.55
Hematoma, n (%)	3 (4.69)	11 (6.75)	0.69
Definition 2	Patients (n=37)	Patients (n=192)	
Bruising, n (%)	20 (54.05)	98 (51.04)	0.74
Swelling, n (%)	8 (21.62)	35 (18.23)	0.63
Corporal rupture, n (%)	0 (0.00)	2 (1.05)	0.75
Hematoma, n (%)	4 (11.11)	10 (5.24)	0.37

disease given the inclusion criteria of patients in the trials (13,25,26). However, lack of efficacious therapies to address debilitating symptoms during the acute phase has prompted what is generally considered off-label use of intralesional collagenase in this context. Our study continues to support the growing evidence that collagenase can be safely used during the acute phase to manage PD.

Intralesional collagenase was first investigated for its use in the acute phase as subgroups in small retrospective studies. In a study by Yang and Bennett evaluating 49 patients treated with collagenase, a subgroup of 12 patients were identified as having "active disease" with symptoms less than 12 months or subjective report of deformity change and showed a mean curvature improvement of 20.0° (30.5% change) (27). Anaissie *et al.* reported on 21 acute phase patients from a total patient population of 77, with curvature decrease of 16.2°. Their definition for acute phase was not explicitly stated (28).

Nguyen *et al.* published the first comparative series of intralesional collagenase in the acute versus chronic phases of PD (30). The acute phase comprised 36 of 162 patients and was defined as symptom duration of less than 12 months with the presence of penile pain. There was no significant difference in change in curvature (16.7° *vs.* 15.6°) or adverse events (11% *vs.* 10%) between the acute and chronic phase respectively (30). Nguyen *et al.* separately presented the first multi-institutional study with a large cohort of 134 acute phase patients out of 918 total PD patients, using a cut-off of 6 months for the duration of symptoms without the consideration of penile pain. Again, there was no significant difference in change in curvature (13.5° *vs.* 15.6°) or adverse events (11.9% *vs.* 9.8%) between the acute and chronic phase groups respectively (31). Our results using either of these definitions of acute phase PD were consistent with these prior studies.

All studies on the acute phase of PD share the difficulty of defining the term "acute phase", since it is characterized by dynamic symptomatology and therefore variables that are difficult to identify retrospectively. Other studies have attempted to use a variety of temporal ranges, none of which have been consistent. The strength of our study is that it validates the current literature while assessing the acute phase using multiple definitions that have been previously studied (30,31). While our results of percent change in curvature do not differ among phases of disease, they are lower (15.7–19.9%) compared to the multi-institutional analysis (30.1%) and phase 3 IMPRESS trials (34%) (26,31). We have previously examined why this may be the case in our patient cohort. First, this may be due to low patient adherence with home penile modeling therapy. Second, our patient population may differ from the IMPRESS trials. For example, our cohort included 10% of patients with ventral curvature and 17% with hourglass deformity, populations that were excluded from the other studies. Additionally, there is some selection bias toward having complete data only for patients who achieved less optimal response (or no response), as 330 men underwent a course of intralesional collagenase (most completing a full course of 8 injections), yet only 229 completed post-treatment penile goniometry and ultrasound. In other words, men may be more likely to

return for post-treatment penile goniometry and ultrasound if their PD is incompletely resolved and therefore wish to undergo further treatment, which may skew this data toward less robust responders to intralesional collagenase. Even with the inclusion of patients with atypical curvature, our results demonstrate comparable safety outcomes to the multi-institutional series, with a 0.9% rate of corporal rupture and 6% rate of hematoma in our cohort versus a 0.8% rate of corporal rupture and 5% rate of severe hematoma (31). Further studies are needed to evaluate the utility of intralesional collagenase for patients with ventral curvature and hourglass deformity.

The results of this study must be noted in the context of its limitations. Besides the aforementioned bias towards post-treatment data for suboptimal responders, the study is limited by its retrospective nature and single institutional focus. Our patient population is largely affluent, college educated, and has nearly ubiquitous commercial insurance coverage. This likely affects the generalizability of this study to the overall population of patients with PD. Furthermore, our focus was primarily on goniometric change and the occurrence of adverse events; the validated Peyronie's Disease Questionnaire (PDQ) was not administered to these patients, and so patient self-reported severity and bother were not available for independent assessment (37).

In conclusion, this study contributes additional data regarding the safety and efficacy of intralesional collagenase during the acute phase of PD, using variable definitions of the acute phase. While this study presents the feasibility of its use in this population, prospective, randomized studies are needed to further characterize the role of intralesional collagenase in the acute phase and identify the ideal time frame to initiate treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-188/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-188/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-188/coif). JNM is a consultant for Endo Pharmaceuticals, Incorporation, Boston Scientific Corporation, and Antares Pharma, Incorporation. AJS has received an investigator-initiated Publication Logistical Support Grant from Endo Pharmaceuticals, Incorporation. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board (IRB # 17-001594) at the University of California Los Angeles and individual consent for this retrospective analysis was waived.

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