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PEYRONIE'S DISEASE

Continuing Collagenase Clostridium Histolyticum Injections Among Initial Nonresponders Results in Significant Curvature Improvements in the Majority of Peyronie's Disease Men

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ABSTRACT

Background: It is currently unclear if men with Peyronie's Disease (PD) who achieve minimal benefits with the first 2 series of Collagenase Clostridium Histolyticum (CCH) injections should continue with additional injections.

Aim: To analyze curvature improvements from the final two series of CCH injections based on amount of improvement during the first 2 series.

Methods: A prospective registry was analyzed of all men undergoing CCH injections for PD at a single institution. Men were included if they had completed a full 4 series (8 injections) of CCH and had baseline, interval (after 2 series), and/or final (after 4 series) curvature assessments available. Men were stratified into cohorts using baseline-to-interval assessments of ≤10° (or ≤20%) and >10° (or >20%), and improvements were compared using interval-to-final assessments.

Outcomes: The primary outcome was interval-to-final curvature improvements stratified by ≤10°/>10° or ≤20%/>20% improvements achieved during the baseline-to-interval period. Secondary outcomes included analyses of demographic and pathophysiologic variables to determine associations with significant improvements during the final 2 CCH series.

Results: A total of 296 PD men were identified as receiving at least one CCH injection, of whom 175 had baseline-to-interval, 84 interval-to-final, and 115 with baseline-to-final measurements. Mean age was 56.6, PD duration 28.6 months, baseline curvature 63.4°, hourglass deformity 36.2%, and calcification 20%. Mean overall curve improvement was −21.5° (33.1%). Among men who experienced ≤20% improvements after 2 series, the mean subsequent curvature change was -24.6% during the final two series (vs +4.3% of those with >20% initial improvement, $P < .001$), and they were 2.7x more likely to experience >20% subsequent curve improvements. Thirty-one percent of those who achieved >10° during the first 2 series experienced benefits during the final 2 series compared to 70% of men who had ≤10° improvement initially. No demographic or pathophysiological variables predicted likelihood for improvements during the final 2 series of injections.

Clinical Implications: Men who fail to achieve significant benefits with 2 series of CCH injections may benefit from completing the final 2 series.

Strengths and Limitations: Strengths including a relatively large, prospective series. Limitations include a single center, nonrandomization, nonblinded assessments, and restriction to men who completed eight injections.

Conclusions: In the current series, approximately 2/3 of men who fail to achieve >10° or 20% curve improvements with an initial 2 series of CCH injections achieved >10° or 20% improvements with the subsequent 2 series. **Alom M, Burgon H, Ziegelmann M, et al. Continuing Collagenase Clostridium Histolyticum Injections Among Initial Nonresponders Results in Significant Curvature Improvements in the Majority of Peyronie's Disease Men. J Sex Med 2021;XXX:XXX–XXX.**

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INTRODUCTION

Peyronie's Disease (PD) is a penile condition affecting 0.4-13% of men between ages 40-70 and is characterized by fibrotic plaque formation in the tunica albuginea.[1-6] Though surgery has historically been the gold-standard therapy for PD, intralesional injections have become a common conservative treatment option which results in curvature improvement without the need for surgery and with fewer long-term comorbidities in the majority of men. Particularly following approval of collagenase Clostridium *histolyticum* (CCH) by The Food and Drug Administration (FDA), treatment patterns have begun to favor injection therapies over surgery as first-line treatment for PD.[7]

Consistent with data from the 2 landmark, phase III, randomized controlled (IMPRESS) trials, the majority of post-FDA release data have further shown that CCH is an effective treatment for most men with PD, with a percentage of men failing to respond to therapy.[8-12] A treatment cost comparison analysis performed by the Mayo Clinic in 2019 found that CCH reduced curvature by ≥20% in approximately 2/3 of cases.[13] These numbers were supported by the largest, multi-institutional series performed to date, which involved 918 men and demonstrated success rates ranging from 63% to 69%.[9] Although the majority of postrelease data report similar outcomes, one series of 45 men reported nonstatistically significant improvements in curvature (5° with primary and 4° with secondary), suggesting that injection technique and postinjection treatment protocols may contribute to overall success rates.[14]

Data from the above-mentioned trials have consistently shown that, on average, individuals receiving CCH are most likely to experience the greatest improvements after the first series of injections, with declining benefits after each subsequent series.[8] However, given the fact that individuals will each respond differently, one key clinical question is how to council men who have failed to respond to initial series of injections. Specifically, should men stop therapy or continue with additional injections if they have failed an initial set of injections? To address this question, we queried our cohort of men undergoing CCH injections to determine final outcomes of men, based on how they responded to the initial two series. We hypothesized that men who failed to respond during the first two series would similarly not benefit from additional injections.

MATERIALS AND METHODS

A prospective registry of all men being treated with CCH for PD was maintained from January 2014 to February 2019 and included detailed information on patient variables, symptoms, and results. Prior to being considered for treatment, physicians performed a physical examination in both the flaccid and erect states along with penile duplex Doppler ultrasound. Men were considered appropriate for therapy if they presented with curvatures 30-90° and exhibited an identifiable plaque. Men were not excluded based on plaque calcification or ventral curvatures, as prior publications have demonstrated successful outcomes in these cohorts.[15,16]

Per CCH labeling, injections were administered in a series given 24-72 hours apart, followed by a minimum 6-week interval before the next series, during which patients were instructed to perform penile modeling. Injections were given at the point of maximum curvature based on assessments obtained with each series of injections. The protocol varied slightly from the original IMPRESS trials, as patients were recommended to perform manual modeling at home and to perform aggressive (at least 10 lbs for 15-30 seconds) penile stretching at least 5 times daily, in addition to penile traction daily. Beginning in October 2017, men were recommended to specifically utilize RestoreX for penile traction therapy (30-60 min daily beginning 48 hours after injection), based on results from prior randomized and non-randomized studies.[17,18] Also in late 2018, we began recommending daily sildenafil during CCH injections, based on data from Cocci and colleagues.[19] Patients were recommended to abstain from penetrative intercourse for 4 weeks following each injection series.

Penile curvature was documented as primary and composite measurements by assessing the curvature in two planes. Men with curvatures in two distinct planes had the larger curvature classified as 'primary,' while the sum of all curvatures was considered as a 'composite' measure. Measurements were performed after correcting for penile angulation in the lateral and vertical orientations. Data were arranged as absolute and percent improvement according to primary curvature direction and reported as dorsal, lateral or ventral. As many patients exhibited multiplanar curvatures, improvements were recorded in each direction. Other deformities (indentation/hourglass/s-shaped) were recorded but not included for analysis given the current study objective and challenges with objective quantification. Assessments were obtained at baseline, immediately prior to the third series (interval) and 6 weeks after the 4th series (final). Calcification was classified as none, mild (stippling), moderate (shadowing), or severe (>1 cm), based on our prior categorical validation in CCH men.[20] The point of maximal curvature was measured using the coronal margin as the reference point after a pharmacologic erection was achieved.

Patients were included if they had received 8 total injections and had interval and/or final curvature assessments available. Reasons for exclusion included ongoing treatment at the time of data query (partial completion of 8 injections), external referral

for completion of injections due to long-distance travel requirements, satisfaction after fewer than 8 injections, or adverse events leading to early discontinuation. Among these, the most common reason for exclusion was a missing final curvature assessment (despite having completed eight injections). This missing data point is likely due to the nature of the practice being a tertiary referral center, wherein patients were not requested to make a specific trip for the sole purpose of obtaining a final measurement.

The primary objective was to compare the outcome of the final two series based on the response during the first two series; secondary endpoints were to evaluate for associations between demographic and pathophysiologic variables and improvements in curvature from baseline measures. For this objective, only men with baseline, interval, and final datapoints were included.

In the current study, we refer to the data collected after the first two series as "interval" and the data collected after the last two series as "final," thus comparing baseline-to-interval and interval-to-final measures. To compare these outcomes, men were classified using 2 categorizations: ≤10° or >10° curve improvement and ≤20% or >20% improvement. These classifications were based on prior PD publications which have identified these cutpoints as clinically-meaningful thresholds.[8,21]

All available data were analyzed using JMP 14.2.0 (SAS Institute, Minneapolis, MN) with no outliers excluded or missing data replaced. Normally distributed data were described using means and standard deviations (SD), while data with skewed distributions were described using medians and interquartile ranges (IQR). Statistical tests were selected depending on data type and included Student's t-test, Wilcoxon Rank Sum, and chi-squared analyses depending on data type. Two-tailed *P* values of <.05 were considered statistically significant.

RESULTS

The study cohort was obtained from a prospective registry of 296 men treated with CCH from January 2014 to February 2019. In total, 175 men completed 8 injections and had baseline and interval measures available, 84 with interval and final measures, and 115 with baseline and final measures (some overlapping individuals within each group).

Demographic data for the total and interval-to-final study cohorts are presented in Table 1. Results demonstrate baseline similarities between the interval-to-final group and overall cohort, suggesting that the group represents a statistically viable sampling of the larger cohort. Mean age for the total cohort was 56.6 years (SD 9.7), with a mean PD duration of 28.6 (SD 50.8) months, mean baseline primary curvature of 52.0° (SD 18.1°) and mean composite curvature of 63.4° (SD 23.1°). Calcification was present in 20% of men, and 13.1% had ventral components with their curvature, 54.7% lateral and 80.6% dorsal.

Table 1. Baseline demographics and disease-specific variables for overall cohort and between men who did or did not experience >10° or >20% curvature improvements during the final two series of CCH injections

Variable	Interval-to-final improvement (degrees) N = 84			Interval-to-final improvement (%) N = 84			Overall cohort N = 296
	≤ 10 degrees	> 10 degrees	P value	≤20%	>20%	*P* value	
Age, yr, mean (SD)	57.2 (8.0)	57.5 (6.6)	0.88	57.7 (7.5)	56.7 (7.8)	.58	56.6 (9.7)
BMI, mean (SD)	29.6 (4.9)	37.7 (29.3)	0.41	29.4 (5)	35.8 (24.2)	.81	29.8 (9.4)
PD Duration, mo, mean (SD)	24.8 (49.5)	17.1 (24.4)	0.44	25.2 (51.8)	17.8 (22.0)	.86	28.6 (50.8)
Duration of Stable Curve, mean (SD)	16.3 (50.8)	16.6 (28.3)	0.3	17.4 (52.8)	14 (26.1)	.95	17.4 (38.1)
Calcification, %			0.59				
None	63.9	36.1		62.3	37.7		80.0
Mild	50.0	50.0		50.0	50.0		8.9
Mod	100.0	0.0		100.0	0.0		7.1
Severe	75.0	25.0		75.0	25.0		4.1
Prior Meds, N (%)	9 (16.4)	4 (18.2)	1	7 (14)	6 (22.2)	.36	42 (17.1)
Prior Injections, N (%)	4 (7.3)	1 (4.6)	1	4 (7.8)	1 (3.9)	.66	25 (10.2)
Prior Penile Trauma, N (%)	15 (26.3)	6 (26.1)	0.98	14 (26.9)	7 (25)	.85	71 (27.4)
Baseline Composite Curvature, deg, mean (SD)	66.5 (25.9)	65.7 (19.7)	0.76	68.8 (26.4)	61.7 (19.0)	.39	63.4 (23.1)
Baseline Primary Curvature, deg, mean (SD)	52.5 (18.1)	57.1 (18)	0.13	54.1 (18.4)	53.5 (17.7)	.9	52.0 (18.1)
Indentation, N (%)	26 (45.6)	9 (40.9)	0.71	25 (48.1)	10 (37.0)	.35	127 (48.3)
Hourglass, N (%)	18 (31.0)	11 (47.8)	0.16	17 (32.1)	12 (42.9)	.34	98 (36.2)
Ventral, N (%)	10 (16.4)	4 (15.4)	1	9 (16.1)	5 (16.1)	1	38 (13.1)
Lateral, N (%)	37 (60.7)	11 (42.3)	0.12	35 (62.5)	13 (41.9)	.07	158 (54.7)
Dorsal, N (%)	48 (78.7)	22 (84.6)	0.52	45 (80.4)	25 (80.7)	.97	233 (80.6)

Deg = Degree; Mo = Months; SD = Standard deviation; Yr = year

Table 2. Curvature improvement outcomes during various time points and by underlying calcification and direction of curvature

	Baseline-to-interval change N = 175[†]	Interval-to-final change N = 84[a]	Base-to-final change N = 115[a]
Absolute and % Improvement, mean (SD)	Abs: −16.5 (21.5) %:−21.5 (34.4)	Abs: −5.2 (18.6) %: −6.7 (39.3)	Abs: −21.5 (19.5) %: −33.1 (30.6)
% of Men with >25% Curve Improvement*	53.1%	31.0%	63.5%
% of Men with >50% Curve Improvement*	15.4%	11.5%	25.2%
Calcification, mean (SD)			
None	Deg: −17.0 (21.9) %: −22.6 (35.1)	Deg: −3.8 (18.7) %: −5.8 (38.4)	Deg: −21.3 (19.8) %: −32.4 (31.1)
Mild	Deg: −8.8 (20.9) %: −10.5 (32.6)	Deg: −11.8 (16.8) %: −13.6 (27.6)	Deg: −18.7 (14.9) %: −35.1 (31.4)
Mod	Deg:−16.1 (25.7) %: −10.9 (46.8)	Deg: 10 (0.0) %: 25.0 (0.0)	Deg: 0.0 (14.1) %: 1.7 (25.9)
Severe	Deg: −24.8 (20.2) %: −31.9 (20.8)	Deg: 6 (19.8) %: 30.5 (75.9)	Deg: -22.5 (18.5) %: -29.1 (18.8)
Ventral Improvement, mean (SD)	Deg: −20.2 (18.9) %: −36.9 (47.6) N = 24	Deg: -4.8 (15.4) %: -15.2 (51.1) N = 11	Deg: -24.2 (19.5) %: −53.5 (46.3) N = 15
Lateral Improvement, mean (SD)	Deg: −11.3 (13.7) %: −36.4 (52.9) N = 103	Deg: −0.4 (11.6) %: 1.6 (58.0) N = 35	Deg: −10.8 (14.7) %: −37.3 (60.3) N = 56
Dorsal Improvement, mean (SD)	Deg: −13.3 (17.8) %: −15.7 (76.3) N = 133	Deg: −5.9 (15.4) %: −11.3 (38.1) N = 69	Deg: −17.4 (16.6) %: −32.2 (33.6) N = 97

*Calculated by change in curvature divided by baseline curvature — e.g. a patient with 100° at baseline who improved to 50° is classified as >25% improvement from baseline to interval. If the same patient experienced further improvement from 50° to 20°, he would be classified as >25% for the interval-to-final time point.

[†]Size of cohort unless otherwise indicated; Abs = Absolute; Deg = Degree; SD = Standard deviation

Overall results from the combined cohort demonstrated an absolute curvature improvement (composite) of 21.5° (33.1%), with 63.5% experiencing a >25% improvement in curvature and 25.2% experiencing >50% improvement (Table 2). When broken down by primary direction of curvature, those with ventral curves experienced a 24.2° improvement (53.5%), while lateral and dorsal had 10.8° (37.3%) and 17.4° (32.2%), respectively. Among men with baseline-to-interval data, the absolute improvement was 16.5° (21.5%), while interval-to-final results were an additional 5.2° (6.7%) improvement.

In reviewing interval (after 2 series) vs final (after 4 series) outcomes, most improvements were observed early on, with a mean

Table 3. Curvature improvements based on baseline-to-interval or interval-to-final curvature outcomes

	Baseline-to-interval improvement						
	≤10°	>10°	*P* value	≤20%	>20%	*P* value	Cohort
Interval-to-Final, Abs, mean (SD)	−15.2 (19.2)	0.9 (15.4)	<.0001	−16.2 (18.7)	1.6 (15.0)	<.0001	−5.2 (18.6)
Interval-to-Final, %, mean (SD)	−22.2 (35.4)	2.8 (38.7)	<.01	−24.6 (33.2)	4.3 (38.9)	<.001	−6.7 (39.3)

	Interval-to-Final Improvement (degrees)						
	≤10°	>10°	*P* value	≤20%	>20%	*P* value	Cohort
Baseline-to-Interval, Abs, mean (SD)	−24.0 (18.1)	−1.4 (13.6)	<.0001	−22.5 (20.5)	−7.7 (14.2)	<.001	−16.5 (21.5)
Baseline-to-Interval, %, mean (SD)	−34.9 (22.6)	−1.2 (20.5)	<.0001	−31.6 (25.0)	−12.6 (26.0)	.001	−21.5 (34.4)

The top portion of the table is interpreted based on baseline-to-interval improvement. As an example, patients who experienced ≤10° improvement after two series of CCH injections later experienced a mean 15.2° improvement during the final two series of CCH. The bottom portion of the table presents data based on the extent of improvements achieved during the interval-to-final period.

Note — measures are reported using composite results (combination of primary and secondary curvatures); Abs = Absolute; SD = Standard deviation.

16.5° (SD 21.5°) improvement from baseline-to-interval, compared to 5.2° (SD 18.6°) during the interval-to-final period. Of all, 53.1% experienced >25% improvements after the first 2 series, and 31% achieved >25% improvement with the final two series (some overlap of patients who experienced >25% during both periods).

The extent of response to the first 2 series of injections was strongly correlated with subsequent outcomes from the final 2 series of injections. Table 3 reports findings using either baseline-to-interval or interval-to-final assessments. Results demonstrate that among men who achieved ≤10° improvements during the first 2 series, the mean subsequent improvement was 15.2° (22.2%), while those who had >10° improvements initially, on average, experienced no additional improvements with the subsequent two series. Similarly, those who ultimately achieved >10° or >20% during the final 2 series of injections were those who had minimal improvements during the initial 2 series (mean improvement of 1.4° and 7.7°, respectively). In contrast, those who experienced <10° or ≤20% improvements during the final 2 series had already experienced significant improvements during the first 2 series (mean 24° and 22.5°, respectively). However, when evaluating the subgroup of men who achieved >10° during the first 2 series, 31% went on to experience further absolute improvements during the final 2 series, 22% improved by ≥10°, and 24% improved by ≥20%. In contrast, among those who achieved ≤10° during the first 2 series, 70% achieved further absolute improvements, 64% improved by ≥10°, and 64% improved by ≥20%. Overall, men who had ≤20% improvements during the initial 2 series were 2.7x more likely to subsequently experience >20% improvements during the final 2 series compared to those who initially achieved >20% curve improvement after 2 series. Figure 1 graphically depicts improvements during the interval-to-final period based on results from the baseline-to-interval assessment.

In comparing baseline demographics and pathophysiologic variables between cohorts who experienced ≤10° or ≤20% vs those with greater improvements, the data revealed no differences in age, BMI, duration of PD, prior treatments, penile trauma, baseline curvature, or other deformities (Table 1).

DISCUSSION

The current study presents several clinically important findings. Specifically, men who initially do not experience significant (defined as >10° or >20%) curvature improvements after the first two series of CCH injections may be counseled that continuing with the third and fourth series will most likely yield significant improvements. In contrast, those who experienced significant improvements with the first two series are less likely to experience as notable improvements during the final 2 series. However, despite the lower overall improvements among men who initially get a good response, roughly one-third will continue to experience further significant improvements. These findings were contrary to our initial hypothesis and provide practicing clinicians with helpful information on how to address this clinical dilemma.

The reason for these findings is unknown, however, it may relate to several potential factors. One explanation may be due to the extent of fibrosis present, which may require more medication in some cases before achieving sufficient weakening of the tunica where curve correction can occur. Another potential factor could be the patient learning curve in performing penile modeling, as, in our experience, men become more comfortable and compliant with more aggressive modeling over time. A third factor may be issues with drug administration, whereby some treatments are less effective than others (injection too deep or superficial to adequately treat the plaque). Additional treatments may, therefore, be more likely administered to the optimal location.

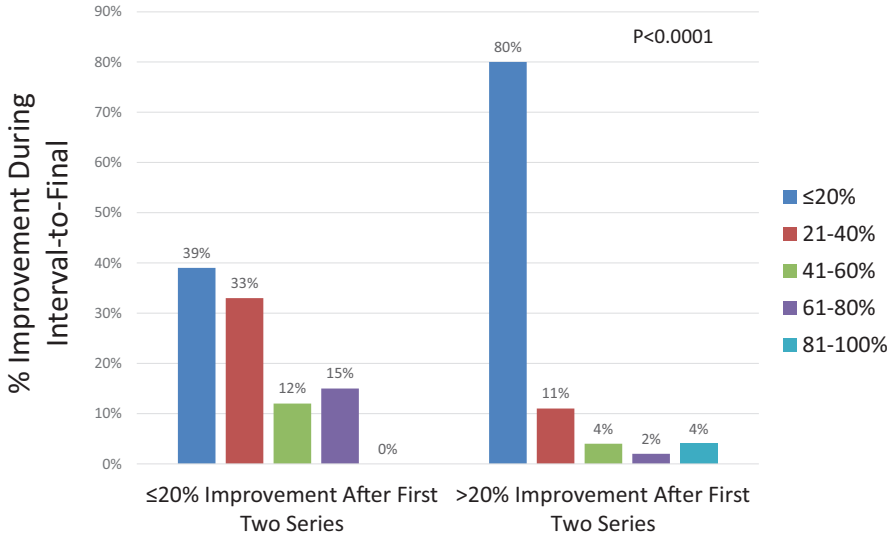

Figure 1. Graphical depiction of outcomes from the interval-to-final period based on results from the baseline-to-interval assessment. www.jsm.jsexmed.org.

It is notable that the current study does not exclude men with ventral curvatures and/or plaque calcification. This was done to provide a more true-to-life representation of men with PD and is based on 2 publications from our CCH cohort.[16,20] Results of men with ventral curvatures demonstrated equivalent or superior efficacy to other directions without additional complications, including a mean improvement of 24.2° (19.5%) compared to 17.4° (16.6%) for dorsal and 10.8° (14.4%) for lateral curvatures.[16] Similarly, in looking at men with calcified plaques, prior data demonstrated that the extent of improvement was linearly correlated with extent of calcification.[15] However, even men with severe calcification experienced some degree of improvements, suggesting that calcification likely does not represent a contraindication to CCH therapy.

This study has some notable limitations including a nonrandomized dataset, nonblinded curvature assessments, single institution, and inclusion of only men who had completed the full eight CCH injections. This latter point is particularly notable, as men who stopped early due to satisfactory improvements would likely have increased the mean curvature improvement, whereas those who stopped early due to dissatisfaction may have reduced outcomes. The study is also limited by the tertiary nature of the institution, which results in a relatively large number of men who fail to return for a final curvature assessment. To address this issue, a comparative analysis was performed of men with complete data and found the group to be similar to the overall cohort, suggesting that it represents a viable overall sampling of the larger group. As these data only represent a single center, it is unclear how outcomes may extrapolate to other centers which utilize a different treatment protocol. The study also has several notable strengths including its prospective, all-comer inclusion and large cohort. It is also the first study to address the important clinical question as to whether CCH injections should be continued in men who fail to achieve benefits with the first two treatment cycles.

CONCLUSION

Data from the current study indicate that men who experienced minimal improvements (≤10° or ≤20%) after 2 series of CCH injections subsequently experienced ≥10° or ≥20% improvements with the final 2 series in roughly two-third of cases. In contrast, men who initially experience greater improvements were less likely to experience as significant changes with the final 2 series, although approximately one-third will go on to experience further benefits. These data are clinically important, as they may help to guide practicing clinicians on the important question as to whether or not to continue administering CCH injections to men who are initially non-responders.

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