Safety and Efficacy of Collagenase Clostridium Histolyticum in Peyronie's Disease Men With Ventral Curvatures

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OBJECTIVE To evaluate the safety and efficacy of collagenase clostridium histolyticum (CCH) in men with ventral penile curvatures secondary to Peyronie's Disease (PD).

METHODS A prospective registry has been maintained of PD men undergoing CCH at our institution. Curvature assessments and subjective questioning were obtained at baseline and following 2 and 4 injection series. Clinicopathologic data were abstracted including history, exam, ultrasound, and end-point curvature assessments. Primary outcomes were adverse events (AE), and secondary outcomes included improvements in curvature by direction and subjective responses to questionnaires.

RESULTS A total of 228 patients undergoing CCH for PD (mean age 57.2 years, mean PD duration 24.3 months) were identified from March 2014 through March 2018. Baseline curvature directions were individually analyzed (total of 329 measures), including 83%, 50%, and 11% with some degree of dorsal, lateral, and ventral angulation. Mean primary and secondary (where applicable) curvatures were 52.9 and 11.4 degrees, respectively. Following treatment, ventral and lateral curvatures experienced greater relative improvements in curvature compared to dorsal (ventral 29.5 degrees [49%], lateral 11.4 [38%], dorsal 15.0 [25%], $P < .05$). Ventral and lateral curvatures were also more likely to experience ≥50%, ≥75%, and ≥90% improvements compared to dorsal. AEs were similar among curvature directions, and no urethral complications occurred.

CONCLUSION Men with ventral PD may be effectively treated with CCH with similar AEs compared to other directions. Ventral and lateral curvatures are more likely to experience significant improvements (50% or more) compared to dorsal. UROLOGY 129: 119–125, 2019. © 2019 Elsevier Inc.

Peyronie's disease (PD) is a condition characterized by the formation of fibrotic plaques in the tunica albuginea. The resultant fibrosis restricts expansion of the penile tunica with erection and results in various deformities, including curvature, narrowing, indentation, palpable plaques, or penile shortening, among others. The fibrosis and associated curvature may ultimately result in pain for the patient or partner and impair penetrative intercourse. Beyond functional limitations, PD also significantly impacts sexual and psychological health, sexual self-image and self-esteem, and is associated with depression in up to 48% of patients.[1,2]

The prevalence of PD ranges from 0.5%-13%, with expert examinations performed in a screening population identifying a rate of 6%-9%.[3-6] Eighty-five percent of men with PD present with pain and penile deformity, and the remaining diagnoses are typically made incidentally during evaluation for erectile dysfunction.[7] Although the majority of PD men demonstrate dorsal or lateral curvatures, an estimated 11%-17% are ventral.[7-10]

Collagenase clostridium histolyticum (CCH) is the first medical treatment approved by the Food and Drug Administration to treat PD. The enzyme acts specifically on subtypes of collagen common to PD plaques leading to dissolution, apoptosis, and eventual remodeling of the tissue. The efficacy and safety of CCH in PD have been demonstrated in 2, phase III randomized trials.[11] In these studies, a combined 832 PD men at multiple sites underwent 8 CCH injections. Results demonstrated a mean curvature reduction of 17° (34%) in the intervention arm compared to 9° (18%) in controls ($P < .0001$). Though adverse events were higher in the intervention group, they were mostly mild and localized. CCH's efficacy has since been confirmed in other clinical series.[12,13]

To date, no studies have evaluated the safety or efficacy of CCH in men with ventral curvatures, including in the IMPRESS trials, which excluded men with ventral curvatures. However intralesional verapamil and interferon have historically been used in this population without higher rates of complications.[14,15]

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In our clinical practice, we began offering CCH injections off-label to men with ventral curvatures following appropriate informed consent. Given the lack of data on the topic, we sought to report our outcomes of CCH in this population and to compare results to men with dorsal/lateral curvatures.

MATERIAL AND METHODS

Study Cohort

A prospective database has been maintained at our institution since March 2014 of all men undergoing intralesional CCH injections for PD. Beginning early in 2015, we began offering CCH to men with ventral curvatures in an off-label manner with the express understanding that safety had not been evaluated in this cohort among all published series. Patients were specifically reviewed for the possibility of developing urethral complications with injections, including the possibility of needing future surgical procedures, and only after indicating full consent and understanding were they permitted to undergo injections. For the current manuscript, we queried the data from inception through March of 2018 and compared outcomes among those with a ventral component of curvature to the remainder of the patients. The current study was approved by the Institutional Review Board, and patients who consented to release data for research purposes were included in the current report.

At the initial clinical visit, men completed a detailed intake questionnaire, underwent a thorough history and physical examination, and received penile Duplex Doppler ultrasonography. See Table 1 for a listing of relevant clinicopathologic variables. Additional clinical and demographic data were retrieved from the medical record as appropriate. Patients were typically offered observation, CCH, traction, CCH + traction, or surgery if they were seeking treatment and had curvatures >30°. Men with PD onset <12 months were not offered surgery, and those presenting within 3 months were recommended traction alone or traction + CCH. No men were recommended to undergo adjunctive injection, topical, or oral therapies for PD during the treatment course. The majority of men elected to proceed with some form of CCH and comprise the current cohort.

Injection Protocol

CCH was administered using a similar protocol to the original phase III trials with a few exceptions. Patients did not return for office modeling but were instead instructed to perform firm self-modeling with every urinary void for 30 seconds until 6 weeks after completion of the final series.[11] Injections were also performed at the point of maximal curvature to an erect penis (pharmacologic), with 0.9 mg instilled (full vial). For men with ventral curvatures, the injection was placed directly into the tunica of the ventral aspect of the penis from the lateral aspect of the penis, between the corpus spongiosum and corpus cavernosum.

Penile Duplex Doppler Ultrasonography Protocol

All men in the current series underwent penile ultrasound at baseline. At the time of the ultrasound, repeated doses of erectogenic medication (alprostadil 10 mcg/mL, papaverine 30 mg/mL

Table 1. Demographic and clinicopathologic variables of men undergoing CCH for PD by baseline curvature direction

	Total Cohort (n = 228)‡	Ventral‡ (n = 25)	Dorsal (n = 189)‡ Lateral (n = 115)	*P*-value
Age, years, mean (SD)	57.2 (9.1)	56.7 (11.5)	57.1 (9.1)	.94
Negative impact on relationship*, *N* (%)	92 (65.2)	9 (64.3)	104 (61.2)	.82
PD duration, months, (SD)	24.3 (26.4)	18.9 (26.9)	24.1 (25.6)	.14
Baseline curvature, mean degree, (SD)	Primary 52.9 (18.5) Composite 62.8 (23.6)	Ventral component 54.6 (23.2)	Dorsal/lateral component 42.6 (21.7)	.01**
PD pain, *N* (%)	68 (45.6)	7 (41.2)	97 (48.3)	.57
PD prevent intercourse, *N* (%)	71 (49.7)	3 (20)	99 (51.0)	.02**
PD partner pain, *N* (%)	35 (26.1)	2 (14.3)	43 (23.8)	.53
Penile shortening, *N* (%)	92 (68.1)	8 (57.1)	129 (70.9)	.36
Any prior PD therapies, *N* (%)	33 (22.4)	2 (12.5)	46 (23.1)	.53
Concurrent use of traction or vacuum with CCH, *N* (%)	80 (35.1)	4 (16)	111 (36.5)	.73
ED, *N* (%)	78 (53.4)	10 (55.6)	106 (53.5)	.87
IIEF (baseline)				
IIEF erectile function*, mean (SD)	18.5 (9.6)	19.3 (10.7)	17.7 (9.8)	.61
IIEF orgasmic function*, mean (SD)	6.6 (3.8)	6.2 (4.5)	6.4 (3.8)	.90
IIEF sexual desire*, mean (SD)	7.1 (2.2)	7.8 (1.7)	6.9 (2.1)	.18
IIEF intercourse satisfaction*, mean (SD)	6.9 (4.5)	7.6 (5.5)	6.5 (4.4)	.39
IIEF intercourse satisfaction*,#, mean (SD)	8.7 (3.1)	11 (2)	8.4 (3.1)	.01**,†
IIEF overall satisfaction*, mean (SD)	5.5 (2.7)	5.8 (3.0)	5.2 (2.7)	.44

CCH, collagenase clostridium histolyticum; ED, erectile dysfunction; IIEF, international index of erectile function questionnaire; PD, Peyronie's disease; SD, standard deviation.

* Patients with current partner only.

† Not significant after controlling for age.

‡ Note that men may have one or more components such that the total is >100% of the overall cohort (eg, dorsolateral would be captured once in the overall cohort but would be captured as a dorsal component and a lateral component); similarly, percentages may not match appropriately compared to overall cohort due to possibility that patients may be represented under more than one component. Denominators for each row also vary slightly based on whether complete data were available.

Intercourse satisfaction after excluding men with answers referring to no sexual intercourse (0 for all Q6, Q7 and Q8).

** Statistically significant relationship.

and phentolamine 1 mg/mL) were administered intra-cavernosally every 10 minutes until a minimum 8/10 erection was achieved or until a maximum of 1 mL of medication was administered. Hemodynamic variables were obtained including cavernosal peak systolic velocity, end diastolic velocity, and resistive index at the ventral aspect of the proximal penile shaft. Plaque characteristics were evaluated including location and presence of calcification (graded as none, stippling, moderate, and severe — note: calcified patients were not excluded from receiving CCH).[16] Other objective measurements such as angle of curvature, indentation, hourglass deformity, buckling, and penile length were obtained. Indentation and hourglass were further defined as mild (<10% of diameter), moderate (10%-25%), or severe (>25%).

Curve Assessment Protocol

Objective curvature assessments were performed following completion of the second and fourth series of injections or sooner if patients elected to discontinue prior to completion of 4 series. At the beginning of each series, all patients were asked a series of questions, including subjective assessments of improvement. For purposes of the current manuscript, the curvature end-point represented the most recent curvature assessment available (final preferred, although interval accepted in the absence of a final curvature).

Curvatures were assessed in 2 planes (dorsal/ventral and lateral) using a goniometer after rotating the penis to its native position. For example, a patient with apparent leftward curvature may actually represent a dorsal curvature with 90° clockwise rotation (viewing the penis anterior-to-posterior). With the current measuring methodology, this patient would be classified as a dorsal curvature. Among men with multiplanar deformities, the largest curvature was classified as the primary curvature, while the other was considered secondary. To better capture the true severity of the condition and treatment impact, results of measurements from all planes were combined to report a "composite" curvature. The specific subjective questions utilized, inclusion of composite measures, and assessment methodologies have been previously reported.[12]

Questionnaires

Subjective questioning was obtained at baseline, after every series of injections, and at the completion of therapy. Baseline questionnaires included the International Index of Erectile Function (IIEF), and an intake survey consisting of 89 items detailing erectile function, PD, testosterone, orgasmic function, ejaculatory function, and various measures of impact on the partner. Surveys obtained after each curvature assessment include Likert-like scales and are nonvalidated (appropriate validated questionnaires detailing the specific information desired are not currently available) and have been published in prior series.[12,16,17]

Adverse Effects

To assess AEs, patients were specifically asked about ecchymosis or hematomas (defined as ecchymosis or swelling which persists for 4 weeks or more) with the prior series at the beginning of each injection and curvature assessments. Other adverse effects were documented in our database if specifically mentioned by the patient (eg, patient calls in with suspected fracture).

Statistical Analysis

To best isolate changes in curvature with CCH, those with primary and secondary curvatures (multiplanar) were analyzed as 2 separate data points. For example, a patient who exhibited a dorsal 45° and lateral 30° at baseline and then was found to have dorsal 30° and no lateral component would be recorded as 15° (33%) dorsal improvement and 30° (100%) lateral improvement. For patients with s-shaped deformities (left curvature + right curvature in 2 distinct regions, n = 2), the 2 lateral curvature angles were averaged and analyzed as 1 data point. Categorical variables were reported as percentages and continuous variables as mean ± standard deviation. Comparisons were performed using Chi-square, Fisher's exact, and regression tests. Patients with missing data were excluded from related analyses. Two-sided P values were reported with $P < .05$ considered statistically significant. Statistical analysis was performed using JMP Pro v13.2 (SAS, Cary, NC, USA).

RESULTS

The study cohort consisted of 228 patients (mean age 57 years) who underwent 1-4 series of CCH injections and had at least 1 interval or final curvature assessment available. Among men with multi-planar curvatures, these were divided into distinct measures to accurately compare outcomes, as noted in the methods section. For example, a man with a dorsal and lateral curvature had each component analyzed separately to evaluate for improvements in each specific direction. This resulted in a total of 329 separate data points for the curvature analyses among the 228 men. The majority of men (85.3%) had sexual partners at the time of CCH injections (mean relationship duration 20.7 years). Mean baseline primary and secondary penile curvatures measured 52.9° and 11.4°, respectively.

Table 1 details clinicopathological and sexual characteristics categorized by curvature directions. No differences were identified by curvature direction based on patient age, patient or partner pain, penile shortening, or prior PD treatments. Surprisingly, compared to men with dorsal and lateral curvatures, men with ventral curvatures were significantly less likely to report that their PD prevented intercourse (20% vs 51%, $P = .02$).

Regarding sexual function, no significant differences were noted on the IIEF by curvature direction. However, after excluding patients who were not having penetrative intercourse, the IIEF intercourse satisfaction domain was significantly higher in patients with ventral curvature compared to those with dorsal and lateral curvatures (11 vs 8.4, $P = .02$). Results were nonsignificant after controlling for age.

Table 2 demonstrates curvature improvements including interval change (baseline to interval [after 2 series]) and end point change (baseline to end point [after 4 series or sooner if patient elected to discontinue]) with both absolute values and percentages reported. Significant curvature improvements were noted with all curvature directions. When comparing differing baseline directions, ventral and lateral demonstrated significantly greater improvements compared to dorsal. To further evaluate the relative changes, thresholds were set including ≤25%, ≥50%, ≥75%, and ≥90% (Supplementary Table 1 and Fig. 1). Results demonstrated no statistically significant differences among directions for ≤25% curve improvement; however, ventral and lateral curvatures exhibited much higher rates of improving ≥50%, ≥75%, and ≥90%.

Table 3 reports AEs and subjective results, categorized by ventral or nonventral curvature components. Overall, 90.3% of patients reported subjective curvature improvement while

Table 2. Improvements in penile curvature by direction at interval and final end-points

	Baseline to Interval Curvature Change		Baseline to End Point Curvature Change	
Curvature	Absolute (degree)*	Relative (%)	Absolute (degree)*	Relative (%)*
Ventral, mean (SD), N	−24.0 (19.1), 15	−39.4 (33.9), 15	−29.5 (22.2), 16	−49.1 (44.9), 16
Lateral, mean (SD), N	−10.8 (14.3), 68	−33.8 (55.1), 68	−11.4 (13.9), 78	−38.0 (61.3), 78
Dorsal, mean (SD), N	−14.2 (17.3), 98	−21.7 (41.9), 98	−15.0 (16.7), 125	−25.0 (40.4), 125
Overall composite, mean (SD), N	−17.1 (21.1), 126	−23.3 (29.4), 126	−18.6 (20.3), 154	−27.4 (31.7), 154

Note: All groupings with statistically significant curvature improvements compared to baseline ($P < .01$).
* Significant differences in curvature improvement among ventral, lateral and dorsal directions (Kruskal-Wallis test).Composite reflects summation of all curvature directions within each patient.

Table 3. Key subjective outcomes and adverse events by curvature direction

	Overall Cohort	Ventral	No Ventral	*P* value
Self-reported curve improvement*, *N* (%)	168 (90.3)	13 (76.5)	226 (90.0)	.1
Self-reported meaningful improvement*, *N* (%)	158 (86.8)	12 (70.6)	215 (87.8)	.06
Subjectively prevent need for surgery, *N* (%)	52 (58.4)	7 (87.5)	69 (60)	.15
Subjectively restored ability to penetrate, *N* (%)	40 (65.6)	4 (57.1)	56 (68.3)	.68
Adverse Events†				
Bruising*, *N* (%)	177 (97.3)	17 (100)	238 (96.8)	1
Hematoma*, *N* (%)	23 (19.2)	6 (35.3)	30 (19.0)	.12

All results reported as end-point measures.
* Reported at any point during injection series.
† Only Hematoma and bruising were captured systemically.

86.8% felt that the improvements were meaningful. No statistically significant differences were noted between ventral and nonventral men regarding subjective assessments of improvement, meaningfulness, prevention of need for surgery, or restoration of ability to penetrate. Importantly, rates of ecchymosis and hematomas were similar between ventral and nonventral baseline curvatures, and no suspected urethral injuries were identified among any CCH patients, including urethral stricture, hematuria, or other urethral injury. Two suspected fractures were identified (both in dorsal curvature patients), although this number likely under-represents the true rate of minor suspected fractures.

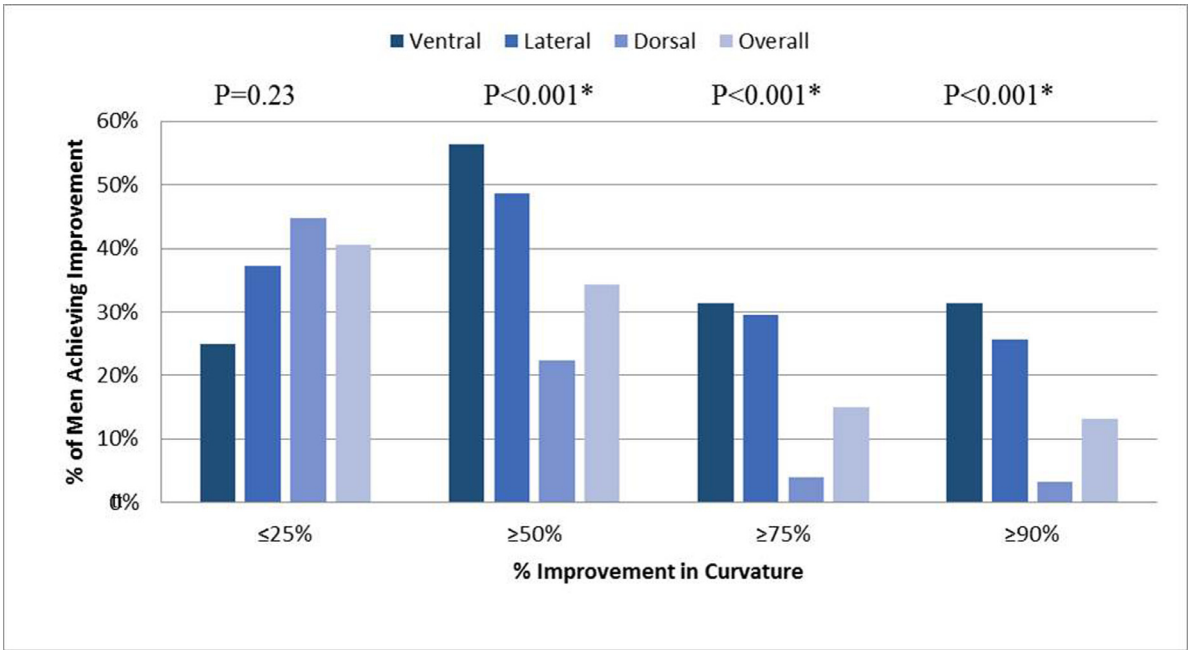

Figure 1. Percentage of men experiencing various categorical levels of final curvature improvement by direction. (Color version available online.)

DISCUSSION

This current study highlights several novel and important findings regarding the viability of CCH injections among men with ventral PD. Most importantly, the data demonstrate that CCH injections for ventral curvatures are safe, with no higher rates of hematomas, ecchymosis, or de-novo urethral complications. Hypothetical AEs which may occur with ventral curvature treatments could potentially include injury to the corpus spongiosum or urethra, resulting in potential hematuria, changes with the urinary stream, urethral stricture, or similar complications. However, none of these symptoms were self-reported by patients in the current series, and they remain hypothetical risks at the present time. Beyond the safety aspects, the current data also indicate that men with baseline ventral or lateral curvatures are more likely to experience significantly greater relative improvements in curvature compared to dorsal curvatures. These findings are notable and suggest that CCH may be offered to men with ventral curvatures pending external validation of findings.

The use of non-CCH injection therapies among men with ventral penile curvatures has been a long-standing practice, with several authors reporting outcomes of intralesional hyaluronic acid, interferon, or verapamil in ventral cohorts.[14,15] In these studies, higher rates of complications have not been identified among men with ventral curvatures, despite the use of multi-puncture techniques. However, in contrast to the other intralesional agents, CCH is specifically formulated to impact collagen types I and III, which are present in the tunica of the corpora as well as in the corpus spongiosum and urethral submucosal layer. Given the unique mechanism and location of collagen subtypes, CCH could hypothetically result in structural changes to the urethra and surrounding tissues. Despite these concerns, the current data suggest that injection of CCH into the ventral corpora does not result in a higher rate of urethral complications.

The other important finding from the current study is that men with ventral and lateral curvatures experience greater relative improvements compared to dorsal curves. Figure 1 and Supplementary Table 1 are particularly noteworthy, as men with dorsal curvatures rarely experienced ≥75 or ≥90% improvements in curvature (4% and 3%, respectively), compared to 30% and 26% for lateral and 31% and 31% for ventral ($P < .0001$). These findings significantly impact counseling in clinical practice, as men with dorsal curvatures may be counseled that there is only a 22% chance that they will experience a ≥50% improvement compared to approximately 50% chance if their curvature is ventral or lateral. Similarly, the likelihood of dramatic (≥75%) improvements is very unlikely with dorsal, while it is relatively common (nearly 1/3) with ventral and lateral curvatures.

When utilizing the current results to counsel patients, it is important to emphasize the methodology used for curvature assessments in the current study. As described in the methods section, the baseline assessments were performed after reorienting the penis to correct for any penile angulation. This is important, as a curvature which may initially appear lateral may actually represent a pure dorsal curvature with rotation. The anticipated success rates will therefore change significantly. This is also relevant when comparing the current outcomes to those of other databases.

The current study has several notable limitations including small numbers of patients with ventral curvatures, limited duration of follow-up, and lack of complete data on all patients. Also, the current series represents an as-treated cohort, with associated biases based on clinical selection criteria. The current results also only represent a single institution and therefore require external validation before the routine adoption of CCH in men with ventral curvatures. Curvatures were also only assessed by measurement with a protractor by experienced providers, and pre/post photographs were not obtained. Adverse event reporting was also limited to those self-reported by patients, with no specific questions asked regarding potential urethral complications, changes in urinary stream, or hematuria.

Despite these limitations, the current study represents a prospective, sequential patient cohort undergoing a systematic injection and measurement protocol with similar data points obtained at baseline and after each series of injections. It also represents the first series reporting outcomes of ventral curvatures and the largest single-location series of PD patients undergoing CCH in the literature, with over 200 total observations by curvature direction compared. Additionally, the study utilizes a robust methodology to individually evaluate the relative changes in distinct components of curvature among men with multiplanar curvatures, which improves the overall reliability of reported outcomes.

CONCLUSION

Based on a single-institution series, the use of CCH to treat PD men with ventral penile curvatures is viable, with a similar safety profile compared to dorsal and lateral curvatures. Compared to dorsal curvatures, lateral and ventral directions experience greater relative improvements and are more likely to experience ≥50%, ≥75%, or ≥90% improvements overall. Although these data suggest that CCH injections may be used in men with ventral curvatures, external validation with long-term outcomes are warranted prior to routine implementation as a standard of care.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.01.055.

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EDITORIAL COMMENT

Collagenase clostridium histolyticum (CCH) is the first medical treatment approved by the Food and Drug Administration for intralesional management of Peyronie's disease (PD). Based on the product monograph developed from Phase I-III trials, CCH is not currently approved for use in complex, hourglass, or ventral curvatures.[1] The incidence of these atypical deformities is significant and the use of CCH in these patients is an evolving area of therapeutics. With this series, the authors provide an important addition to the literature addressing the question of efficacy and safety of treating ventral curvatures.

This is the first published report that describes and analyzes the use of CCH in men with ventral PD. The authors use multiplanar rather than uniplanar measurements for penile curvature, which more accurately characterizes baseline deformity. Interestingly, the ventral PD men have significantly worse baseline curvature. Despite the larger degree in curvature only 20% of the ventral patients report interference with sexual function, which also questions the need for intervention in this population. Only 4 of the 7 ventral curvature patients that could not initially have penetrative intercourse were able to achieve this after CCH treatment. Given that most patients had a curve that did not interfere with sexual function, it is not surprising that after treatment men rarely needed additional therapy. An additional intriguing result is that over 30% of ventral curvature patients had improvement of >90%, which implies that a large proportion of study patients completed treatment with a negligible residual curve. The small number of ventral curvature patients (n = 16) and the large standard deviation in measurements make this result interpretation difficult. In addition, since there is a significantly larger curvature in the ventral patients, both the absolute and relative differences may appear larger, when ultimately the clinical outcomes are not impressive.

The claim that CCH is efficacious based on the limited sample size and short-term follow-up appears to be overreaching. We would agree that the most important finding discussed in this report is that CCH injections for ventral curvature appear safe, which is consistent with the literature of other intralesional injections.[2] The clinical concern that CCH use in ventral curvatures may result in urethral injury and hematoma was not observed in this limited series. Long-term outcomes are needed to confirm there is no delayed risk of urethral complications. This result is encouraging and may prompt other clinicians to consider utilizing this treatment for this patient population, the caveat being that this report has very limited numbers of men studied over a short period of time, as such caution is needed prior to widespread use and acceptance.

Further evaluation of CCH to treat complex PD curves is needed to advance the therapeutic field of PD. These authors have demonstrated clinical safety of CCH in ventral curves in a limited population which should act as a catalyst for larger randomized-controlled trials with longer follow-up and less confounding variables to truly evaluate treatment efficacy.

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AUTHOR REPLY

We very much appreciate the comments and are in complete agreement with the majority of points raised. The take-home message of this manuscript should be that based on very preliminary data, Xiaflex injections in PD men with ventral curvatures are reasonably safe and offer equivalent, if not better, outcomes compared to other directions. However, more data and external validation are mandated prior to routine implementation of this practice. This is further supported by our impression that ventral curvatures are more challenging to accurately inject and are probably best avoided until sufficient experience is gained with other curvatures.

It is worthwhile to mention that it is a very common belief among Urologists that Xiaflex is contraindicated with ventral curvatures, calcified plaques, complex curvatures, >90°, or hourglass/indentation deformities. However, although many of these characteristics were excluded in the phase III trials, the only true labeling "contraindication" is plaques involving the urethra, and the only indications are palpable plaques and ≥30° baseline curvature.[1] The contraindication is somewhat irrelevant, as, to our knowledge, there are no clinical reports that have shown PD plaques involving the urethra directly. Additionally, several studies have now shown benefits in men with hourglass deformities or calcified plaques (although blunted depending on severity).[2,3] Interestingly, the FDA label also cautions against injecting into the corpus cavernosum, nerves, or blood vessels, which is highly impractical, given that the intended target is often a few millimeters thick and is located immediately adjacent to those structures.

Another key point to mention is that the current article evaluated curvature based on individual directional components. For example, a man with a dorsolateral curvature may have been classified as having 55° dorsal and 20° lateral components. This was done intentionally to better isolate how much each of these individual directions improved with therapy. In Table 1 of the manuscript, we lumped the dorsal and lateral components together, since the intent was to emphasize ventral curvatures. Although it may appear that ventral men had greater baseline curvatures, they actually had similar severity compared to dorsals. However, because lateral components were included with the dorsals for that particular table, it diluted the mean curvature and made ventrals appear larger overall. This is further supported by Table 2, where each direction is specifically isolated, and a dorsal improvement of 15° equates to a 25% improvement compared to 30° (49%) for ventrals. We highlight this because it emphasizes one of the key (and surprising) findings, which is that ventral components experienced greater relative improvements compared to other directions: 49% versus 38% (lateral) and 25% (dorsal, $P < .05$). This is plausible from an anatomic standpoint, given that the thicker tunica and neurovascular structures lie along the dorsal aspect of the penis.

We again appreciate and support the very astute commentary and fully agree that a randomized trial would be preferred to evaluate this topic. However, as this may never occur (unfortunately), we are left to rely on the next highest level of evidence from prospective series reporting outcomes.

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