



# Intralesional collagenase *Clostridium histolyticum* vs. verapamil injections in males with Peyronie's Disease: A prospective, matched-pair, non-blinded, randomised clinical study comparing clinical outcomes and patient satisfaction rates

Eric Chung<sup>1,2,3</sup> , Juan Wang<sup>1</sup>

<sup>1</sup>AndroUrology Centre, Brisbane, QLD and Sydney, NSW, <sup>2</sup>University of Queensland, Princess Alexandra Hospital, Brisbane, QLD, <sup>3</sup>Macquarie University Hospital, Sydney, NSW, Australia

**Purpose:** To compare clinical outcomes and patient satisfaction rates between intralesional verapamil (ILV) and collagenase *Clostridium histolyticum* (CCH) injections in males with Peyronie's disease (PD).

**Materials and Methods:** Following ethics approval, PD patients were prospectively enrolled in this open-label non-blinded study. Patients were randomised to receive ILV or CCH injections with penile remodelling every fortnightly for 6 courses. Patient demographics, change in penile curvature, International Index of Erectile Function-15 and Peyronie's Disease Questionnaire (PDQ) scores as well as overall patient satisfaction and Patient Global Impression of Improvement (PGI-I) scores were recorded at pre-treatment and 6-, 12- and 24-month post-treatment.


**Results:** A total of 50 males were recruited and divided into ILV (n=25) and CCH (n=25) groups. The mean changes in penile curvature were -16.8 (standard deviation [SD] 7.65) degrees in ILV and -28.2 (SD 11.5) degrees in CCH groups ( $p < 0.01$ ). Patients in the CCH group scored better than the ILV group on the PDQ psychosexual symptoms (-2.14 vs. -2.9;  $p < 0.01$ ) and symptom bother score (-3.88 vs. -4.16;  $p = 0.08$ ). Minor treatment-related adverse events were more common in the CCH group. The overall satisfaction rate on a 5-point scale was 4.1 in ILV and 4.5 in CCH groups, and there was no statistically significant difference in the PGI-I scores between the 2 groups ( $p = 0.14$ ).

**Conclusions:** CCH therapy is more effective than ILV to treat a carefully selected group of males with PD, with a reasonable safety profile and a higher high level of patient satisfaction rate in the short term.

**Keywords:** Collagenases; Injections, intralesional; Patient satisfaction; Penile induration; Verapamil

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**Received:** 11 April, 2022 • **Revised:** 13 June, 2022 • **Accepted:** 22 June, 2022 • **Published online:** 21 July, 2022

**Corresponding Author:** Eric Chung  <https://orcid.org/0000-0003-3373-3668>  
AndroUrology Centre, Suite 3, 530 Boundary St, Brisbane, QLD 4000, Australia  
TEL: +61-7-38321168, FAX: +61-7-38328889, E-mail: ericchg@hotmail.com

## INTRODUCTION

Peyronie's disease (PD) is a complex penile disorder causing significant psychosexual dysfunction, with spontaneous resolution occurring in the minority of cases only [1,2]. At present, the optimal management strategy for PD is largely dependent on the patient's needs and expectations, coupled with the clinician's expertise and access to available treatments.

Intralesional plaque injection offers a minimally invasive treatment option for males who want to avoid potential surgical complications. The recent International Consultation on Sexual Medicine guideline for PD gave a Grade B recommendation for the use of intralesional therapy [1]. The systematic review of various intralesional plaque injectable agents have highlighted mixed clinical outcomes, and most of these agents are used as an off-label indication apart from collagenase *Clostridium histolyticum* (CCH) [1,3]. Intralesional verapamil (ILV) injection has been around for more than 3 decades and is shown to improve penile curvature and plaque volume [1,2,4]. The publication of 2 large-scale phase III clinical trials, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and II [5], has demonstrated that CCH significantly reduces penile curvature and plaque volume, and improves PD-associated symptom bother scores. A recent systematic review comparing CCH with other intralesional and/or mechanical therapy showed clinically significant improvement in penile curvature and preservation of penile length with intralesional CCH therapy [3].

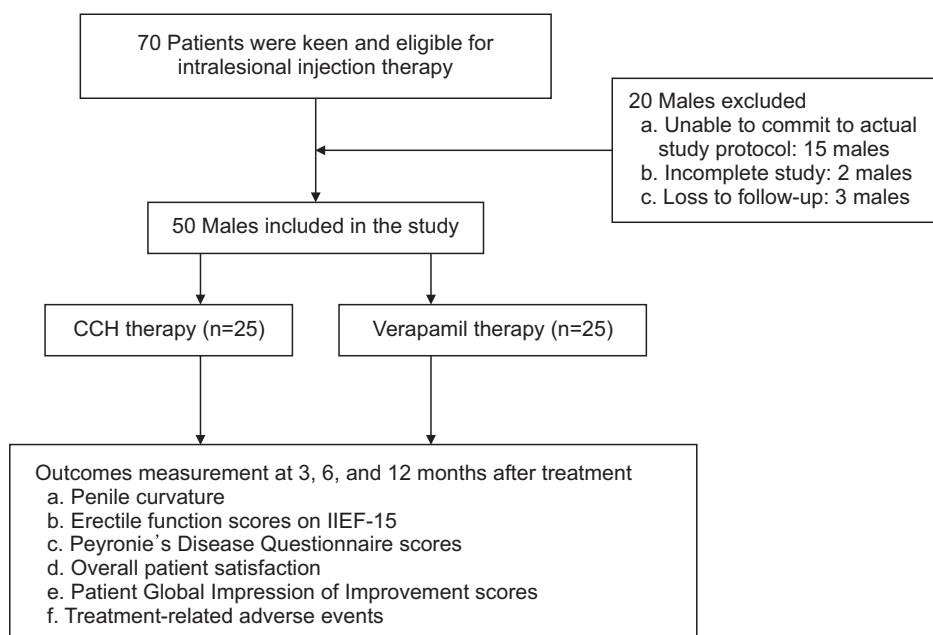
To date, there is no published head-to-head comparative study between ILV and CCH in PD. This open-label non-blinded randomised study evaluates the clinical outcomes and patient satisfaction rates between males with PD who received ILV and CCH to determine if CCH is more effective and safer than ILV.

## MATERIALS AND METHODS

### 1. Patient population

Following formal ethics approval by the Human Research Ethics Committee (HREC) of University of Queensland (approval no. HREC/12/QPAH/178) and written informed consent, patients with PD were prospectively enrolled in this open-label non-blinded study between January 2016 and January 2018. Penile curvature was measured on an erect penis using a goniometer. Patients were randomised openly to receive intralesional CCH or ILV (Fig. 1) using a computer-based random number generator. To standardise the treatment protocol, six courses of once a fortnightly intralesional injection were administered with ILV consisting of 10 mg in 4 mL of verapamil injection, while the males in CCH received 0.58 mg of CCH mixed in 0.5 mL of saline. A fortnightly injection schedule was chosen to ensure a comparable frequency of intralesional injections between both groups. Males in both groups adhered to the modelling of both flaccid and erect penis, based on the IMPRESS manual modelling of penis protocol [5].

Inclusion criteria included patient age  $\geq 18$  years, stable PD (penile deformity unchanged for 6 months), failed oral



**Fig. 1.** Flow diagram of study recruitment. CCH, collagenase *Clostridium histolyticum*; IIEF, International Index of Erectile Function.

therapy (such as pentoxifylline or tadalafil), presence of a palpable plaque, and has a single axis penile curvature (less than 90 degrees). All patients received a penile colour duplex ultrasound to confirm the presence of a penile plaque, and penile curvature was measured with a goniometer. Exclusion criteria were the presence of hinge or lateral indentation or hour-glass deformity, previous Peyronie’s surgery, and significant erectile dysfunction (defined as International Index of Erectile Function (IIEF)-15 score  $\leq 16$ ). Adjunctive measures such as penile traction devices were ceased during the study period to ensure no additional or synergistic effect with intralesional therapy.

**2. Data collection**

Patient demographics, the change in penile curvature, IIEF-15 and Peyronie’s Disease Questionnaire (PDQ) scores were recorded pre-treatment and at 6, 12, and 24 months after treatment. The overall patient satisfaction rate on a 5-point scale (1 being least satisfied and 5 being most satisfied) and Patient Global Impression of Improvement (PGI-I) scores were obtained too. Treatment-related adverse events (TRAE) such as penile bruising, swelling and pain were documented.

**3. Statistical analysis**

Statistical analysis was performed with SAS 9.13 (SAS Institute, Cary, NC, USA) computer software with values of the study parameters compared using the student t-test or Wilcoxon signed-rank test as indicated. A chi-squared contingency analysis was used to examine the relationship between improvement in penile curvature and treatment satisfaction, with a  $p < 0.05$  considered statistically significant.

**Table 1.** Baseline characteristics in both groups after the pair-matching

Variable	ILV (n=25)	CCH (n=25)	p-value
Age (y)	50.4±14.5	51.5±12.8	0.81
Duration (mo)	13.8±6	14.5±6	0.68
Penile curvature (degree)	48.6±26.4	49.2±25.8	0.76
IIEF-15	57.24±8.18	58.08±7.83	0.74
PDQ-PS	9.26±4.18	9.08±3.88	0.62
PDQ-PP	3.60±4.82	4.32±4.44	0.28
PDS-SB	16.88±6.92	15.60±7.60	0.58

Values are presented as mean±standard deviation. ILV, intralesional verapamil; CCH, collagenase *Clostridium histolyticum*; IIEF-15, 15-question International Index of Erectile Function; PDQ-PS, Peyronie’s Disease Questionnaire (psychosexual symptoms); PDQ-PP, Peyronie’s Disease Questionnaire (penile pain); PDQ-SB, Peyronie’s Disease Questionnaire (symptom bother).

**RESULTS**

A total of 50 males were included in this study and divided into ILV (n=25) and CCH (n=25) groups. The mean penile curvature was 48.8 (standard deviation [SD] 26.2) degrees, and the mean PDQ was 29.2 (SD 14.5) (Table 1). There was no significant difference in medical co-morbidities and the PDQ domains between the 2 groups. All patients conformed to the study protocol including the penile modelling penile exercises and no patient used penile traction or vacuum device during the review period.

There was a statistically significant difference found in the improvement in penile curvature between ILV and CCH groups, with the mean change for penile curvature of -16.8 (SD 7.65) degrees in ILV and -28.2 (SD 11.5) degrees in CCH groups were observed ( $p < 0.01$ ). Furthermore, four (16%) patients who received CCH reported complete resolution of penile curvature as compared to one (4%) patient in the ILV group. These patients had an initial curvature of less than 60°. Significant improvements in most PDQ domains were observed from baseline to 6 months in both groups (Table 2). These positive changes were sustained at 12- and 24-month visits. Patients in the CCH group scored better than those in the ILV group in terms of psychosexual symptoms (-2.14 vs. -2.9;  $p < 0.01$ ) and symptom bother score (-3.88 vs. -4.16;  $p = 0.08$ ). Similarly, there was a significant improvement in the erectile function score (based on IIEF-15) for the CCH group compared to the ILV group (mean improvements of 10.4 vs. 6.8;  $p < 0.01$ ). There was no significant difference detected in penile pain scores between the 2 groups.

**Table 2.** Mean changes from baseline to after treatment in both groups at 24 months

Variable	ILV (n=25)	CCH (n=25)	p-value
Penile curvature (degree)	-16.8±7.65	-28.2±11.5	<0.01
IIEF-15	6.8±12.76	10.4±8.8	<0.01
PDQ-PS	-2.90±2.02	-2.14±2.24	<0.01
PDQ-PP	-1.2±3.62	-1.2±4.18	0.69
PDS-SB	-4.16±4.44	-3.88±4.16	0.08
Overall satisfaction rate <sup>a</sup> , mean	4.1	4.5	0.06
Penile bruising and swelling	5	18	<0.01
Penile pain	1	14	<0.01
Penile fracture	0	0	N/A

Values are presented as mean±standard deviation or number only. ILV, intralesional verapamil; CCH, collagenase *Clostridium histolyticum*; IIEF-15, 15-question International Index of Erectile Function; PDQ-PS, Peyronie’s Disease Questionnaire (psychosexual symptoms); PDQ-PP, Peyronie’s Disease Questionnaire (penile pain); PDQ-SB, Peyronie’s Disease Questionnaire (symptom bother); N/A, not applicable.

<sup>a</sup>:On a 5-point scale (1=very unsatisfied, 2=unsatisfied, 3=neutral, 4=satisfied, 5=very satisfied).

Common and minor TRAE such as penile bruising, swelling and pain were more common in the CCH compared to ILV groups. There was a strong correlation between penile bruising and swelling, and penile pain following CCH ( $p < 0.01$ ), but none of these patients required analgesia. No patient reported penile fracture and/or required surgical intervention. The overall satisfaction rate on a 5-point scale was 4.1 in ILV and 4.5 in CCH groups, and there was no statistically significant difference detected in the PGI-I scores between the 2 groups ( $p = 0.14$ ).

## DISCUSSION

Scientific advances in our understanding of PD coupled with emerging therapeutic options have changed the way clinicians manage PD these days. Before CCH was licensed for PD, several injectable agents have been used in an off-label manner to treat males with PD [1,2]. The strict inclusion and exclusion criteria set forth by the IMPRESS I and II studies [5] confirmed that CCH can be effective in PD provided these males have mild to moderate penile curvature, with a small clinically stable and palpable, non-ossified plaque disease [1,2,6].

The proposed mechanisms of action between ILV and CCH are different. *In vitro* studies suggested that verapamil interferes with fibroblast cellular proliferation [7] and ILV causes a decrease in collagen and elastin fibres within the Peyronie's plaque in an animal model [8]. In contrast, commercially marketed CCH consists of a combination of synergistically acting collagenases AUX-I and AUX-II, both responsible to degrade collagen type I and III which is pathognomonic of PD plaque [6]. Furthermore, CCH can directly induce apoptosis of fibroblasts, downregulate the abnormal expression of collagen types I and III, and destroy pathological collagen plaques that are responsible for PD [6,9].

Published studies including systematic review and meta-analysis [10] showed that CCH is superior to ILV in terms of penile curvature improvement and plaque size reduction. In our study, there was a statistically significant difference found in the improvement in penile curvature between ILV and CCH groups, with a greater number of males who reported complete resolution of penile curvature in the CCH group. Furthermore, there was also a significant improvement in PDQ scores in the CCH group with statistically better outcomes in psychosexual symptoms and symptom bother scores compared to the ILV group. The lack of significant difference detected in penile pain scores between the 2 groups likely reflects that penile pain is often a transient symptom in males with PD [1].

The variation in treatment protocol between ILV and CCH could potentially play a role in the difference between the observed improvements in penile curvature and PDQ scores. While most of the published PD studies reported positive outcomes, many studies lack standardized outcome measures to allow for direct comparison [11]. Studies have shown that the volume and duration of the ILV protocol could play a role, too [1-4]. While the 6 courses of verapamil given in our study protocol were similar to Levine's original study [4], the volume of injection was different (10 mL in Levine's vs. 4 mL in our study). Another study showed that prolonged ILV treatment with 12 injections over six months had a greater reduction in penile curvature compared to 6 injections over three months period [12], while higher dilutions of verapamil resulted in a greater reduction in plaque size and pain relief [13]. Interestingly, some studies have shown improvements in penile curvature and smaller plaque size among those who received placebo injections, highlighting the possible impact of the volume of saline injection alone is enough to cause hydrostatic disruption of the penile plaque [10]. In contrast, a modified CCH regime using three CCH injections as compared to the IMPRESS treatment protocol with eight CCH injections was reported to be equally effective and safe [14]. The efficacy of this modified CCH schedule was confirmed in another study [15]. Despite the larger volume in the ILV in our study, i.e., 10 mg/4 mL of verapamil vs. 0.58 mg/0.5 mL CCH reconstituted injections, the CCH group showed greater improvement in the penile curvature compared to the ILV group ( $p < 0.01$ ) across all treatment interval periods.

The positive change in penile curvature and plaque size with CCH therapy is augmented with manual penile modeling performed following each treatment cycle [6]. Previous histologic studies have demonstrated that the application of mechanical forces, i.e., penile remodelling or traction can result in cellular changes to the Peyronie's plaques [16]. In our study, males in both groups were advised on similar penile remodelling techniques on both flaccid and erect penis based on the IMPRESS study protocol. However, further studies are required to determine the optimal time and duration of each episode of penile remodelling. Furthermore, recent studies have highlighted the additional benefits of concurrent oral therapy and penile traction device used in males who are receiving intralesional CCH injection therapy [17,18]. Unfortunately, CCH is currently not readily available in every country and the cost for each vial of CCH can vary depending on the local distributor price and payment by a third-party insurer [6]. For the uninsured, the cost of the CCH drug is significantly more expensive than verapamil and this would need to be factored into the cost-effective

analysis [19]. However, our study is not designed to perform a cost-effective analysis comparison between ILV and CCH.

The TRAE such as penile pain, bruising and swelling were more common following CCH therapy, and this is likely related to its mechanisms of action. The pooled analysis of six clinical trials including IMPRESS I and II reported at least a single TRAE in 86% of participants following CCH therapy [20]. The severity of TRAE reported was generally minor to moderate in severity since CCH remains inactive against alternative collagen forms such as type IV which is expressed in abundance within the basal lamina of blood vessels and perineurium of peripheral nerves [21]. In our study, there was a statistically significant higher complication reported in the CCH compared to ILV groups. While corporal ruptures can occur on the same side as the plaque or penile curvature after the second intralesional injection of each cycle [22], none of the patients in our study reported penile fracture nor required surgical intervention. While one study found that patients with penile curvature less than 30 degrees were more likely to report higher rates of penile swelling [23], and late-onset penile fracture has been reported in the literature to occur outside of the 14-day observation period [24], this observation was not detected in our cohort during the 12-month study period.

To our knowledge, this is the first study that directly compares the clinical outcomes and patient satisfaction rates between ILV and CCH in a select group of patients with PD. We acknowledged several limitations in our study including the lack of a placebo group, small cohort size, different volume of intralesional injection, patient self-directed use of penile manual modelling, penile plaque and length measurements as well as the absence of penile colour duplex ultrasound post-treatment. Each of these factors could introduce statistical biases in our analysis. Furthermore, cost analysis has not been factored and this is a major limitation given the cost of CCH if there is no medication rebate or private funding. Nonetheless, the present matched-pair comparison with the use of validated questionnaires and a minimum 24-month follow-up, are strengths in this study. The strict inclusion and exclusion criteria in this study also allowed for standardization of treatment outcomes based on published literature. While the IIEF-5 score has not been validated in the PD sample, the use of PDQ allows for objective measures in this study. Despite the difference in the actual dose of intralesional injections, CCH was more effective ILV in terms of penile curvature and PDQ scores improvement, and patients were satisfied despite higher complication rates.

## CONCLUSIONS

Intralesional CCH therapy is more effective than ILV to treat a carefully selected group of males with PD, with a reasonable safety profile and a higher high level of patient satisfaction rate in the intermediate-term. Nonetheless, ILV appears to offer effective alternative therapy in PD in the absence of CCH therapy.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## FUNDING

None.

## AUTHORS' CONTRIBUTIONS

Research conception and design: Eric Chung. Data acquisition: Juan Wang. Data analysis and interpretation: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript: all authors. Obtaining funding: none. Administrative, technical or material support: Juan Wang. Supervision: Eric Chung. Approval of manuscript: all authors.

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