Peyronie’s disease: intrallesional collagenase injections

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While surgery is currently the standard treatment for Peyronie’s disease it is not without adverse effects, including erectile dysfunction. In this article the authors review the evidence for intrallesional injections of collagenase clostridium histolyticum.

Peyronie’s disease (PD) is a connective tissue disorder characterised by the deposition of fibrous plaques within the tunica albuginea of the penis, resulting in penile shortening, curvature and gross disfigurement. It has been postulated to occur from a combination of trauma and genetic predisposition to abnormal wound healing. PD is associated with significant physical and psychological stress to the patient.

Pharmacological management of PD has faced considerable difficulty. The aim of treatment is to directly disrupt the inflammation and collagen plaque deposition, while minimising damage to the delicate surrounding neurovascular structures. A variety of treatment modalities have been trialled including oral/topical medications, electromotive drug administration, extracorporeal shockwave therapy and intrallesional injections. However, the effectiveness of these treatments is currently limited, with many patients eventually requiring surgery.

Currently, surgery remains the gold standard treatment. However, surgery is only indicated in patients with stable disease for at least 12 months and curvature that prevents penetrative sexual intercourse; and it carries significant risks of erectile dysfunction, penile shortening and sensory loss.

Collagenase clostridium histolyticum (CCH; Xiapep) is an isolated mixture of two microbial collagenases, AUX-I and AUX-II, contained in a phosphate buffer. These work to enzymatically degrade the type I and III collagen fibrils commonly found in PD plaques, while sparing type IV collagen present in surrounding neurovascular tissue. CCH is administered as an intrallesional injection. AUX-I and AUX-II work synergistically by cleaving tropocollagen from different sites within the collagen fibrils. The enzymes remain localised at the point of injection, concentrating their action, minimising haematogenous spread and therefore reducing systemic side-effects.

University College London Hospitals NHS Foundation Trust has recently developed a new modified treatment protocol for intrallesional CCH, forming the current best practice for PD management within the UK. Under a penile block, three
intraliesional CCH injections of 0.9mg are administered at four-weekly intervals. Daily home remodelling techniques, stretching and vacuum devices are then used between injections to mechanically stretch the plaque. This protocol has demonstrated equivalent improvements in penile curvature (36.9°; 12–75; \( p < 0.001 \)) to the standardised practice of eight injections. Furthermore, the treatment was well tolerated, with reported improvements in International Index of Erectile Function (IIEF), Peyronie’s Disease Questionnaire (PDQ) and Global Assessment of Peyronie’s Disease (GAPD).

Initially, an erosion is induced in the patient via an intracavernosus injection of a vasoactive agent, allowing direct visualisation and manual palpation of the PD plaque. The area of maximum curvature is then determined and marked on the patient. A penile block is then administered using 10ml of clear lignocaine 1%, before a full vial of 0.9mg CCH is drawn up (preferentially into a hubless syringe with 0.01ml gradations). Once the penis is flaccid, the needle should be inserted through the width of the plaque, in line with the point of maximum concavity, and the entire dose of CCH is injected in multiple positions at the apex of the curvature (see Figure 1). Penile compression is applied and patients are given anti-inflammatory medication for two to three days. Patients are told to refrain from sexual intercourse and to keep the penis elevated for two weeks.

It is recommended that two to three days after the CCH injection, adjunctive treatments are used. These include manual modelling, stretching or use of a vacuum device. With manual modelling, when they achieve a spontaneous erection, patients are advised to gently bend the penis in the opposite direction to the PD curvature for 30 seconds. Stretching involves gentle manual stretching of the penis for 60 seconds after every urination. The vacuum pump is a mechanical device that should be used twice daily to mechanically stretch the penis; however, this should be done slowly and only to a moderate pressure to avoid complications.

### The evidence base

Principally, an intraliesional injectable agent must specifically degrade abnormal fibrous plaques without causing tunical damage, ensuring the preservation of tunical elasticity with a normal erection. There has been a significant history of intraliesional injections with other agents in the management of PD, including interferon-α and verapamil. Both agents have demonstrated evidence of decreasing penile pain and curvature, but they did not translate effectively into routine clinical practice. Intraliesional CCH has been proposed as a more effective treatment for PD than previous agents. It has been extensively evaluated through clinical trials and a number of high quality randomised trials have demonstrated the benefits of this therapy (Table 1).

The phase III trials, Investigation for Maximal Peyronies’ Reduction Efficacy and Safety Studies (IMPRESS) I and II, started in 2013. These two large double blind randomised controlled trials of 832 males in America and Australia showed a statistically significant reduction in penile curvature from intraliesional CCH compared to placebo (intraliesional CCH: 34% reduction, \([\pm 17.0^\circ \pm 14.8^\circ] \) versus placebo: 18% reduction \([\pm 9.3^\circ \pm 13.6^\circ] [p <0.0001] \)). Furthermore, there was an reduction in penile plaque consistency after CCH injections and big improvements in sexual function as quantified by the IIEF to a statistically significant level. The efficacy demonstrated in these trials resulted in intraliesional CCH gaining FDA approval for the treatment of PD with a palpable plaque and a curvature of >30° pre-treatment. Levine et al/ conducted a phase III clinical trial of 347 patients also looking at mean reduction in penile curvature and PDQ/IIEF symptom scores with intraliesional CCH. The results were robust, with 56% of patients achieving a decrease in penile curvature of at least 20%, and a concomitant decrease of one or greater points in the symptom bother domain of the PDQ. Overall mean decrease in penile curvature was 34% \((-18.3^\circ \pm 14.02^\circ) \) for all study participants.

However, current evidence fails to recognise the disparity between objective changes in curvature and how this translates to improvements in sexual function and the need for future surgery. Intraliesional CCH is also associated with adverse effects (AEs). In a pooled data analysis of 1044 PD patients, 85.8% patients reported at least one treatment-related AE; most commonly bruising (82.7%), pain and swelling. Further analysis revealed the majority of AEs were mild (75.2%), with 14.2% experiencing no treatment-related AEs. Severe AEs were rare (five patients with penile haematoma, and four with corporal rupture). In addition, there were no immunogenicity-related hypersensitivity reactions.

Some patients will still not achieve sufficient symptomatic improvement, and in these cases surgical correction is required. There is currently a paucity of longitudinal experience with intraliesional injections of CCH and its effects on future surgery are not well defined.

A small study of seven men who underwent salvage surgery with plaque excision and grafting (PEG) and/or tunica albuginea plication (TAP) following CCH treatment demonstrated that CCH was not a contraindication for future surgery in patients with PD. The study showed comparable intraoperative times with standard PEG/TAP procedures (range: 88–146 mins). Furthermore, there were no reported anatomical difficulties or
## Table 1. Summary of clinical trials using intralesional collagenase *Clostridium histolyticum* (CCH) injection for the treatment of Peyronie’s disease, including treatment regimens, efficacy and prevalence of adverse effects (AEs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Population</th>
<th>Regimen</th>
<th>Efficacy</th>
<th>Serious AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raheem <em>et al</em> (2017)</td>
<td>Prospective single centre study of the use of CCH in a modified shortened protocol</td>
<td>CCH: 53</td>
<td>Each cycle was 1 x 0.9mg CCH injection. Cycles were repeated after 4 weeks for a total of 3 cycles</td>
<td>Mean improvement in angle of curvature: 17.36°</td>
<td>7 penile haematomas (5 due to vacuum pump)</td>
</tr>
<tr>
<td>Anassie <em>et al</em> (2016)</td>
<td>Retrospective analysis on impact of number of CCH cycles on outcomes</td>
<td>CCH: 78</td>
<td>Each cycle was 2 x 0.58 mg CCH injections 24 hours apart. Cycles were repeated after 6 weeks for between 1-5 treatment cycles</td>
<td>Regardless of number of cycles, mean improvement in penile curvature: 16.5°</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yang and Bennett (2016)</td>
<td>Analysis of CCH use at a single centre</td>
<td>CCH: 49 (12 active PD; 37 stable PD)</td>
<td>Each cycle was 2 x 0.58 mg CCH injections 24 hours apart. Cycles were repeated after 6 weeks for ≤5 treatment cycles</td>
<td>Average penile curvature improvement: 15.4°</td>
<td>4 penile haematomas 1 penile fracture/tunical rupture</td>
</tr>
<tr>
<td>Levine <em>et al</em> (2015)</td>
<td>Phase III: open label</td>
<td>CCH: 347</td>
<td>Each cycle was 2 x 0.58mg CCH injections 24-72hours apart. Cycles were repeated after 6 weeks for ≤4 treatment cycles</td>
<td>Mean reduction in penile curvature: 34.4%; 95% CI (±3.2%)</td>
<td>2 penile haematomas 1 corporeal rupture</td>
</tr>
<tr>
<td>Gelbard <em>et al</em> (2013)</td>
<td>Phase III: Two identical randomised double-blind placebo-controlled studies</td>
<td>IMPRESS I CCH: 227, placebo: 140 IMPRESS II CCH: 274, placebo: 141</td>
<td>Each cycle was 2 x 0.58mg CCH injections 24-72hours apart. Cycles were repeated after 6 weeks for ≤4 treatment cycles</td>
<td>Mean reduction in penile curvature: CCH: 34%, placebo: 18%</td>
<td>Nil</td>
</tr>
<tr>
<td>Gelbard <em>et al</em> (2012)</td>
<td>Phase IIb: double blind, randomised placebo-controlled study</td>
<td>CCH: 111, placebo: 36</td>
<td>Each cycle was 2 x 0.58mg CCH injections 24-72hours apart. Cycles were repeated after 6 weeks for ≤3 treatment cycles</td>
<td>Mean reduction in penile curvature: CCH: 29.7%, placebo: 11.0%</td>
<td>3 penile haematomas 3 corporal ruptures</td>
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<td>Jordan (2008)</td>
<td>Phase II: open label</td>
<td>CCH: 25</td>
<td>The cycle was 3x 0.58mg CCH injections over 7-10 days. Repeated once after 3 months</td>
<td>Proportion of patients with significantly reduced penile curvature: 52.6% Proportion of patients with significantly reduced plaque size: 94.7%</td>
<td>Nil</td>
</tr>
<tr>
<td>Gelbard <em>et al</em> (1993)</td>
<td>Phase II: double blind placebo-controlled randomised control trial</td>
<td>CCH: 22, placebo: 27</td>
<td>0.348mg, 0.580mg and 0.812mg CCH</td>
<td>Positive response in penile curvature in: CCH: 8/22 (36.4%), placebo: 1/27 (3.7%)</td>
<td>Nil</td>
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<tr>
<td>Gelbard <em>et al</em> (1983)</td>
<td>Phase I</td>
<td>CCH: 31</td>
<td>6 patients: mean 0.047mg CCH 25 patients: B-aminoproprionitrile fumberate + mean 0.156mg CCH</td>
<td>Objective improvement in penile curvature seen in 20/31 (64.5%)</td>
<td>Nil</td>
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Peyronie’s disease may have on the need for future surgery to make it a viable treatment option. Until then the importance of correct patient selection is imperative in avoiding ineffective and costly use of CCH injections.

**Declaration of interests:** none declared.

**References**