SEXUAL MEDICINE REVIEWS

Intralesional Injection of Collagenase *Clostridium histolyticum* May Increase the Risk of Late-Onset Penile Fracture

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ABSTRACT

Introduction: The use of intralesional injection of collagenase *Clostridium histolyticum* (CCH) has become a valid treatment option in the management of Peyronie's disease (PD). Multiple studies have shown the drug's safety and efficacy. However, sparse literature exists on the utility of the injection protocol's 14-day "observation period," in which patients are instructed to abstain from all sexual activity.

Aim: To summarize the contemporary literature and report on our series of patients treated with CCH in an effort to explore the effectiveness of the postinjection observation period.

Methods: We retrospectively reviewed the clinical course of men treated with at least one CCH injection at our institution from April 2014 through February 2017.

Main Outcome Measures: The main outcome measure for our cohort was complication rate (hematoma, fracture). Secondary outcomes included progression to corrective surgery.

Results: Of the 102 patients treated, 5 (4.9%) developed a corporal fracture. Four of these occurred outside the 14-day observation period. One fracture was managed conservatively and the rest underwent surgical exploration and repair. Twelve penile hematomas were reported; one of these patients was surgically explored because of suspicious magnetic resonance imaging findings. Seven patients (6.9%) progressed to corrective surgery.

Conclusion: Penile hematoma and corporal fracture are serious complications that must be discussed with patients before initiation of intralesional CCH treatment. Little evidence exists to direct physicians on the proper management of post-CCH penile fractures; many caregivers and patients elect to treat these injuries conservatively and avoid surgical exploration. Further studies are warranted to generate discussion and reassessment regarding the safety and effectiveness of this 14-day observation period. **Beilan JA, Wallen JJ, Baumgarten AS, Morgan KN, Parker JL, Carrion RE. Intralesional Injection of Collagenase *Clostridium histolyticum* May Increase the Risk of Late-Onset Penile Fracture. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Xiaflex; Collagenase *Clostridium histolyticum*; CCH; Penile Fracture; Corporal Rupture; Observation Period

INTRODUCTION

Peyronie's disease (PD), which can affect more than 10% of the male population, is a soft tissue disorder in which the functional, fibroelastic tunica albuginea of the penis is converted into inflexible fibrin scar by unregulated deposition of collagen and fibrin.[1–3] Traditionally, PD has been characterized by local changes in the collagen composition of the tunica after trauma to the penis.[3] Fibrin and collagen scar deposition in focal areas along the tunica can limit penile expansion during erections. This is the hallmark of PD and the cause of the signs and symptoms listed in Table 1.[4–6]

Many topical, oral, and injectable medications have been tried with and without electromotive forces and/or stretching exercises for the treatment of this physically and psychologically altering disease process. Gelbard et al[7,8] first described the application and intralesional injection of collagenase *Clostridium histolyticum* (CCH) in PD more than three decades ago. However, it was not until the publication of the results of the IMPRESS I and II trials (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) in the *Journal of Urology* in 2013 that CCH (Xiaflex, Endo Pharmaceuticals, Malvern, PA, USA) was approved by the US Food and Drug Administration (FDA) for the treatment of men with a palpable plaque and a curvature of 30° to 90°.[1] CCH, a collagenase derived from

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Table 1. Peyronie's disease signs and symptoms

Penile curvature
Penile pain
Palpable penile plaques or cords
Hourglass or bottle neck of penis during erection
Penile shortening
Erectile dysfunction
Inability for intromission

the *Clostridium* bacterium, which selectively degrades type I and III collagen, became the first and only FDA-approved intralesional injection therapy for PD. Patients were eligible to undergo up to four treatment cycles consisting of two injections spaced 48 to 72 hours apart in addition to stretching exercises between cycles. A 14-day observation period without sexual activity was recommended after the second injection of each cycle. In these initial studies, the adverse event (AE) rate was low and only 6 of 832 patients had a more serious AE, including three corporal ruptures and three penile hematomas. More commonly observed AEs included penile pain, swelling, ecchymosis, blister formation, pain at the injection site, and pruritus; these resolved without intervention within 14 days after injection.[1] The risk of corporal rupture in this series was less than 0.5%, and all occurred within the 14-day observatory period. Corporal rupture is one of the most devastating AEs of CCH and occurs by one of two mechanisms: transmural degradation of the tunica by the collagenase or tearing of the tunica at a site of weakened integrity during vigorous activity. The purpose of this review is to summarize the current literature and report on our series of patients treated with CCH, including our five cases of corporal rupture.

METHODS

A database was created consisting of all patients who received a CCH injection at one of our men's sexual health centers in Tampa, Florida. After approval from the institutional review board (USF IRB Pro00030099), a retrospective review was conducted to collect peri-procedure demographics and post-procedure outcomes. The following discussion serves to summarize the authors' experience and provide a comparison point to the existing literature.

RESULTS

From April 2014 through February 2017, a total of 102 men received at least one CCH injection at our institution. All injections were performed by Xiaflex REMS-certified physicians. Patients followed the standard cycle protocols outlined by the Xiaflex guidelines: each cycle consisted of an initial injection followed by a second injection 1 to 3 days later. In-office and at-home modeling procedures also were performed according to protocol.[9]

The average age of treated individuals was 56.8 years; the average body mass index was 28.3 kg/m^2. Preprocedure examination in this cohort showed an average curvature of 54.5° (range = 30–90, SD = 19.1). Curvature was estimated based on examination of the phallus in an erect state, with the aid of a goniometer. The breakdown of curvature severity, number of cycles administered, and progression to surgery is presented in Table 2.

Table 2. Correlation among preprocedure curvature, number of cycles administered, and progression to corrective surgery

	Cycles, n						
Curvature (°)	Total	1	2	3	4	≥5	Progression to surgery, n (%)
30	14	6	6	0	2	0	0 (0)
31–45	38	5	14	6	12	1	1 (2.6)
46–60	24	5	7	2	7	3	1 (4.2)
61–90	26	8	10	4	4	0	5 (20)
Total	102	24	37	12	25	4	7 (6.9)

Preprocedure curvature was separated into four divisions: 30°, 31° to 45, 46° to 60°, and 61° to 90°. Approximately one fourth of patients had a preprocedure curvature of 46° to 60° and another fourth had a curvature of 61° to 90°. More than one third of treated patients had a measured angle of 31° to 45°; half these patients received no more than two cycles. One patient in this 31° to 45° group elected to undergo five cycles of CCH injections and the remaining 18 patients received three or four cycles. Similar to the 31° to 45° group, exactly half the patients with 46° to 60° curvature were treated with one or two cycles. This is in contrast to the 30° group, in which 86% of patients were treated with no more than two cycles.

No patient with a 30° curve underwent an "off-label" fifth injection cycle or progressed to surgical intervention. Of the patients who elected to proceed with corrective surgery, most (71%) were in the most severe curvature group. Approximately 19% of all patients in the 61° to 90° group ultimately underwent a surgical procedure vs 4.2% and 2.6% of patients who progressed to the 46° to 60° group and 31° to 45° group, respectively. Of the five men in the 61° to 90° group who progressed to surgery, one elected surgery because his insurance no longer covered CCH injections. The remaining four underwent penile plication procedures because of unsatisfactory results with CCH treatments. This included one man who developed a penile fracture 15 days after CCH injection; plication was performed at the time of repair. This case scenario is reviewed in more detail in a later discussion.

The clinical follow-up after each patient's most recent CCH injection was variable, with an average length of 62.5 days (median = 35 days). There are many possible reasons to explain the wide range of follow-up, including cessation of treatment because of complication or resolution of curvature, changes in insurance coverage, and change in urologic providers. Most of our patients did not live in the same city as our urologic clinics; they frequently followed up with their local provider after they were deemed stable to undergo surveillance elsewhere.