MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Outcomes of Surgery in Peyronie's Disease Following Intralesional Collagenase Clostridium Histolyticum Injections

Mahdi Bazzi[1] · Marcus L. Jamil[1] · Ali A. Dabaja[1]

Abstract

Purpose of Review To explore the potential hurdles surgeons may encounter when preforming surgical correction of penile curvature in patients with Peyronie's Disease following intralesional collagenase clostridium histolyticum injections.

Recent Findings Although limited data exists, retrospective analysis of surgeon experiences in surgical treatment of refractory penile curvature in patients with Peyronie's disease appears to not result in more post-operative complications and may only slightly increase intra-operative difficulty.

Summary As the use of intralesional collagenase clostridium histolyticum continues to increase and patients who demonstrate persistent curvature despite treatment seek further management, the role of investigating the feasibility of surgery demonstrates significant importance. Although limited data exists, it appears that surgery following intralesional collagenase clostridium histolyticum is safe without added post-operative complications. At the present time, however, further data on intra-operative findings and post-operative outcomes remain necessary, and as the use of this intralesional therapy continues to rise, further information should become readily available.

Introduction

Peyronie's disease (PD) describes a penile curvature, as the result of a fibrotic plaque, comprised of collagen and fibrin, within the tunica albuginea [1]. The reported prevalence of PD is approximately 0.4–3.2%, with some estimations as high as 9% in specific patient populations [2–5]. PD is known to cause significant impairments in male sexual performance, overall quality of life, results in erectile dysfunction, causes penile pain and pain during intercourse to both the patient and the partner, which has been reported to adversely affect

relationships [6–8]. Several studies have described the association between PD and psychological distress and anxiety. Prospective investigations have discovered that appearance as opposed to pain may result in more psychological distress, with correlations demonstrated between the degree of the angle of curvature and sexual dissatisfaction; further, men affected by PD report significantly less sexual intercourse [9].

In the reported literature, various risk factors for PD have been described. Aging has been noted to be the most significant risk factor, with a linear increase in incidence of PD between the ages of 30 and 49 and an exponential increase after the age of 50 [2, 4, 10]. It is theorized that the correlation between age and PD is due to increased trauma to the tunica albuginea over longer periods of time [10]. Other risk factors include diabetes mellitus, use of beta-blockers, erectile dysfunction, Dupuytren's disease (DD), hypogonadism, radical prostatectomy and pelvic surgery, penile fracture, urethral catheterization or cystoscopy, and history of infectious processes such as urethritis [11–14]. However, despite extensive and large-scale investigations into the many postulated causes of PD, data on the true etiology continues to remain inconsistent [2, 15].

✉ Ali A. Dabaja
Adabaja2@hfhs.org

Mahdi Bazzi
Mbazzi5@hfhs.org

Marcus L. Jamil
Mjamil1@hfhs.org

1 Henry Ford Health System, Vattikuti Urology Institute, 2799 West Grand Boulevard, Detroit, MI 48202, USA

The treatment of PD ranges from conservative management and assurance, with counseling of the afflicted couple and management of penile pain, to medical treatment with intralesional injection therapy (ILI) to surgical correction when indicated. Over the years, there has been an abundance of published literature in the medical management of PD. Oral medications have been investigated and include, but are not limited to, potassium para-aminobenzoate (POTABA), vitamin E, colchicine, tamoxifen, and carnitine. Despite the multiple options and various mechanisms of actions, there is a lack of evidence to support their use and currently are not recommended by the most recent American Urological Association (AUA) guidelines [1]. Injection-based treatment is another, more frequently used, option for patients affected by PD. This includes the use of either a single agent or a combination of the following agents: corticosteroids, botulinum, interferon-alpha2b, and verapamil. All of which have been investigated and utilized and have ultimately demonstrated limited benefit [16]. Certain agents, such as verapamil, have demonstrated efficacy in controlling penile pain in those patients with PD [17–19].

Recently, new evidence, based on randomized controlled trials, has demonstrated that collagenase clostridium histolyticum (CCH) may provide benefit in the treatment of PD as a non-surgical alternative [20–22]. As CCH is being deployed more in clinical practice, it has been noted that there is a population of men who have persistent bothersome curvature despite receiving the recommended scheduled treatment [23, 24•]. Therefore, we reviewed the current literature to assess the feasibility of surgical management following CCH treatment in men with persistent curvature.

Material and Method

We performed an extensive PubMed, Medline, and Embase search from 1946 to 2019 in order to identify all publications related to surgical intervention in the treatment of Peyronie's disease following intralesional CCH injections. Keywords and phrases used for the search included the following: "Peyronie's," "refractory Peyronie's," "penile curvature," "refractory penile curvature," "Xiaflex," "collagenase clostridium histolyticium," "Peyronie's surgery," and "penile plaque."

Review of Collagenase Clostridium Histolyticum

Historical Perspective and Mechanism of Action

Initially, CCH was investigated in patients with burns and skin ulcers to assist with wound debridement [25]. It was first investigated in 1996, and underwent further clinical trials in 2000 as an injectable treatment for DD [26, 27]. Similar to PD, DD also forms fibrotic plaques within the palmar fascia of the hands and can therefore result in contractures of the fingers [28]. Therefore, CCH can be used to degrade the collagen tissue that forms within these fibrotic plaques [26]. Previous investigations have demonstrated significant benefit in the treatment of patients with DD, improving nodular consistency and hardness when compared to placebo [29]. It was due to the pathophysiological similarities between DD and PD that it was investigated in the latter.

CCH consists of a purified mixture of two microbial collagenase isoforms, AUX-I I and AUX-II [30]. AUX-I cleaves the internal segments of collagen while AUX-II cleaves at the carboxyl end [31]. Ultimately, these enzymes work synergistically and result in hydrolysis of type I and type III collagen fibers, the primary collagen types found within PD plaques, while sparring type IV, which is found in vascular and nervous tissue [30, 32].

Efficacy in Peyronie's Disease

The efficacy of CCH has been demonstrated in the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and II), which was a randomized, phase-3, double-blind, placebo-controlled investigation. The investigators assessed approximately 900 men, between the two studies, and reported an approximate 34.0% improvement in penile curvature when compared to the 18.2% improvement seen in the placebo group [33]. Subsequent investigations and reviews, some with variable dosing regimens when compared to the original IMPRESS cohorts, have been reported and demonstrated similar efficacy [32, 34]. CCH is now recommended in the AUA guidelines in the treatment of PD, and the first licensed drug by the United States Food and Drug Administration (FDA) in the treatment of PD [1, 34].

Surgical Options in the Treatment of Peyronie's Disease

Surgical treatment may be offered to patients following a period of stability for 3–6 months [1]. Various surgical techniques have been described, including, but not limited to, tunical plication (TP), plaque excision and grafting (PEG), plaque incision and grafting, or inflatable penile prosthesis (IPP) placement in those with erectile dysfunction [1, 35]. All three surgical options have demonstrated success in correcting penile curvature and improve patient satisfaction [36, 37•]. However, selecting the proper surgical modality requires an extensive pre-operative evaluation, including penile ultrasound and counseling the patient in regard to the expectations, differing success rates, and complications.

TP, first described in 1965, in the treatment of congenital abnormalities, involves shortening the contralateral corpora cavernosum, opposite of the plaque [38]. It was later adopted

in the treatment of PD in 1977, and over time, many modifications to the original technique have been reported [39]. Currently, this surgical approach is recommended to patients who have penile curvature less than 60°, acceptable pre-operative penile length, good pre-operative penile rigidity, and absence of hour-glass deformity or hinge [40]. In general, this procedure is well tolerated and 90% of patients report satisfaction post TP with only 10% recurrence at 24 months. The most commonly reported complication being loss of penile length, penile pain, and persistence of penile curvature [40].

Plaque incision or excision and grafting is another available surgical modality for patients with PD, first performed in 1974 by Devine and Horton [41], typically reserved for more complex presentations, curvature greater than 60–70°, extensive plaque calcification and shaft narrowing, hour-glass deformity or hinging [37•, 42]. Following plaque incision, a graft is required to repair the newly made defect. Several different types of graft materials have been thoroughly investigated and used [43]. Currently, there is no consensus on the ideal graft material [43, 44]. The most commonly used grafts in practice today are either autologous grafts, which can include saphenous vein or buccal tissue, and non-autologous grafts, which may include human dermal or pericardial tissue or bovine/porcine alternatives [43]. Large retrospective analysis have demonstrated penile straightening rates of 80.0–96.4% and reported mean satisfaction between 88.0 and 92.0%. Complications include, most frequently, ED, with reports as high as 25% of men, in addition to penile shortening, rates reported between large ranges of 4.9 and 40.0% [45, 46].

Placement of an IPP is reserved for patients with PD and concurrent erectile dysfunction [1]. The surgical approach mirrors that of an IPP placement in those patients with isolated ED with the potential addition of manual penile modeling or incision of the Peyronie's plaque with or without grafting in cases of more severe curvature [40, 47]. Post-operative satisfaction rates at 2-year follow-up have been reported to be greater than 80% [48].

Residual Curvature Following Intralesional CCH and the Feasibility of Surgery

Despite the promise of intralesional CCH, a certain group of patients may fail CCH injections and might present with refractory penile curvature resulting in dissatisfaction therefore necessitating further treatment. As the use of intralesional CCH continues, this population of patients will only continue to increase. Due to the recent approval of intralesional CCH by the FDA in patients with PD, and despite the extensive data on outcomes following surgery and refinements in those surgical techniques, limited data exist on the potential challenge's surgeons encounter when performing surgery on those patients who failed prior intralesional CCH. The question of whether or not surgery following intralesional CCH may

result in poorer outcomes or increased post-operative complications is rooted in the notion that intralesional injection therapy results in an inflammatory response, and therefore leads to alterations in the normal anatomical planes resulting in a far more difficult dissection [24•]. It has previously been described by Levine et al. that the inflammatory process of PD itself may distort normal anatomical planes, specifically between Buck's fascia and the tunica albuginea; this same outcome can also be observed in other intralesional therapies such as interferon alpha2b or verapamil [23].

An observational study conducted by Hay et al. assessed the outcomes of surgical treatment in patients with DD with persistent contracture following intralesional collagenase. The investigators surveyed 9 surgeons, all of which were involved in the initial investigations in assessing the efficacy of collagenase injections in the treatment of DD, on the potential challenges and outcomes of surgery in refractory DD following collagenase injections. A 5-point grading scale was used to assess surgical difficulty. Seven out of nine surgeons reported no increased surgical difficulty or complex anatomical features following collagenase injections in the 15 total patients identified. Two out of nine surgeons reported increased difficulty, using the study grading scale, 2 patient operations were characterized as being equivalent to a revision surgery and 4 patient operations being characterized as being harder than a revision surgery. In all, 9 out of the 15 total patients identified were characterized as equivalent to a primary operation [49].

To date, there exists two retrospective studies investigating the intraoperative and postoperative outcomes and complications of surgery in patients with refractory curvature following intralesional CCH. The first retrospective analysis conducted by Levine et al. investigated a cohort of 7 patients with a mean pre-surgical penile curvature was 59°. Patients underwent either PEG, TP, or both. In total, 2 patients underwent TP, 1 underwent PEG, and the remainder underwent combination PEG and TP. Except for 1 patient, the time from the last intralesional CCH injection to the day of surgery exceeded 90 days (range 64–366, mean 182.85) As described by Levine et al., no anatomical difficulties or complications, believed to be as a result of intralesional CCH, were noted. Mean operative time for all patients who underwent both PEG and TP was 131.8 min. Surgical success was described as penile curvature less than 20°, which all patients who were investigated demonstrated. One patient, who underwent PEG only, developed a sub-graft hematoma which required aspiration. Six of seven patients reported satisfaction post-surgery. Ultimately, concluded by the authors, no significant differences were noted in surgical difficulty and outcomes in comparison to other patients who undergo surgical correction of residual curvature following other types of intralesional injection therapies [23].

The second retrospective analysis performed by DeLay et al. also investigated a similar cohort of 10 patients. All

Table 1 Descriptive characteristics of all available patients within Levine et al. and DeLay et al. investigations who underwent surgical correction following intralesional CCH injections

Patient number	Age	Surgery	Days from last CCH to surgery	Intra-operative time	Pre-CCH curvature	Post-CCH curvature	Post-surgical Curvature	EBL	Intra-operative fibrosis	Post-operative complications
1	59	PP	185	88	60	60	< 20		No	None
2	63	PP+PIG	64	123	45	40	< 20		No	None
3	51	PIG	114	146	45	45	< 20		No	None
4	48	PP+PIG	328	123	65	65	< 20		No	None
5	56	PP+PIG	366	130	65	65	< 20		No	None
6	56	PP	96	105	68	60	< 20		No	None
7	55	PP+PIG	127	137	65	70	< 20		No	None
8	48	PP	89	58	90	45	0	15	No	None
9	60	PP	89	77	85	65	0	25	Yes	None
10	56	PP	171	56	60	40	0	10	No	None
11	61	PP	114	61	60	40	0	10	No	None
12	65	PP	97	70	70	65	0	10	No	None
13	59	PP	89	68	65	60	0	5	No	None
14	58	IPP	264	62	70	60	30	25	No	None
15	54	PIG	99	145	60	55	0	25	Yes	None
16	58	IPP	148	73	60	45	15	50	Yes	None
17	61	IPP	349	51	45	35	0	10	No	None
Mean			164	92.5	63.4	53.8				

CCH collagenase clostridium histolyticum injection, *PP* penile plication, *PIG* penile graft and incision, *IPP* inflatable penile prosthesis, *EBL* estimated blood loss

patients received 4 treatments of intralesional CCH prior to surgery. Six patients underwent TP, 3 underwent IPP placement (of which, 1 required a relaxing incision), and 1 patient underwent PEG. The mean time from last injection to time of surgery was 150.9 days (range 89–349 days). Mean operative time was 72.1 min (range 54–145 min). One of the 10 patients demonstrated post-operative curvature, defined as greater than 20°. Reported by the authors was the mention of fibrosis within the operative report. In the 10 patients assessed, 3 patient operative reports had mention of increased fibrosis. All three of these patients underwent different surgical procedures, the 1st patient underwent TP, the 2nd patient underwent plaque incision and grafting, and the 3rd patient underwent IPP placement with relaxing incision. The mean operative time of these three cases was 98.3 min (range 73–145 min), the longest surgery of the three being plaque incision and grafting, and average estimated blood loss (EBL) was 33.3 ml (range 25–50 ml). However, it should be noted that no post-operative complications were noted. As stated by the authors, no significant difference was noted in these patients when assessing operative time, EBL, or post-operative curvature. A commonality among all three of these patients with reports of increased fibrosis within the operative report, and highlighted by the investigators, was that surgery occurred less than 180 days from date of last intralesional CCH injection, 2 of those 3

patients underwent surgery less than 100 days from time of the last intralesional CCH injection; however, of the 10 patients within the original cohort, only 2 underwent surgery beyond 180 days [24•].

A summary of all patients from both studies can be found in Table 1. Universal to both of these investigations is the small sample sizes and retrospective nature of the studies; therefore, it is difficult to extrapolate any definitive conclusions. However, given the available data, previous intralesional CCH should not preclude one from undergoing subsequent surgical correction of refractory curvature; however, it may slightly increase intra-operative difficulty without an increase in post-operative complications.

Conclusion

Based on the available data, it would appear that surgery following intralesional CCH is safe with potential for slight increase in difficulty intra-operatively without any increase in post-operative complications or outcomes.

Compliance with Ethical Standards

Conflict of Interest Mahdi Bazzi and Marcus L. Jamil each declare no potential conflicts of interest.

Ali A. Dabaja is a section editor for *Current Urology Reports*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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