Collagenase Clostridium Histolyticum Injection for Dupuytren Contracture: 2-Year Follow-up

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Background: Dupuytren disease is characterized by the development of palmar fibrous tissue that can lead to fixed flexion contracture (FFC) and contribute to functional loss of the involved digits. Our goal was to investigate rates of contracture resolution and recurrence in patients who underwent enzymatic fasciotomy for Dupuytren contracture consisting of collagenase clostridium histolyticum (CCH) injection followed by passive manipulation combined with splinting and home-based therapy.

Methods: We prospectively enrolled 34 patients (44 metacarpophalangeal [MCP] and 33 proximal interphalangeal [PIP] joints) treated by one orthopaedic hand surgeon between November 2010 and November 2014. On day 1, CCH was injected into a palpable fibrous cord of the involved fingers. The next day, the finger was passively extended to its maximal corrective position. FFC was measured for each joint before injection and immediately after manipulation. Patients were instructed to wear an extension splint at night and perform stretching exercises at home and were re-evaluated at 6 weeks, 4 months, 1 year, and 2 years. Resolution was defined as improvement of contracture to ≤ 5° of neutral. Recurrence was defined as an increase in FCC of ≥ 20° after treatment.

Results: Immediate contracture resolution occurred in 42 of 44 MCP joints ($p < 0.001$), improving from 50° to 1.5°, and in 14 of 33 PIP joints ($p = 0.182$), improving from 44° to 16°. Four joints had recurrence within 6 weeks. Of the 48 joints with minimum 4-month follow-up (mean, 26 months), 12 had recurrence at 2-year follow-up (MCP, 6; PIP, 6). At 2-year follow-up, MCP and PIP contractures measured 17° and 35.5°, respectively. Older age and multiple digit involvement were associated with higher recurrence rates.

Conclusions: CCH offers a safe, nonoperative option to correct FCC in Dupuytren disease with greater success for MCP joints compared to PIP joints. There is a tendency of reoccurrence within 2 years of treatment. Further investigation is needed to determine optimal timing of repeat CCH injection to improve upon or extend the period of contracture resolution.

Keywords: *Dupuytren contracture, Collagenase clostridium histolyticum, Fixed flexion contractures, Metacarpophalangeal joint, Proximal interphalangeal joint*

Dupuytren contracture is characterized by the development of fibrous tissue in the form of nodules and cords within the palmar fascia. This process has features similar to wound-healing tissue, with associated contraction and maturation.[1,2] The process occurs in the fibro-fatty layer between the skin and deep structures of the palmar surface of the hand, which has a precisely ordered network of subcutaneous ligamentous fibers. The abnormal fibrous Dupuytren tissue develops within and/or around these longitudinally oriented ligamentous fibers.[3]

Nodules and cords develop at precise locations, typically in line with the digital rays in the palm and/or fingers. The disease appears to follow tension lines within the palmar fascia. Nodules may later mature to form longitudinally oriented cords. The normal palmar fascia and cord

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form a diseased band of tissue with thickening in response to increased tension. As the fibrous tissue matures and contracts, patients develop progressive flexion contractures of the hand and fingers. Over time, this contributes to a progressive loss of function in the involved extremity.[3]

In the past, emphasis has been placed on surgical treatment. Outcomes have been highly variable because they depend on the integrated treatment plan consisting of surgical technique selection, timing of surgery, patient expectations, and postoperative rehabilitation program.[1,4,5] Surgical treatment carries major risks including injury to digital nerves or vessels, resultant proximal interphalangeal (PIP) joint hyperextension, and wound healing complications related to hematoma, skin necrosis, and infection.[5] Surgical treatment may also result in recurrent stiffness, complex regional pain syndrome, and stiffness elsewhere in the affected hand.[3,4]

In February 2010, the United States Food and Drug Administration approved collagenase clostridium histolyticum (CCH) (Xiaflex; Auxilium Pharmaceuticals Inc., Malvern, PA, USA) as a nonoperative treatment for Dupuytren contracture. CCH contains two microbial collagenases in a defined mass ratio: collagenase AUX-I and collagenase AUX II, which are isolated and purified from the fermentation of *Clostridium histolyticum* bacteria. This nonsurgical option can be performed in an office setting and was designed to avoid complications associated with surgery. Initial studies showed promising results and minimal morbidity after in-office injection.[3-6] Furthermore, this nonoperative option does not require the extensive physical therapy that is needed after surgery to prevent stiffness and maintain correction.

The purpose of this study was to examine the rates of contracture resolution and recurrence in patients who underwent enzymatic fasciotomy consisting of CCH injection, manipulation, splinting, and home-based therapy for treatment of Dupuytren contracture involving the metacarpophalangeal (MCP) or PIP joint. Given the successful maintenance of contracture resolution described by multiple studies at 1 year[7-10] and the tendency for recurrence during longer follow-up periods,[11-13] we hypothesized that contracture resolution would be maintained at 1 year but would tend to return by 2 years after CCH injection.

METHODS

Patient Selection
After Institutional Review Board approval, 34 patients (10 women) were enrolled in this prospective trial between November 2010 and November 2014. Enrolled patients were treated by one fellowship-trained, orthopaedic hand surgeon at a community hospital. We included patients with symptomatic Dupuytren contracture (with functional limitation) with a palpable cord and fixed flexion contracture (FFC) $\geq 30°$ at the MCP joint and/or PIP joint of any digit other than the thumb who preferred nonoperative treatment. We excluded patients for the following reasons: previous treatment for FFC (both surgical and nonoperative), previous hand trauma resulting in scarring deformity, documented neurological and/or musculoskeletal disorder as a cause of finger/hand contractures, current breast-feeding or pregnancy, bleeding disorders, recent stroke, or a neuromuscular disorder affecting the hands. Overall, 77 joints were treated (44 MCP and 33 PIP joints). The mean patient age was 71 years. Consent was obtained in all cases.

Treatment
Initial treatment involved a 2-day process. Before injection (on day 1), FFCs were measured by the same fellowship-trained hand surgeon or a senior resident under direct supervision using a standard goniometer. Xiaflex (0.9 mg of CCH) was injected using a 27-gauge, 12-mm length needle at three sites 2–3 mm apart along each affected cord. All patients received the same total volume of CCH per digit. On day 2 (the next day), the affected finger was anesthetized with 1% lidocaine and then manipulated by passively extending it to its maximal corrective position. Moderate and steady stretching pressure was applied while slowly extending the finger for 10- to 20-second intervals for a maximum of three attempts, each spaced 5 minutes apart. We avoided jerking the finger with sudden movement to avoid tendon rupture. At this point, contracture was measured again, as on day 1. After manipulation, the finger was placed in an extension splint for night use. Skin tears associated with manipulation were treated with local wound care. We evaluated the maintenance of correction at 6 weeks, 4 months, 1 year, and 2 years after the procedure. No patient in this series underwent surgical treatment during the duration of this study.

Physical Therapy
The physical therapy protocol then started with extension splinting at night for up to 4 months if residual contracture had not corrected by 6 weeks. During the day, patients performed both active and passive finger/hand stretching exercises at home, which were taught to each patient by a certified hand therapist. These exercises included lifting each finger individually off a flat surface holding full extension for 5 seconds; abducting and adducting each fin-

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ger in a windshield wiper motion; and extending the MCP joints while holding the distal and PIP joints in full flexion. Each exercise was repeated ten times per finger four times a day up to 6 weeks. Patients were instructed to wear their extension splint during the day when not performing these exercises.

Statistical Analysis

Chi-square testing was used to determine successful initial treatment and recurrence for all joints. Resolution was defined as improvement of contracture to ≤ 5° of neutral. Recurrence was defined as an increase in FCC of ≥ 20° after treatment. Nonparametric *t*-tests were used to compare median FFCs at baseline and 2-year follow-up.

RESULTS

Immediate Contracture Resolution

The mean preinjection contracture for all 77 joints was 47° (50° for MCP and 44° for PIP joints). After manipulation, on the day after CCH injection (day 2), the mean residual contracture was 7.7° for all joints (1.5° for MCP and 16° for PIP joints). Immediate postmanipulation FCC resolution was recorded in 56 joints (42/44 MCP and 14/33 PIP joints) on day 2. Of the 21 joints that did not correct to ≤ 5°, 19 involved the PIP joint. Preinjection contracture severity for MCP joints had no effect on postmanipulation resolution. While more severe preinjection contracture involving PIP joints trended toward incomplete contracture resolu-

tion, this was not an appreciable relationship.

Maintenance of Contracture Resolution

At 6-week follow-up, the mean residual contracture had increased from 7.7° to 10°. The mean contractures of the MCP and PIP joints were 5.5° and 17°, respectively. At 4-month, 1-year, and 2-year follow-up visits, the FFC gradually increased in both joints, affecting the PIP more so than the MCP joint (Fig. 1). At 2-year follow-up, the mean FFCs for the MCP and PIP joints were 17° and 35.5°, respectively. Although a significant contracture improvement for MCP joints remained from pretreatment to 2 years (*p* < 0.001), there was no improvement for PIP joints during the same period (*p* = 0.642).

Contracture Recurrence

The rate of early recurrence, within the first 6 weeks, was 5.2% (4/77). Forty-eight joints had long-term follow-up (at least 4 months after treatment). This represented 28 MCP and 20 PIP joints, with a mean follow-up of 26 months. Of the 48 joints available at 4-month follow-up, there were 12 recurrences, for a success rate of 75% (36/48, *p* = 0.001). Of the 12 recurrences, six were in MCP joints, and six were in PIP joints. Six of the patients who experienced FFC recurrence had multiple fingers and joints involved. Their mean age was 75 years.

Complications

There were only minor complications observed in our patient cohort. There were no iatrogenic flexor tendon ruptures. Nine patients had skin tears during manipulation. All were treated successfully with Epsom salt soaks and local wound care until they healed. No infections were noted in our study group. There was one small finger nerve neuropraxia, which was asymptomatic but had not resolved at the final follow-up visit.

DISCUSSION

In this small, community hospital patient cohort, there was near-complete immediate contracture resolution in 42 of 44 of MCP joints (95%) and 14 of 33 PIP joints (42%). This selective improvement of MCP contracture is likely attributable to the fact that cords proximal to the MCP joint are often more distinct and palpable compared with cords distal to the MCP joint. For the 48 joints that experienced contracture resolution and were available for 2-year follow-up, 12 (six MCP and six PIP) experienced contracture recurrence. In general, we observed the majority of FFC progression to occur after the 4-month follow-up
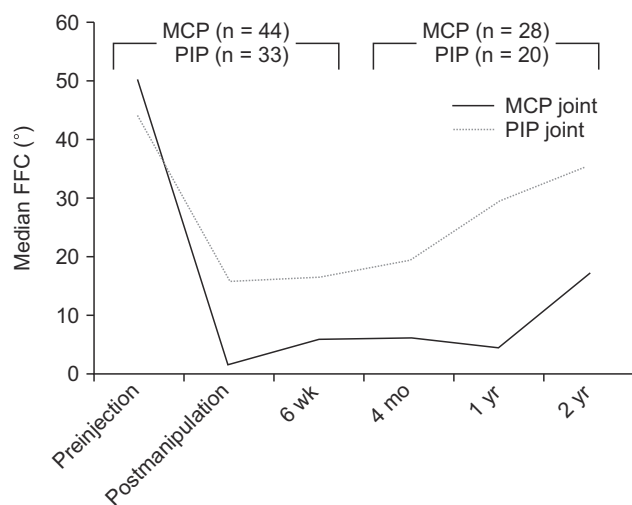
Fig. 1. Fixed flexion contracture (FFC) measurement for 77 joints after collagenase clostridium histolyticum injection. Only 48 joints were available for follow-up after the 4-month evaluation period. MCP: metacarpophalangeal, PIP: proximal interphalangeal.

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visit for PIP joints and after the 1-year follow-up visit for MCP joints. Given these results, within the first and 2-year follow-up periods may be an important time to reconsider repeat injection and manipulation for PIP and MCP joints, respectively. Finally, although the overall mean FFC increase did not reach our definition of recurrence (≥ 20° increase), there was a gradual contracture increase during the follow-up period, which is likely to increase even further over time.

During the past several years, studies with short-term (< 3 months)[14-19] or 1-year[7-10,20] results have reported promising FFC resolution after CCH injection. Longer-term studies have also shown similar resolution rates and contracture improvement but showed mixed results with recurrence. One study including 57 patients with 2-year follow-up showed FFC improvement for MCP joints (54° to 9°) and PIP joints (30° to 16°), with complete resolution in 80% of MCP joints and in less than half of PIP joints.[11] Another 2-year study with 87 patients showed improvement from 39° to 14° in MCP joints and from 54° to 32° in PIP joints.[21] In a third study of 47 patients with 2-year follow-up, isolated MCP cords showed improvement from 42° to 11°.[12] Our study reports rates of resolution and magnitude of correction of FFC that are similar to those of these 2-year follow-up studies.

Multiple reviews have shown the benefits of CCH injection but limited follow-up periods and high recurrence rates should be noted.[22,23] One study with 25 patients with a longer-term follow-up (32 months) showed contracture improvement from 43.5° to 3.6° in MCP joints and from 30.0° to 17.5° in PIP joints.[24] These results are superior to those cited in 2-year follow-up studies; however, it should be noted that the sole author of the study was a consultant for Auxilium Pharmaceuticals, the parent company of Xiaflex. One of the largest studies to assess the long-term efficacy of clostridium injection was the CORDLESS trial, which reported 5-year follow-up data for 623 joints.[13] At 3-year follow-up, the authors reported recurrence (defined as ≥ 20° in FFC) rates of 16% for MCP joints and 38% for PIP joints, which increased to 39% and 66% by 5 years, respectively. Compared with other methods of treating Dupuytren contracture, such as needle or open fasciotomy, the authors noted lower complications rates for neurovascular injury and complex regional pain syndrome with equal efficacy in contracture resolution and recurrence.

Our study has limitations. We included only 34 patients in our study with some loss to follow-up; however, the rates of recurrence and degree of FFC resolution were similar to those of other studies at 1- and 2-year follow-up. While this was not a large multi-center study, we were able to assess our patients with greater granularity and under the care of a single surgeon, eliminating heterogeneity introduced by different providers. The definitions of recurrence (≥ 20° increase in FFC from baseline manipulation) and "successful" contracture resolution (≤ 5° residual contracture) are arbitrary and are reported in a manner consistent with previous studies, which may under-represent patient-perceived success of treatment. For example, if an initial contracture of 70° was corrected to 10°, this would be an unsuccessful manipulation according to our definition; yet, the patient might be satisfied with this improvement.

In conclusion, CCH injection for Dupuytren contracture is a viable nonoperative option for contracture resolution, showing greater improvement for contractures of the MCP joint compared with the PIP joint. Similar to previous studies, we report a tendency for contractures to recur over time. Further investigation is needed to determine optimal timing of repeat CCH injection to improve upon or extend the period of contracture resolution.

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