Collagenase Enzymatic Fasciotomy for Dupuytren Contracture in Patients on Chronic Immunosuppression

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Abstract

Collagenase enzymatic fasciotomy is an accepted nonsurgical treatment for disabling hand contractures caused by Dupuytren disease.

We conducted a study to investigate use of collagenase in an immunosuppressed population. We retrospectively reviewed data from 2 academic hand surgical practices. Eight patients on chronic immunosuppressive therapies were treated with collagenase for digital contractures between 2010 and 2011. Thirteen collagenase enzymatic fasciotomies were performed in these 8 patients.

Mean preinjection contracture was 53.0°. At mean follow-up of 6.7 months, mean magnitude of contracture improved to 12.9°. Mean metacarpophalangeal joint contracture improved from 42.0° to 4.2°. Mean proximal interphalangeal joint contracture improved from 65.8° to 21.7°. Three of the enzymatic fasciotomies were complicated by skin tears. There were no infections.

As more patients seek nonsurgical treatment for Dupuytren disease, its safety and efficacy in select cohorts of patients should continue to be evaluated prospectively.

The incidence of Dupuytren disease increases with advancing age,[1] as do the medical comorbidities of patients seeking treatment for disabling hand contractures. For patients with significant comorbidities, open surgical fasciectomy, the current standard of treatment for Dupuytren disease,[2,3] may be associated with increased perioperative risks.

Collagenase enzymatic fasciotomy has become an accepted nonsurgical treatment alternative to traditional fasciectomy or surgical fasciotomy for significant digital contractures caused by Dupuytren disease.[4-6] *Clostridium histolyticum* collagenase (CHC) is a foreign protein, made up of 2 collagenases isolated from the bacteria *C histolyticum*.[7] The collagenases are zinc-dependent matrix metalloproteinases that cleave the triple helical structure of collagen molecules.[8] Also known as Xiaflex (Auxilium Pharmaceuticals), CHC was approved by the US Food and Drug Administration (FDA) in February 2010 for use in patients with Dupuytren contractures.

Enzymatic rupture is safe and efficacious at midterm follow-up and offers the theoretical advantage of avoiding palmar and digital fasciectomy and the associated risks of surgical-site infection and wound-healing complications.[6] The risks of surgical wound complications are magnified in immunosuppressed patients, particularly those on chronic steroid therapy; wound-healing complication rates may be increased 2 to 5 times compared with controls.[9] In a pooled literature review, wound-healing complications were reported after 22.9% of open primary fasciectomies, with infection occurring in 2.4%.[10] A nonsurgical alternative is therefore particularly appealing for a patient cohort that may be at higher risk for a frequently described complication of surgery for Dupuytren contracture.

The exclusion criteria in the trials for FDA approval were extensive and included breast-feeding, pregnancy, bleeding disorder, recent stroke, use of tetracycline derivative within 14 days before start of study, use of anticoagulant within 7 days before start of study, allergy to collagenase, and chronic muscular, neurologic, or neuromuscular disorder affecting the hands.[6] Safety and efficacy of collagenase in patients requiring chronic immunosuppressive therapy for medical comorbidities have not been previously documented. Furthermore, although skin tears were reported in 11% of patients after manual cord rupture in the CORD (Collagenase Option for the Reduction of Dupuytren's) I trial,[6] the likelihood of deep and superficial infection and delayed wound healing has not been quantitated.

In this article, we report on outcomes of 13 collagenase enzymatic fasciotomies performed in 8 patients who were on chronic immunosuppressive therapy.

Methods

Institutional review board approval was obtained at both academic hand surgery institutions. We retrospectively reviewed prospectively collected clinical data within our 2 centers' databases of patients with Dupuytren disease. Eight patients on

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chronic immunosuppressive therapies treated with collagenase for metacarpophalangeal (MP) or proximal interphalangeal (PIP) joint contractures between February 2010 and December 2011 were identified. Three of these patients received collagenase injections into 2 or more separate Dupuytren cords at different encounters, resulting in a total of 13 individual collagenase enzymatic fasciotomies.

Collagenase injections were administered following CORD I trial protocol,[6] except we injected Dupuytren cords crossing the PIP joint using a lateral approach to minimize risk of flexor tendon rupture. Manipulation of the treated joint was performed between 24 and 48 hours after collagenase injection under local anesthesia with 3 mL of 1% mepivacaine or lidocaine without epinephrine. After manipulation and cord rupture, patients were placed in a hand-based extension splint to wear at night for up to 3 months. Patients were followed at 1 and 12 months.

Results

Patients' baseline characteristics are summarized in **Table 1**. Four patients were maintained on chronic prednisone therapy, 3 on methotrexate, and 1 on azathioprine. Therapy duration, medication dose, and diagnoses requiring immunosuppressant therapy varied among patients.

Outcomes and adverse events are summarized in **Table 2**. Mean number of joint contractures per hand treated was 2.8

Table 1. Patients' Baseline Characteristics

Patient No.	Sex	Age, y	Diagnosis	Medication	Dose	Duration[a]
1	M	69	Rheumatoid arthritis	Methotrexate	15 mg/wk	2 y
2	M	59	Rheumatoid arthritis	Methotrexate	7.5 mg/wk	8 y
3	M	55	Psoriatic arthritis	Methotrexate	10 mg/wk	5 y
4	M	58	Post–kidney transplant	Prednisone	10 mg/d	6 mo
5	F	75	Polymyalgia rheumatica	Prednisone	4 mg/d	1 y
6	M	75	Chronic obstructive pulmonary disease	Prednisone	10-60 mg/d	11 mo
7	F	66	Emphysema	Prednisone	5 mg/d	4 y
8	F	71	Pulmonary fibrosis	Azathioprine	50 mg/d	11 y

[a]Duration for which patient had been taking immunosuppressant at time of first collagenase injection.

Table 2. Summary of Outcomes and Adverse Events

		Contracture, °			
Patient No.	Treated Joint	Preinjection	Latest Follow-Up	Follow-Up, mo	Adverse Events[a]
1	L–RF–PIP	55	30	6	—
	R–SF–PIP	45	20	3	Skin tear, blood blister
2	R–RF–PIP	90	10	9	—
	L–RF–PIP	90	0	8	—
3	R–SF–PIP	40	45	22	—
4	L–MF–MP	50	—[b]	—	—
5	R–MF–MP	30	0	1	—
6	R–RF–MP	39	0	14	—
7	R–RF–PIP	75	25	1	Skin tear
8	L–SF–MP	80	10	8	Skin tear
	L–RF–MP	35	10	6	Blood blister
	R–SF–MP	20	0	1	—
	R–RF–MP	40	5	1	—
Mean		53.0	12.9	6.7	

Abbreviations: L, left; R, right; MF, middle finger; RF, ring finger; SF, small finger; MP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.
[a]Other than pain, peripheral edema, and bruising.
[b]Patient was lost to follow-up after injection and manipulation.

(MP, 1.4; PIP, 1.4). However, not all joints met the intervention criteria. Of the 13 joints treated, 7 were MP joints, and 6 were PIP joints. Mean preinjection contracture of the treated joints was 53.0° (range, 20°-90°). Twelve of the 13 joint contractures improved. At mean follow-up of 6.7 months (range, 1-22 months), mean magnitude of contracture improved to 12.9° (range, 0°-45°). Mean MP joint contracture improved from 42.0° to 4.2° (range, 0°-10°), and mean PIP joint contracture improved from 65.8° to 21.7° (range, 0°-45°).

All 13 collagenase injections were well tolerated, and there were no systemic reactions. Injection-site pain was common. Mild injection-site bruising and edema were reported in all cases. Enzymatic fasciotomy was performed in all patients, and immediate improvement in contracture after manipulation 24 to 48 hours after injection was recorded.

Three of the 13 injections were complicated by skin tears during manipulation and cord rupture. All 3 skin tears were treated with local wound care, which included use of povidone-iodine and wet-to-dry dressings. There was no evidence of subsequent superficial or deep, local or regional infection. In 2 cases, the wound healed within 1 week; in the third case, wound healing was present by 2 weeks. Once the wounds showed early re-epithelialization, hand-based extension splinting in a position of comfort was used at night for up to 3 months after injection. Two of the 13 injections were complicated by small blood blisters. These were treated with observation and resolved spontaneously.

Discussion

Collagenase enzymatic fasciotomy appeared to be a safe and efficacious alternative to surgical treatment of Dupuytren contractures in this cohort of patients maintained on chronic immunosuppressive agents. MP contractures responded more substantially than PIP contractures did, as expected.[6] No previously undescribed adverse outcomes were noted in these 8 patients on chronic immunosuppressive therapy beyond those reported in the CORD I trial. Three (23%) of the 13 collagenase injections in our series were complicated by skin tears after manipulation. Skins tears were reported in 22 (11%) of 204 patients after manual cord rupture in the CORD I trial.[6] Given the limited numbers in this series, it remains unclear if chronic immunosuppression truly increases the risk of skin tears in this subset of patients. Other common treatment-related adverse events seen in the CORD I trial—injection-site hemorrhage (37%), pruritis (11%) and lymphadenopathy (10%)—were not seen after the 13 injections in our case series. We are prospectively following all patients with Dupuytren disease, and this is an area of ongoing research at our centers.

The immunosuppressive actions of prednisone, azathioprine, and methotrexate are well documented. Prednisone is a glucocorticoid, converted in the liver to prednisolone, which suppresses inflammation and immune responses by regulation of gene expression. Its immunosuppressive actions are multifactorial, relating to inhibition of lymphocytes, neutrophils, and monocytes. These effects are dose- and time-dependent[11] and may become evident in patients receiving low doses over prolonged periods. Skin atrophy[12] and delayed wound healing[9] are side effects of long-term prednisone use. Skin atrophy may make the prednisone-treated patient more susceptible to skin tears after collagenase injection and manipulation. Azathioprine inhibits purine synthesis, which is especially important in the proliferation of immune cells.[13] It has been shown to inhibit both cellular immunity at low doses and humoral immunity at higher doses.[14] Methotrexate inhibits lymphocyte folic acid metabolism. The immunosuppressive properties of low-dose methotrexate have been linked to the induction of apoptosis in activated T cells.[15]

A more complex process in immunosuppressed patients is the immunogenicity of injected collagenase. As CHC in current use is a mixture of 2 foreign proteins, an immunologic response is expected in the host after injection. It has been shown that, after 3 injections of CHC into Dupuytren cords, 100% of patients developed antibodies to both enzymes in their serum.[6] More than 85% demonstrated anti-CHC antibodies after a single injection. However, no patients showed signs of anaphylaxis or allergic reaction, and there was no correlation between serum levels of anti-CHC and adverse events. It has been hypothesized that there is a potential for cross-reactivity of the anti-CHC antibodies with human matrix metalloproteinases, causing enzymatic dysfunction within the host.[16] This has yet to be reported clinically, and Xiaflex is currently under postmarketing surveillance. Immunocompromised people, with suppressed humoral and cellular immune responses, may produce less of an antibody response to the foreign CHC proteins. Whether this conclusively leads to a change in the side effect profile of the medication in these individuals is beyond the scope of this article. However, we identified no new side effects in this small but higher risk cohort. The issue should be continually monitored as collagenase is used in wider clinical settings.

Collagenase enzymatic fasciotomy is a new nonsurgical therapeutic option for Dupuytren disease. Indications and guidelines for use continue to evolve. This case series highlights the use of collagenase in 8 patients who were on long-term immunosuppressive therapy. This study has the limitations inherent to retrospective analyses. It is difficult to generalize results across broader immunosuppressed populations. A larger cohort, with long-term follow-up assessing recurrence of contracture, is needed to make definitive conclusions about use of collagenase in this challenging subset of patients. Based on our observations in this limited cohort, it appears appropriate to pursue further studies on use of collagenase enzymatic fasciotomy. A randomized, prospective or case–control series comparing surgical fasciectomy with enzymatic fasciotomy would yield further meaningful data. As more patients seek nonsurgical treatment for Dupuytren disease, its safety and efficacy in select cohorts of patients should continue to be evaluated.

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