

Collagenase Injection as Nonsurgical Treatment of Dupuytren's Disease: 8-Year Follow-Up

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Purpose Collagenase has been investigated in phase II and phase III clinical trials for the treatment of Dupuytren's disease. The purpose of this study is to report 8-year follow-up results in a subset of patients who had collagenase injection for the treatment of Dupuytren's contracture.

Methods Twenty-three patients who participated in the phase II clinical trial of injectable collagenase were contacted by letter and phone. Eight patients were enrolled, completed a Dupuytren's disease questionnaire, and had independent examination of joint motion by a single examiner.

Results Eight patients completed the 8-year follow-up study: 6 had been treated for isolated metacarpophalangeal (MCP) joint contracture, and 2 had been treated for isolated proximal interphalangeal (PIP) joint contracture. Average preinjection contracture was 57° in the MCP group. Average contracture was 9° at 1 week, 11° at 1 year, and 23° at 8-year follow-up. Four of 6 patients experienced recurrence, and 2 of 6 had no evidence of disease recurrence at 8-year follow-up. Average preinjection contracture was 45° in the PIP group. Average contracture was 8° at 1 weeks, 15° at 1 year, and 60° at 8-year follow-up. Both patients experienced recurrence at 8-year follow-up. No patients had had further intervention on the treated finger in either the MCP or the PIP group. Patients subjectively rated the overall clinical success at 60%, and 88% of patients stated that they would pursue further injection for the treatment of their recurrent or progressive Dupuytren's disease.

Conclusions Enzymatic fasciotomy is safe and efficacious, with initial response to injection resulting in reduction of joint contracture to within 0°–5° of normal in 72 out of 80 patients. Initial evaluation of long-term recurrence rates suggests disease recurrence or progression in 4 out of 6 patients with MCP contractures and 2 patients with PIP contractures; however, recurrence was generally less severe than the initial contracture in the MCP group. In addition, patient satisfaction was high. (*J Hand Surg* 2010;35A:534–539. © 2010 Published by Elsevier Inc. on behalf of the American Society for Surgery of the Hand.)

Type of study/level of evidence Therapeutic IV.

Key words: Collagenase, Dupuytren's contracture, Dupuytren's disease, injectable collagenase.



DUPUYTREN'S DISEASE, WITH its progressive nature and high rates of disease recurrence, presents a formidable challenge for hand surgeons. During the past three decades, great advances have been made in defining the underlying molecular mechanisms and cellular pathophysiology that transform normal fascial struc-

tures into fibrotic, diseased cords. This increased understanding offers the potential for novel therapeutic clinical targets.^{1–6}

Currently, surgical fasciectomy remains the treatment mainstay. Hand surgeons recognize that surgical fasciectomy does not offer a definitive cure, and the

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Received for publication November 18, 2009; accepted in revised form January 6, 2010.

C.M.C. received compensation for participation in the phase III clinical trial of injectable collagenase.

Institutional funding of phase III clinical trials provided by Auxilium. No funding was received by the authors or the institution for the completion of this study. The authors have no financial interest in injectable collagenase or Auxilium. No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

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0363-5023/10/35A04-0002\$36.00/0
doi:10.1016/j.jhsa.2010.01.003

disease has a high recurrence rate, often requiring reoperation.⁷⁻¹⁰ Surgical treatment carries significant morbidity, with a reported overall complication rate of 17%, including skin complications, hematoma, digital nerve injury, and reflex sympathetic dystrophy or complex regional pain syndrome.^{10,11} Revision surgery is even more challenging, with an even higher rate of complications.¹² Because of the risks of primary surgery and the challenges of additional surgery on a previously scarred bed, hand surgeons have long been searching for nonsurgical treatments to this common problem.

The use of clostridial collagenase has been investigated in phase II and recently completed phase III clinical trials for the treatment of Dupuytren's disease. The proposed advantage of collagenase is that it specifically targets collagen for degradation, resulting in decreased strength of Dupuytren's cords by 93%.¹³ A phase II clinical trial demonstrated that 10,000 units of collagenase injected into the cord resulted in a correction of joint contracture to within 0°–5° of normal in 45 of 55 subjects with metacarpophalangeal (MCP) joint contractures and in 11 of 25 subjects with proximal interphalangeal (PIP) joint contractures. Three MCP contracture recurrences among 36 subjects were noted at 2-year follow-up, and one PIP contracture recurrence among 13 subjects was noted at 3-month follow-up.¹⁴ The phase III clinical trial—Collagenase Option for Reduction of Dupuytren's I study, a randomized, placebo-controlled, multicenter trial—has reported similarly favorable results. In 308 patients, 197 met the primary end point of reduction of contracture to within 0°–5° of full extension within 30 days of injection. In total, 102 of 133 MCP contractures and 28 of 70 PIP contractures met this primary end point, with higher rates of response occurring in less severe contractures. Total range of motion improved from an average of 44° before injection to 81° after injection.¹⁵ The long-term outcomes after collagenase treatment for Dupuytren's disease are not known.

This study's purpose is to provide 8-year follow-up for a subset of subjects who had collagenase injection for the treatment of Dupuytren's contracture as part of the phase II clinical trial.

MATERIALS AND METHODS

The phase II clinical trial of injectable collagenase was originally designed to determine dose-response, efficacy, and safety. Subjects were randomized to receive placebo, 2,500 units, 5,000 units, or 10,000 units of collagenase as a single injection. Patients then returned 24 hours after injection for manual manipulation. These

subjects were then examined 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, and 1 year after injection. At each visit, standard goniometric measures of the affected joint were recorded as degree of extensor lag. Subjects were also monitored for adverse response to injection, including lymphadenopathy, allergic reactions, and tendon rupture.

All 23 subjects who had participated in a single arm of the phase II, randomized, clinical, controlled trial of injectable collagenase in 1999–2000 were eligible for study enrollment and were contacted by letter and phone. Nine subjects were enrolled for follow-up examination and consented to enrollment in the follow-up study. One of these nine subjects had received placebo injection and was excluded from follow-up analysis. Fourteen of the 23 eligible subjects were unavailable for follow-up examination. Three subjects were deceased. Two subjects were confined to acute care facilities, one with end-stage congestive heart failure and one with advanced dementia. Two subjects declined participation citing travel constraints. Seven letters were undeliverable due to change of address, and telephone contacts were also unsuccessful.

We reviewed original records and abstracted the initial degree of contracture, response to injection, and dose response to injection.

Subjects returned for 8-year follow-up examination, which was performed by an independent examiner who had not been involved in the phase II clinical trial. The examiner was blinded to the original location of injection. Goniometric measurements were obtained at both the MCP and PIP joint level of the index through little fingers of both hands and were expressed as degree of extensor lag. Subjects then completed a Dupuytren's disease questionnaire ([Appendix A](#) can be viewed at the *Journal's* Web site, <http://www.jhandsurg.org>). This questionnaire confirmed basic clinical history, including age at diagnosis, family history, and prior treatment, including surgical fasciectomy, needle aponeurotomy, and therapy. Subjects answered questions related to disease recurrence and progression and were asked to judge the overall clinical success of the collagenase injection.

Recurrence was defined as any increase in the degree of contracture of the injected joint compared with maximal extension achieved after injection. Disease progression to involve adjacent joints was not considered to be recurrence.

This study was reviewed and approved by the insti-

TABLE 1. Patient Data

	MCP Contracture	PIP Contracture
Number of patients	6	2
Age at injection	60 (46–62)	74 (70–78)
Age at follow-up	67 (52–70)	82 (77–86)
Hand dominance	R: 6 L: 0	R: 2 L: 0
Preinjection contracture	57° (30–76°)	45° (35°, 55°)
1 wk after injection	9° (0–35°)	8° (0°, 15°)
6 mo after injection	8° (0–35°)	13° (0°, 25°)
1 y after injection	11° (0–35°)	15° (0°, 30°)
8 y after injection	22° (0–55°)	60° (50°, 70°)
Recurrence rate (%)	67%	100%

tutional research compliance office and the human subjects research board.

RESULTS

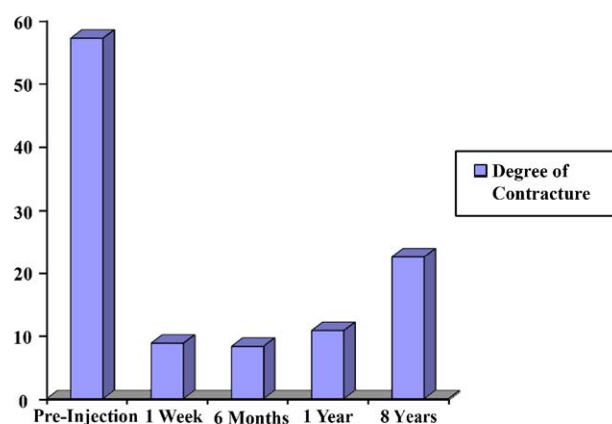
Eight subjects participated in this 8-year follow-up study. Average age at 8-year follow-up examination was 69 years (range, 52–86). Average age at initial diagnosis of Dupuytren's disease was 44 years (range, 30–66). Seven of 8 subjects had a family history of a first-degree relative with Dupuytren's disease. Five of 8 subjects had previously had surgery on the contralateral hand before participating in the collagenase study. Six subjects received collagenase for isolated MCP joint contracture, and 2 subjects were treated for isolated PIP joint contracture. All patients had a single injection (Table 1).

Metacarpophalangeal contracture

Six patients had been treated for isolated MCP joint contracture. Four patients received 10,000 units of clostridial collagenase as a single injection, one patient received 5,000 units, and one patient received 2,500 units. Average preinjection contracture was 57° (range, 35°–55°) in the MCP contracture group. Average contracture was 9° at 1 week, 11° at 1 year, and 22° (range, 0°–55°) at 8-year follow-up (Fig. 1). Four of 6 patients experienced recurrence, whereas 2 of 6 had no evidence of disease recurrence at 8-year follow-up. No patients had had further intervention on the treated finger (Table 2).

Proximal interphalangeal contracture

Two patients had been treated for isolated proximal interphalangeal joint contracture. One patient received a single 10,000-unit dose of clostridial collagenase, and the other patient received 5,000 units. Preinjection con-

**FIGURE 1:** Metacarpophalangeal joint contracture.

tracture was 35° and 55° in the 2 subjects in the PIP group, respectively. Contracture was 0° and 15° at 1 week, 0° and 25° at 1 year, and 50° and 70° at 8-year follow-up (Fig. 2). Both patients experienced disease recurrence. No patients had had further intervention on the treated finger (Table 3).

Subjective results

Overall clinical success was determined on a visual analog scale from 0 (no benefit) to 100 (maximal benefit/complete resolution of contracture). Patients subjectively rated the overall clinical success at 60% (range, 0%–100%) and 7 of 8 patients stated that they would pursue further collagenase injection for the treatment of recurrent or progressive disease.

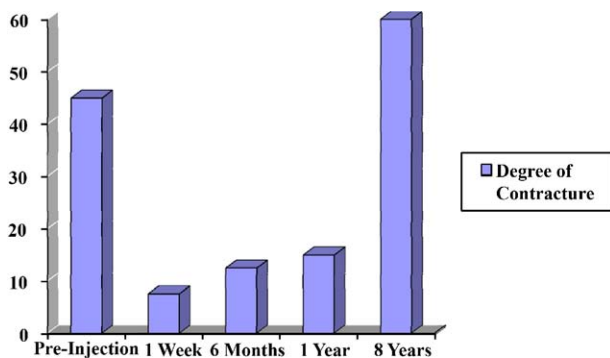
DISCUSSION

Dupuytren's disease is a recalcitrant disease process that can cause significant functional morbidity. Surgical excision remains the mainstay of treatment; however, there are high rates of recurrence and complications with these procedures. Reported complication rates for surgical fasciectomy have been reported from 17% to 29%.^{11,12,16,17} Hematoma and skin necrosis remain the most common complications, and nerve injury rates range from 0% to 9.6%.^{12,17–19} Disease recurrence following palmar fasciectomy ranges from 41% to 54% at 5 years,^{7–9} and 15% of these patients will require reoperation to address disease recurrence.¹⁰ Secondary procedures are often more challenging. Coert demonstrated increased incidence of nerve injury with revision surgeries, reporting a 5% incidence of nerve injury in the setting of primary surgeries compared to 12% in secondary surgeries.¹²

Given the limitations of surgery, hand surgeons have pursued nonsurgical treatment. Multiple therapies have

TABLE 2. Metacarpophalangeal Joint Contracture: Individual Patient Data

Patient	MCP Joint Contracture	Age (at Injection/ at Follow-Up)	Preinjection	Dose (Units)	1 d	1 wk	1 mo	2 mo	3 mo	6 mo	9 mo	1 y	8 y
MCP1	R ring	53/61	60	10,000	20	8	0	0	10	15	20	30	20
MCP2	R ring	57/65	76	10,000	26	10	0	0	0	0		0	0
MCP3	R little	78/86	70	5,000	5	0		5			0		40
MCP4	R little	61/69	52	2,500	50	35	25	40	38	35			20
MCP5	L little	62/70	55	10,000	0	0	0	0	0	0	0	0	55
MCP6	R little	44/52	30	10,000	0	0	0	0	0	0	0		0
Mean		59/67	57		17	9	4	8	8	8	3	5	22

**FIGURE 2:** Proximal interphalangeal joint contracture.

been investigated, including external beam radiation, dimethyl sulfoxide, vitamin E, methylhydrazine, allopurinol, interferon- γ , corticosteroids, and ultrasonic and physical therapy.^{20–29} This array of treatments underscores both patient and physician desire to develop a nonsurgical intervention for Dupuytren's disease. The concept of targeting abnormal collagen deposition with an "enzymatic fasciotomy" was first reported by Bassot in 1965, with his technique of "exeresis pharmacodynamique."³⁰ This therapy used a mixture of trypsin, alpha-chymotrypsin, hyaluronidase, thiomucase, and lignocaine, which degraded proteins, permitting rupture of the pathologic cords. Bassot's results in 1969 showed an impressive correction of severe contractures in 34 patients.³⁰ In 1971, Heuston reported his experience with a simplified formula consisting of trypsin, hyaluronidase, and marcaine, achieving favorable initial results.³¹ McCarthy reported his experience with enzymatic fasciotomy in 14 patients, noting recurrence of initial contracture in 75% of patients at an average of 2 to 3 years of follow-up. He concluded that there was a similar rate of recurrence with both enzymatic fasciotomy and surgery. McCarthy also was concerned about the possibility of tendon rupture and neurovascu-

lar injury in the setting of a nonspecific enzymatic degradation of the palmar fascia, yet no frank ruptures or neurologic sequelae were reported in his studies.³² After these early studies, enzymatic fasciotomy languished.

Collagenase emerged as a possible agent for enzymatic fasciotomy in 1996 and offered a potential advantage over nonspecific degradative enzymes by targeting collagen. *In vitro* biomechanical testing has demonstrated a 93% decrease in the tensile modulus of Dupuytren's cords injected with a 3,600-unit dose of collagenase.¹³ Initial human studies focused on dose-response, collagenase pharmacokinetics, and immunologic response. Complications of treatment in these phase II trials included pain with injection and manipulation, edema, ecchymosis, lymphadenopathy, and skin tears. The phase II trials showed an initial response to injection results in reduction of joint contracture to within 0°–5° of normal in 90% of patients.^{14,33} Our evaluation of long-term recurrence rates in a small sample of phase II subjects demonstrated a recurrence of 67% of MCP joint contractures and 100% of PIP joint contractures. Despite this high rate of recurrent disease, recurrence for MCP disease was generally less severe than the preinjection contracture, and no subjects had surgical treatment for recurrence. In addition, patient satisfaction is high, with 88% of patients stating that they would pursue further injection for treatment of recurrent or progressive disease.

Future work will focus on establishing the long-term efficacy of collagenase injection within a larger population of subjects and determining its role in the treatment of Dupuytren's disease, with direct comparison to palmar fasciectomy and needle aponeurotomy. Subjects who participated in the recently completed phase III clinical trials will be evaluated over a 5-year period for recurrence, disease progression, and satisfaction. Ultimately, a multicenter, randomized, controlled trial com-

TABLE 3. Proximal Interphalangeal Joint Contracture: Individual Patient Data

Patient	PIP Joint Contracture	Age (at Injection/ at Follow-Up)	Preinjection	Dose (Units)	1 d	1 wk	1 mo	2 mo	3 mo	6 mo	9 mo	1 y	8 y
1	R ring	78/86	55	10,000	20	15	12	17	15	25	25	25	70
2	R ring	69/77	35	10,000	5	0	0	0	0	0	0	0	50
Mean		74/82	45		13	8	6	9	8	13	13	13	60

paring fasciectomy, needle aponeurotomy, and collagenase injection will further delineate the role of each of these modalities in the treatment of Dupuytren's disease.

It is evident that neither surgical excision of the diseased cords nor enzymatic fasciotomy offers a definitive cure. Collagenase injection offers a potential nonsurgical treatment for Dupuytren's disease. Collagenase injection presents the potential advantages of early return of hand function and avoidance of potential surgical complications; however, it is not without notable risk of complications, including flexor tendon rupture and neurovascular injury. This study supports a role for collagenase injection in the treatment of Dupuytren's disease, particularly in patients with isolated MCP joint contractures and those who are reluctant to proceed with surgical intervention or who wish to minimize recovery time. The MCP recurrence rate at 8 years was 22°, a degree of contracture that does not meet many surgeons' threshold for recommending surgical intervention in primary disease. Efficacy in the treatment of PIP contractures is less clear and will require a larger sample size to draw valid conclusions. Further investigation is required to clarify the rate and extent of disease recurrence and to compare the efficacy and durability to other currently used forms of treatment, including needle aponeurotomy and fasciectomy.

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APPENDIX A**Dupuytren's Questionnaire**

1. What is your current age?
2. What was your age when you were diagnosed as having Dupuytren's disease?
3. Do you have a family history of Dupuytren's disease?
4. Before participating in the Dupuytren's clinical trial in 1999–2000, had you had any treatment for your disease? If so, what treatment?
5. Which finger was injected as part of the trial?
6. How would you judge the success of the injection? Please use the following scale, where 0 is no effect and 100 is a fully satisfactory effect:
0 10 20 30 40 50 60 70 80 90 100
7. Have you developed a recurrent contracture in a previously injected finger?
8. Have you developed any new areas of disease?
9. Have you had any treatment for your disease since the clinical trial? If so, please circle all that apply:
 - a. Surgery
 - b. Needle fasciotomy (aponeurotomy)
 - c. Therapy