Original Communications

Collagen as a Clinical Target: Nonoperative Treatment of Dupuytren's Disease

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The cellular events leading to abnormal synthesis of collagen are important to our understanding of pathologic processes leading to impaired joint function. The contracture of Dupuytren's disease is a notable example. In a series of controlled phase-2 clinical trials, excessive collagen deposition in Dupuytren's disease has been targeted by a unique nonoperative method using enzyme (Clostridial collagenase) injection therapy to lyse and rupture finger cords causing metacarpophalangeal and/or proximal interphalangeal joint contractures. Forty-nine patients were treated in a random, placebo-controlled trial of one dose of collagenase versus placebo at one center. Subsequently 80 patients were treated in a random, placebo-controlled, dose-response study of collagenase at 2 test centers. The results of these studies indicate that nonoperative collagenase injection therapy for Dupuytren's disease is both a safe and effective method of treating this disorder in the majority of patients as an alternative to surgical fasciectomy. Phase-3 efficacy trials are now being planned to further develop and test this method under Food and Drug Administration regulatory guidelines. The findings of our study may lead to simpler and less invasive nonoperative treatments of joint limitation in which collagen plays a major pathologic role. (J Hand Surg 2002;27A:788–798.

Key words: Dupuytren's disease, collagenase injection.

Dupuytren's disease was first recognized in the 17th century in the early European medical literature.[1] Since then only surgery has proven successful in the treatment of this disorder. It was not until the 1970s that a definitive report[2] on the specialized fibroblast, termed the myofibroblast, was reported underlying the importance of the cell to the pathogenesis of the disorder. These investigators postulated that the contraction of the collagenous palmar fascia and overlying skin and fingers was directly related to the contractile abilities of myofibroblasts. Other investigators have since substantiated this finding[3,4] and have defined the cellular basis of contracture of the palmar fascia. These reports suggested that the transmission of intracellular force from myofibroblasts to each other and the surrounding collagenous matrix was caused by the arrangement of intracellular bundles of actin microfilaments result-

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ing in specialized transmembranous association. Bundles of the filamentous extracellular material were found to extend from the surface of the myofibroblast connecting it with the surrounding extracellular matrix, including collagen, and also with adjacent myofibroblasts.

In the early 1980s it was established that a so-called immature type 3 collagen was important to the pathogenesis of Dupuytren's disease and that it was proportionately increased in relation to normally occurring type I collagen within affected palmar fascia.[5] These investigators proposed that the active cellular process of contraction draws the distal extremities of the affected tissue closer together at the same time that the original tissue is being replaced. The result is a shorter, smaller piece of tissue fabric with collagen fibers and fibrils of normal lengths.

Subsequently interest in how myofibroblasts were regulated led many investigators into studies on endogenous substances such as prostaglandins[6,7] and growth factors, including platelet-derived growth factor,[8] transforming growth factor β,[9] and basic fibroblast growth factor.[10] The contractile mechanism of myofibroblasts was defined as the well-known adenosine triphosphatase energy pathway,[11] and platelet-derived growth factor[8] and transforming growth factor $\beta 1$ and $\beta 2$[9] were reported to be responsible for substantial proliferative ability in myofibroblasts.

As our understanding of the cell biological mechanisms increases, it may be possible in the future to interfere with either the production of collagen or growth factors or to block cellular receptors as clinical interventions in the treatment of Dupuytren's disease. These underlying mechanisms may be important to other conditions in which fibrous adhesions manifest themselves to limit joint motion. Therefore the techniques described in this article that are directed as a nonoperative injection therapy in Dupuytren's disease may translate to clinical practice in other medical disorders in which scar tissue or fibrous tissue shortening is a major factor in limitation of joint motion.

The concept of nonsurgical intervention in Dupuytren's disease has been tested previously but without clinical success.[12–21] It is well understood that metacarpophalangeal (MP) and proximal interphalangeal (PIP) joint contractures, which are treated by surgery, are not cured of Dupuytren's disease. Recurrence rates are reported to be quite high especially in the PIP joint, ranging from 26% to 80%.[22,23] The concept of nonsurgical treatment has a high degree of patient satisfaction. Patients often express satisfaction in terms of surgical correction for this disorder but are not always satisfied in terms of the overall surgical process. Common patient complaints relate to time out of work, having to endure the surgery itself, being in pain after surgery, having limited use of the hand for activities of daily living, and sometimes prolonged and extensive postoperative therapy. Clearly these patients are looking for a valid and simpler treatment alternative.

Targeting the collagen cord by nonsurgical, so-called enzyme fasciotomy has been attempted in the past[24,25] by using an enzymatic mixture of trypsin, hyaluronidase, and lidocaine. This treatment was conducted during surgery, however, and although full passive extension in all patients was achieved the study provided no long-term results. These researchers noted recurrence of initial preoperative deformity in 75% of the study subjects 2 to 3 years after injection. Enzyme fasciotomy using collagenase, whose specific substrate is collagen, does offer an advantage over less specific enzymes in inducing cord rupture in Dupuytren's disease. The present authors previously tested this theory in the laboratory by biomechanical testing of cords[26] and *in vivo* in a rat tail tendon model to investigate potential collagenase toxicity.[27] The laboratory studies lead directly to an open-label clinical trial[28] that showed that collagenase injection of Dupuytren's cords had potential merit.

The purpose of this study was to test the clinical safety and efficacy of Clostridial collagenase injection as a nonsurgical therapy in inducing rupture of Dupuytren's cords and return to normal hand function in phase-2 random, placebo-controlled, double-blind, clinical trials.

Materials and Methods

Two clinical trials were conducted under a Food and Drug Administration (FDA) investigational new drug number and institutional review board approvals. The first trial (clinical trial IIA) was a randomized, double-blind, placebo-controlled study of Clostridial collagenase injection (Advance Biofactures Corp, Lynbrook, NY) at a single dose of 10,000 U versus placebo at a single center (State University of New York [SUNY], Stony Brook, NY). Patients with either MP joint contractures or those with PIP joint contractures (only) entered the study. Thirty-six patients with MP joint contractures were enrolled: 31 men, 5 women, mean age 65 years, 19 right and 17

Table 1. Range of Finger Contractures Treated and Number of Patients

Collagenase Dose	*20°–29°*	*30°–39°*	*40°–49°*	*50°–59°*	*60°–69°*	*70°–79°*	*80°–90°*
MP joints: clinical trial IIA							
10,000 U	2	5	3	4	2	2	0
Placebo	2	4	2	3	5	1	1
PIP joints: clinical trial IIA							
10,000 U	0	3	1	0	1	1	1
Placebo	1	0	1	0	2	2	0

left hands (Table 1). These included 20 small fingers, 13 ring fingers, 2 middle fingers, and 1 thumb. Thirteen patients with PIP joint contractures entered the study: 11 men, 2 women, mean age 64.3 years, 11 right hands and 2 left hands (Table 1). These included 5 ring fingers and 8 small fingers.

Eighteen patients with MP joint contractures were randomized to receive collagenase injection at a single dose of 10,000 U. Eighteen patients with MP joint contractures received placebo assignment. The placebo consisted of sterile normal saline containing 2 mmol/L calcium chloride. Seven patients with PIP joint contractures were assigned to the 10,000-U dose group and 6 patients with PIP joint contractures were assigned to placebo. The investigators were masked to the control/treatment code. Insulin syringes containing the test material were prepared by the investigational pharmacist and were similar in appearance such that no bias was introduced owing to the appearance of the solution within the syringes. Total volume used was 0.25 mL for MP joints and 0.20 mL for PIP joints.

Before each injection ultrasound was used to visualize the underlying flexor tendon of the affected finger and to measure the depth from the skin to the surface of the flexor tendon sheath. This was done to identify a safe zone between the skin and flexor tendon sheath to avoid inappropriate injection of the tendon. Ultrasound was not used to guide injection but to further ensure that only the cord was injected, even though the cord was easily visualized and palpated. There were no inappropriate tendon injections in any patient. Nor were there inappropriate nerve or vessel injections in any patient. All patients retained preinjection active motion and normal sensation and normal capillary refill.

The protocol involved the first blind injection into the cord causing the finger contracture. The results of the first injection were evaluated for 30 days, at days 1, 7, 14, and 30. If the finger contracture did not respond to 0° to 5° of normal extension (0°) there was a retreatment option for a potential 4 additional injections using 10,000 U of collagenase on an open-label basis. Subsequent retreatments using 10,000 U of collagenase were based on patient's response to treatment with clinical success being defined as to within 0° to 5° degrees of normal extension (0°). If the initial target joint was successfully treated and if patients presented with other involved joint contractures these were treated on an open-label basis by using 10,000 U of collagenase. The total maximum dose that a patient could receive was 50,000 U of collagenase with an interval of 4 to 6 weeks between each retreatment injection.

Patients were seen the next day when passive extension, within the patient's pain tolerance, was applied to rupture the cord. No local anesthetic was used when attempting cord rupture. The patients tolerated this well. If cord rupture did not occur on day 1 after injection the patients were instructed to apply extension force themselves. On day 1 after injection a therapist fitted the patients with a night extension splint that was to be worn for 4 months. Patients were also instructed by the therapist to do extension exercises at home. Daily vitamin E massage for 4 months was also suggested to keep the treatment area soft and pliable. Serial follow-up examinations occurred on days 7 and 14 and at months 1, 2, 3, 6, 9, and 12. The patients were also examined annually in years 2 to 5 after injection(s). To test for potential adverse immune effects serial immune immunoglobulin E titers were obtained at each follow-up visit, excluding day 1 and day 14.

At each follow-up visit the degree of joint contracture of the target joint was assessed by using a digital goniometer and measured in degrees. Secondary variables that were followed-up were the range of

motion of the target joint(s) in degrees by goniometer measurement (extension/flexion) and grip strength in kilograms. Finally, at each follow-up visit adverse events were carefully monitored.

Clinical Trial IIB: Dose-Response Study

Because the results of clinical trial IIA clearly indicated that 10,000-U collagenase injection had substantial merit in restoring patients to normal hand function, discussions were held with the FDA Center for Biologics Evaluation and Research to determine the design of subsequent clinical testing. It was decided that a random, placebo-controlled, double-blind dose study of collagenase injection for Dupuytren's disease should be performed to test whether 10,000 U of collagenase was indeed the minimum safe and effective dose.

Clinical trial IIB was then initiated. Eighty patients entered the clinical trial IIB at 2 centers, SUNY Stony Brook and Stanford University Medical Center. The total number of patients at both centers was 80. There were 64 men and 16 women, mean age 63.9 years. Fifty-seven patients were treated at SUNY Stony Brook, 37 MP joint contractures and 20 PIP joint contractures. At Stanford University Medical Center 23 patients were enrolled, 18 of whom had MP joint contractures and 5 with PIP joint contractures. Thus in total 55 patients had MP joint contractures and 25 had PIP joint contractures (Table 2). There were 32 left hands and 48 right hands, 50 small fingers, 23 ring fingers, and 7 middle fingers.

Patients were randomized to receive a placebo injection or 2,500 U, 5,000 U, or 10,000 U of a collagenase injection. As in the previous clinical trial the placebo consisted of sterile normal saline containing 2 mmol/L calcium chloride. Seventeen patients received placebo, 18 patients received 2,500 U, 22 patients received 5,000 U, and 23 patients received 10,000 U of collagenase. The investigators were masked to the control treatment code. The investigational pharmacist prepared insulin syringes for injection and the solution contained within was similar in appearance so as not to bias the study investigators. Total volume used was 0.25 mL for MP joints and 0.20 mL for PIP joints.

The parameters investigated at follow-up evaluation (joint contracture, range of motion, grip strength) were the same as in clinical trial IIA. Retreatment options to the target finger or other contractures of the same or contralateral hand, after a first blind injection, on an open-label basis with 10,000 U of collagenase was the same as in clinical trial IIA (4 additional injections). Follow-up intervals were the same as described in clinical trial IIA. Finally, serial monitoring of serum immunoglobulin E for potential allergic effects was the same as described in clinical trial IIA.

Clinical Trial IIB: Collagenase Pharmacokinetics

To determine the acute phase pharmacokinetics of collagenase, 4 male Dupuytren's (MP) patients (mean age 63 y) were enrolled in an open-label substudy to investigate absorption of collagenase into serum and excretion in urine. A 10,000-U dose was delivered to the target finger cord and blood samples were obtained before injection and 1, 10, 30, 60, and 180 minutes after injection. An additional blood sample was obtained at day 1 after injection (19.5 h). Urine samples were obtained before injection, at 30, 60, and 180 minutes after injection, and at day 1 after injection (19.5 h). All serum and urine

Table 2. Range of Finger Contractures Treated and Number of Patients

Collagenase Dose	*20°–29°*	*30°–39°*	*40°–49°*	*50°–59°*	*60°–69°*	*70°–79°*	*80°–89°*	*90°–99°*
MP joints: clinical trial IIB								
2,500 U	1	3	2	3	3	1	1	0
5,000 U	4	3	2	0	2	2	1	1
10,000 U	4	5	1	1	1	2	1	1
Placebo	1	1	0	1	5	1	1	0
PIP joints: clinical trial IIB								
2,500 U	1	3	1	0	1	0	0	
5,000 U	1	1	1	1	0	0	1	
10,000 U	0	1	1	1	2	2	0	
Placebo	1	1	1	0	1	3	0	

samples were analyzed for collagenase content by using a 2-site polyclonal antibody–based immunoenzymetric assay, with a sensitivity of 4 ng/mL.

Clinical Trial IIB: Lidocaine Local Anesthesia

An open-label substudy in 5 male Dupuytren's (MP) patients (mean age 58 y) was conducted by using 5 mL of 1% injectable lidocaine as local hand anesthesia on day 1 after injection before cord manipulation/rupture. This substudy was performed to test the lidocaine anesthesia as an option to offer patients who were unwilling or unable to tolerate the momentary pain of cord rupture. A 10,000-U collagenase dose was injected into the target finger cord. On day 1 after injection, 5 mL of 1% lidocaine was injected into the target hand as a field block without injecting the cord and, once the anesthetic had taken effect, the target finger was passively extended by the investigator to rupture the cord.

Results

Clinical Trial IIA: MP Joints

The mean initial contracture in patients with MP joint disease was 44° ± 17.4°, range 20° to 90°. In the 10,000-U collagenase treatment group (n = 18), 9 of the 18 patients showed a reduction in contracture to within 0° to 5° within 7 days after injection, compared with only 2 of the 18 patients in the placebo treatment group. At 1 month after injection, 14 of the 18 patients in the collagenase treatment group showed correction of contracture to within 0° to 5°, compared with 2 of 18 patients in the placebo treatment group (Figs. 1, 2). The success of treatment for each group is shown in Figure 3 for MP joints (Kaplan-Meier estimation technique). Based on a log rank test of the time to return to normal extension for both treatment groups the differences between the placebo and collagenase groups were statistically significant ($p = .001$).

In 4 patients with MP contractures in the collagenase treatment group who failed to respond to a first injection, second open-label injection with 10,000 U of collagenase corrected their contractures to within 0° to 5° at 1 month. Retreatment of the 16 placebo patients who did not respond to first blinded injection resulted in correction of flexion contracture to 0° to 5° in 10 patients after a first 10,000-U, open-label injection, in 2 patients after a second 10,000-U, open-label injection, and in 1 patient after a third 10,000-U, open-label injection by 1 month. There were 3 failures in the placebo group that did not achieve reduction of contracture to 0° to 5°. One patient had 5 PIP joint cord injections, one had 3 injections, and one had 1 injection. All 3 patients required surgical fasciectomy.

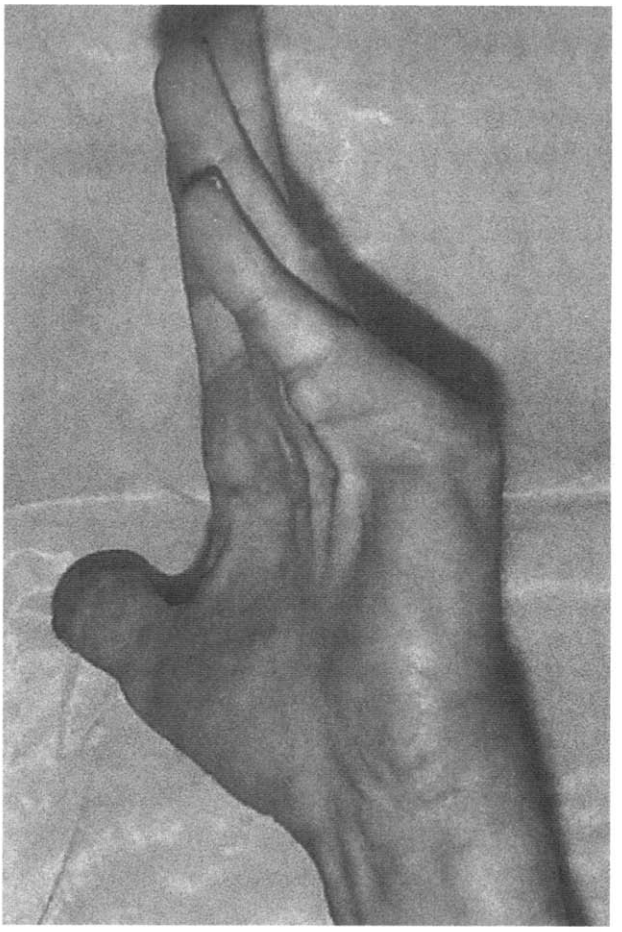

Figure 1. A patient with a left small finger MP joint contracture of 50° and ring finger MP joint contracture of 25° before a 10,000-U collagenase injection, clinical trial IIA. (A color version of this figure can be viewed at the Journal's Web site, www.jhandsurg.org).

In 6 patients with MP joint contractures who were in the collagenase treatment group there were multiple finger corrections after one 10,000-U injection (Figs. 1, 2). This occurred as follows: in 4 patients, MP joints on adjacent fingers corrected to normal extension (0°); in one patient an MP/PIP joint contracture in the same finger corrected to normal extension; and in one patient an MP/PIP contracture of one finger and an adjacent MP joint contracture of another finger all corrected to normal extension. These double corrections occurred because a single

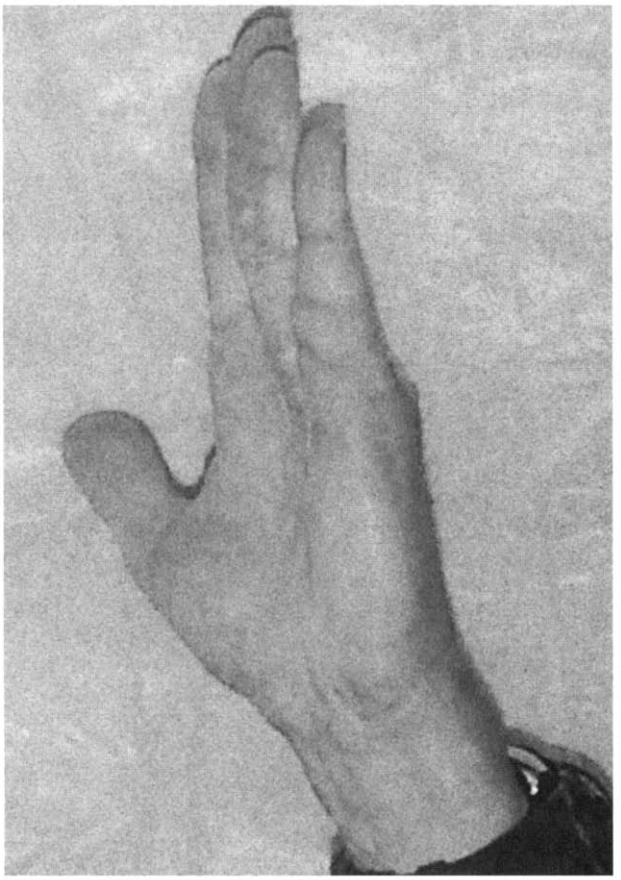

Figure 2. The same patient shown in Figure 1, 1 month after one 10,000-U collagenase injection. Both the small and ring finger contractures responded to 0° after one collagenase injection. (A color version of this figure can be viewed at the Journal's Web site, www.jhandsurg.org).

cord was contracting 2 joints (MP and PIP) in a single digit or because of Y-shaped central/natatory cord connection of one cord to a cord in an adjacent finger.

The mean follow-up period in MP joint patients is 4 years. There were 4 recurrences of MP joint contracture during that period.

PIP Joints

The mean initial PIP joint contracture in all patients was 53° ± 18.7°. Five of 7 patients with PIP joint contractures who were in the 10,000-U collagenase treatment group corrected to within 0° to 5° after one injection after 1 month, one patient corrected to normal extension after a second 10,000-U injection after 1 month, and there was one failure. Six of 6 patients who received placebo did not respond to normal extension after one injection. On retreatment with 10,000 U of collagenase, after 1 month 4 of the 6 placebo patients with PIP joint contractures corrected to normal extension (0°). There was a failure to achieve clinical success in one patient and one patient was lost to follow-up evaluation.

The mean follow-up period in PIP joint patients is 3.8 years. There were 4 recurrences of PIP joint contracture during that period.

Secondary Variables

The percent change from baseline in range of motion (extension/flexion in degrees) in treated fingers after injection over time for both groups showed that the collagenase treatment group improved the extension significantly (analysis of variance [ANOVA], $p = .001$) compared with placebo, as described previously for degree of contracture. The placebo treatment group showed no significant change in extension over time (ANOVA, $p = .213$). Flexion was not significantly increased over baseline values. No statistical significance (ANOVA, $p \geq .195$) was seen between groups for grip strength, 35.41 kg (collagenase) versus 32.89 kg (placebo). It should be noted that there were no significant declines from baseline flexion or from baseline grip strength in either treatment group.

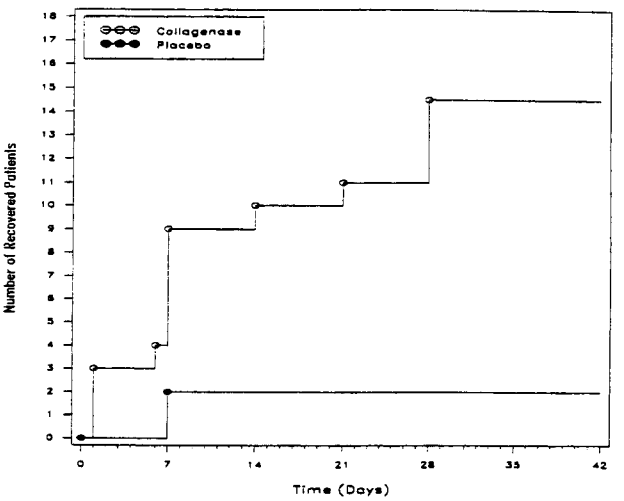

Figure 3. Clinical trial IIA. Success rate of recovered patients over time by treatment group for MP joints, placebo versus 10,000 U of collagenase. N = 18 for each treatment group. Log-rank p value for testing for equality of 2 curves = .0001. Using the Kaplan-Meier estimation technique, because the sample sizes were equal, percentages were converted to number of patients.

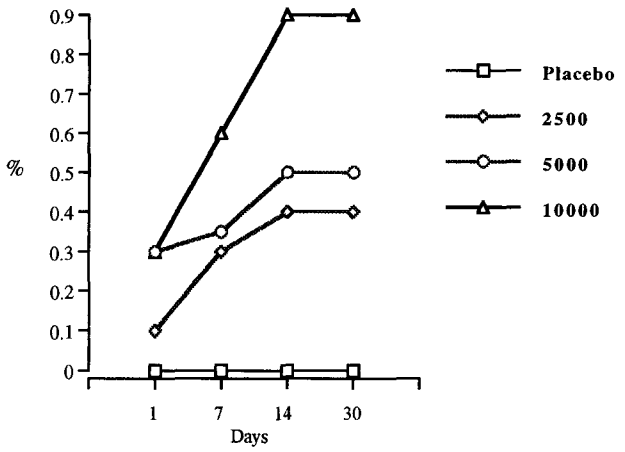

Figure 4. Clinical trial IIB. Success rate of patients in the dose-response trial by treatment group for MP joints. A 10,000-U collagenase treatment was the minimum safe and most effective dose in restoring patients to normal extension (hazard function test, log rank p = .0002).

Adverse Effects

Adverse effects of collagenase injection appeared to be local and minimal and were well tolerated by patients. These included pain when the cord ruptured, pain to pressure at the injection site, dorsal and volar edema, minimal hematoma, and occasional limited ecchymosis involving the treated hand. In approximately a third of patients (especially those who received PIP joint injections) an elbow and/or axillary lymphadenopathy was noted. All effects resolved within 5 to 14 days of injection without event.

There were 3 skin tears in 3 patients on cord rupture. These happened because the contractures were severe (>80°) and had been in a contracted state for many years. All skin tears were treated with Carrasyn gel (Carrington Labs, Irving, TX) and dressed in soft gauze. The skin tears healed well and without adverse event in 2 weeks and did not affect correction of the joint contractures.

Serum immune titers of immunoglobulin E were present in 26 patients. In one patient who received 6 collagenase injections, with special FDA permission, for contractures in other fingers there was an episode of hives on the forearm. This was treated with 25 mL of intramuscularly injected Benadryl (Parke-Davis, Morris Plains, NJ) after which the hives resolved without adverse event in 10 minutes.

Twelve patients were treated on an open-label basis with 10,000 U of collagenase for other associated contractures. This resulted in correction to normal extension (0°) in 4 MP joints, 11 PIP joints, and one DIP joint.

Clinical Trial IIB: Dose Response Study

The mean degree of contracture in patients with MP joint disease (n = 55) was 50° ± 4.9°, range 20° to 92°. The mean degree of contracture in patients with PIP joint disease (n = 25) was 49° ± 9.8°, range 20° to 80°.

Comparison of dose groups showed that the success rate using Fisher's exact test in return to normal extension (0°–5°) was markedly higher in patients treated with 10,000 U of collagenase at 1 month. Eighteen of the 23 patients who received the 10,000-U dose responded to normal extension by 1 month, compared with 10 of 22 patients in the 5,000-U group and 9 of 18 patients in the 2,500-U group. There was no response to placebo injection in any patient. Figure 4 shows the success rate (hazard function) for each treatment group in the MP joints indicating that by day 14 after the 10,000-U injection there was a 90% success rate. A log rank test was performed for evaluation of treatment differences and was significant at p = .0002. The overall clinical success (hazard function) in the PIP joint patients is shown in Figure 5 and shows significance at 10,000 U and a 70% success rate (log rank p = .0397). Figures 6 and 7 show the recovery of extension in the PIP joint.

In those patients who responded to collagenase injection, regardless of dose, extension in range of

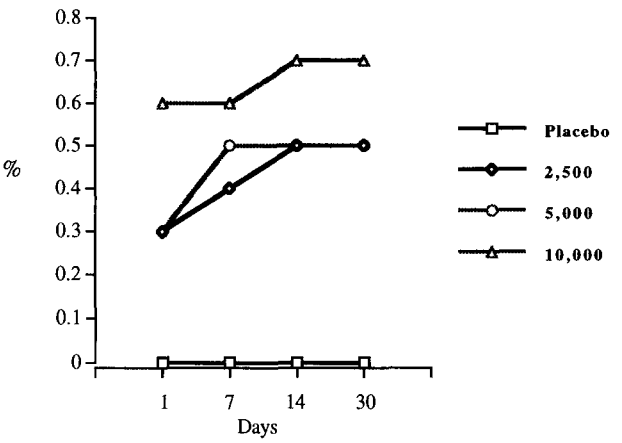

Figure 5. Clinical trial IIB. Success rate of patients in the dose-response trial by treatment group for PIP joints. A 10,000-U collagenase treatment was the minimum safe and most effective dose in restoring patients to normal extension (hazard function test, log rank p = .0397).

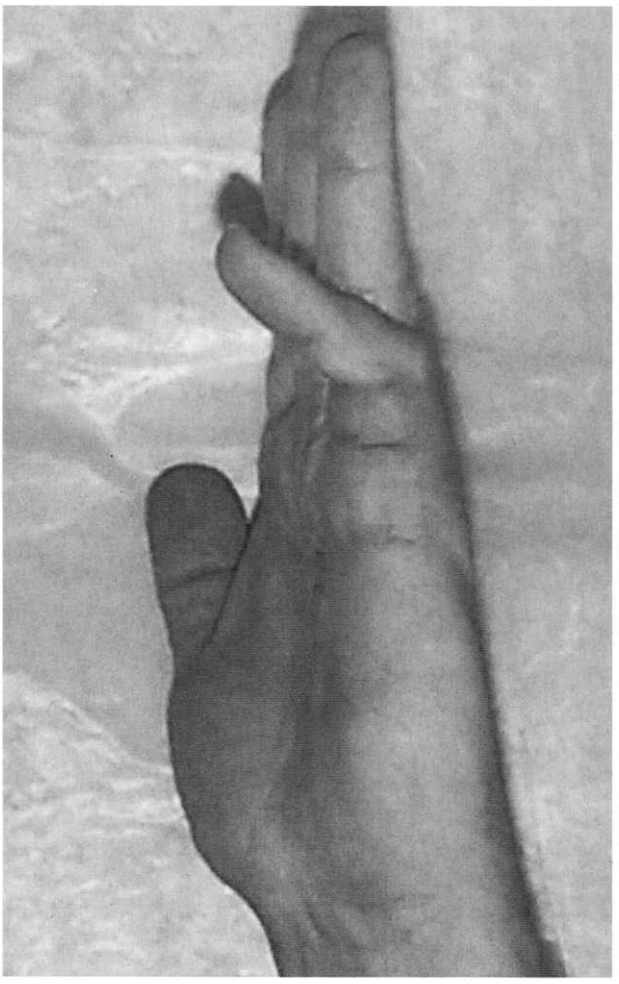

Figure 6. A patient with a left small PIP joint contracture of 30° before a 10,000-U collagenase injection, clinical trial IIB. (A color version of this figure can be viewed at the Journal's Web site, www.jhandsurg.org).

motion (extension/flexion degrees) improved significantly, as described for contractures, after analysis by Tukey trend test ($p = .0001$). Flexion did not improve significantly from baseline, but flexion was not significantly decreased from baseline values in patients or between groups (42.5 kg placebo vs 49.2 kg collagenase). Grip strength analysis showed no significant differences from baseline.

In patients who failed to respond to normal extension after first blinded injection, and who were treated with open-label 10,000 U of collagenase repeat injection(s), the success rate was also approximately 90% for MP joints and 70% for PIP joints for return to normal extension. Other involved joints of the same finger/hand, or contralateral hand, also treated with open-label 10,000 U collagenase repeat injection(s) responded to normal extension at similar success rates as cited. These included 13 MP joints, 25 PIP joints, and one DIP joint in 25 patients. A mean of 3 open-label injections was used.

In 11 patients there were multiple finger corrections after one 10,000-U collagenase injection. This resulted in MP joint corrections to normal extension of adjacent fingers in 4 patients, correction of the MP/PIP joint of the same finger in 5 patients, and correction of the PIP/DIP joints of the same finger in 2 patients.

Mean follow-up period for MP joints is 2 years and for PIP joints 12.5 months. There was recurrence of contracture in one MP joint and one PIP joint.

Adverse events of collagenase injection were similar to those that were seen in clinical trial IIA. The

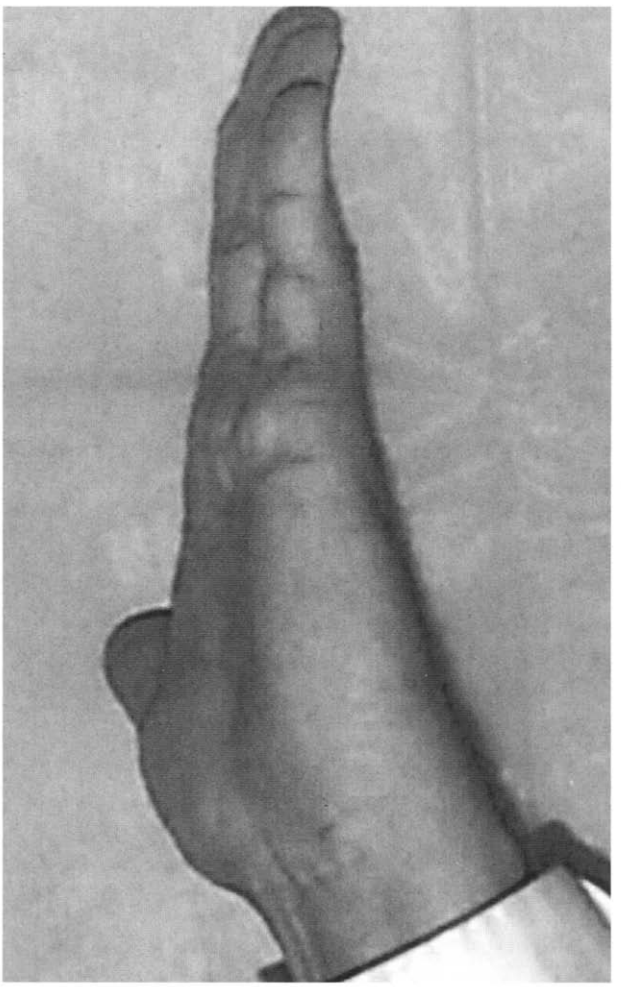

Figure 7. The same patient shown in Figure 6 one month after one 10,000-U collagenase injection. (A color version of this figure can be viewed at the Journal's Web site, www.jhandsurg.org).

local adverse effects included pain at cord rupture and pain to pressure at the injection site, volar and dorsal edema, minimal hematoma, and occasional lymphadenopathy, which was present at the elbow and/or axilla. All these effects resolved without event within 5 to 14 days of injection. Serum titers of immunoglobulin E were present in 2 patients after first injection but titers increased if patients received repeat injections. Twenty-four patients showed serum immunoglobulin E titers after repeat injections. There were no clinically significant adverse immune events.

Clinical Trial IIB: Pharmacokinetics

No collagenase was detected in any of the serum specimens collected from 1 minute to 19.5 hours after 10,000-U injection. The limit of the assay was 4 ng/mL. From a theoretical perspective, a 10,000-U collagenase injection was known to be equivalent to 1 mg of collagenase. If it is assumed that 2 mg was injected into a 70-kg man with a total blood volume of 4 L, a 50% hematocrit, and all was released into the blood at once, one would expect a concentration of 125 ng/mL collagenase in the serum. Thus the fact that we detected <4 ng/mL in the serum indicates that it may not all be released immediately into the circulation. Alternatively it is possible that the collagenase does diffuse into the circulation and may be denatured. The second alternative seems less likely because we detected collagenase in patient urine samples.

Urine samples showed detectable levels of collagenase (Fig. 8). An estimated 7% to 28% of the collagenase was recovered, mostly in the 30- to 60-minute samples. This may indicate the ability of the kidney to concentrate collagenase.

The mean degree of MP flexion contracture in the 4 patients was 44° ± 24.7°. All 4 patients with MP joint contractures in the pharmacokinetics study achieved normal extension (0°) at 1 month after injection. Mean follow-up period was 22 months with no recurrences.

Clinical Trial IIB: Lidocaine Local Anesthesia

The mean degree of MP flexion contracture in the 5 patients was 56° ± 17.8°. All patients tolerated the 1% lidocaine injection and the passive manipulation of the involved digit very well. Four patients achieved normal extension (0°) after passive manipulation and cord rupture by 1 day after 10,000-U injection. The remaining patient required a second

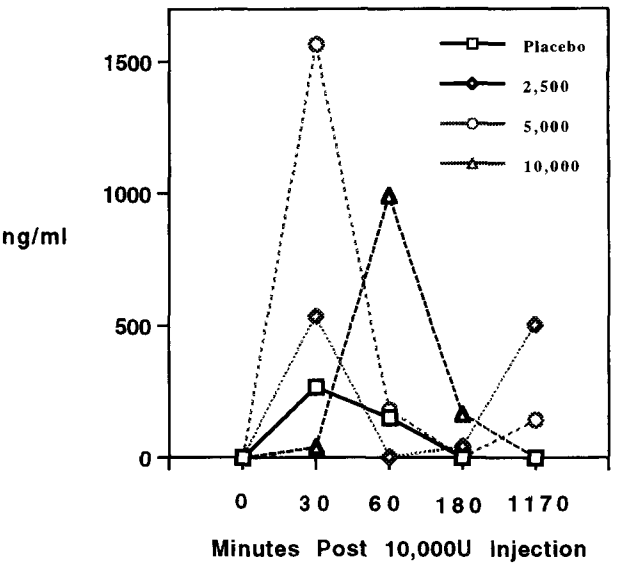

Figure 8. Concentration of excreted collagenase in urine samples (n = 4 patients). The highest concentrations of the enzyme were seen 30 to 60 minutes after injection.

10,000-U collagenase injection and achieved normal extension (0°) at 1 month. Mean follow-up period in these 5 patients is 22 months with no recurrences.

One percent lidocaine injection before cord manipulation seems to be a safe clinical option in those patients unwilling or unable to tolerate the momentary pain of cord rupture.

Discussion

These studies have shown that collagenase injection into the cord causing MP and/or PIP joint contractures in Dupuytren's disease is a safe and effective method in the majority of patients in restoring normal finger extension and thus improving range of finger motion. Flexion and grip strength were not adversely affected by collagenase injection.

A random, placebo-controlled, dose-response study in clinical trial IIB showed that 10,000 U of collagenase is the minimum safe and effective dose for cord injection. Clinical trial IIB substantiated the results of clinical trial IIA, in which 10,000 U of collagenase was tested versus placebo. Further, our results show that the adverse effects of collagenase injection are essentially a local tissue reaction consisting of pain, edema, ecchymosis, and an occasional elbow and/or axillary lymphadenopathy. These effects resolved well in the short term and have been very well tolerated by patients. Compared with the well-known postoperative effects of surgery

we consider the adverse effects of collagenase injection to be minor in comparison. In fact some of our patients who have had fasciectomy on one hand but have been treated in our trials for the contralateral hand have commented in glowing terms that the less invasive injection treatment was far superior to their surgical experience.

It is also important to note that collagenase injection, even when administered repeatedly, did not induce an allergic reaction as evidenced by our serial immune testing of immunoglobulin E titers. We consider this to be very important because we anticipate that those patients with multiple finger joint involvement of one or both hands will most likely need several injections. We also anticipate that there will be a recurrence rate after collagenase injection, just as there is after fasciectomy. To date our recurrence rates are low in the clinical trials described and are <5% at 4 years from our first open-label clinical trial using 10,000 U of collagenase. There have been no disease extensions to other fingers. We expect that recurrences and/or extensions of disease will be treated with repeat maintenance collagenase injections. We continue to follow-up annually with all our patients for potential recurrences and/or disease extension for a total of 5 years.

The substudies performed in clinical trial IIB have shown that collagenase is not absorbed into the circulation in high concentration and is efficiently excreted in urine. Also local lidocaine anesthesia is a viable option for those patients who are unable or unwilling to endure the momentary pain of cord rupture.

Multicenter, phase-3 trials are now planned for collagenase injection in Dupuytren's disease. The method is safe, effective, and less invasive than surgery, more cost effective, and has a high degree of patient satisfaction.

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