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Collagenase Treatment for Dupuytren Disease of the Thumb and First Web

Marieke M. Dreise, BA,* Martin W. Stenekes, MD, PhD,* Paul M. N. Werker, MD, PhD*

Purpose To evaluate the short-term effectiveness of collagenase *Clostridium histolyticum* to treat thumb and first web contractures in Dupuytren disease.

Methods We prospectively included 14 thumbs in 12 patients with a contracture at the metacarpophalangeal or interphalangeal joint of at least 20° with a palpable cord in the thumb (n = 8) or an adduction contracture of the thumb with palpable cords in the first web (n = 6). They received an injection containing 0.58 mg of collagenase *Clostridium histolyticum* in the fibrous cord divided over 3 spots. The contracture was released by carefully manipulating the thumb under local anesthesia 1 day later. The extension and abduction deficits were measured before and after the intervention (follow-up at 7 and 30 days and 6 months). Wilcoxon signed rank test was used to analyze the data.

Results In the total sample, postintervention extension deficits were statistically significantly lower than preintervention deficits except in one patient who had a recurrence at 6 months compared with the 30-day posttreatment result. Intermetacarpophalangeal head distance (IMD) also improved significantly. In an analysis of subgroups, we compared the separate contributions of treatment of a pretendinous cord and a first web cord on both extension deficit and IMD. Treatment of pretendinous cords significantly affected both extension deficit and IMD. However, treatment of first web contractures did not significantly improve extension or IMD.

Conclusions Collagenase *Clostridium histolyticum* is a good treatment option for pretendinous cords in thumbs affected with Dupuytren disease because it provides good results, is minimally invasive, and has minor adverse events. (*J Hand Surg Am.* 2016;41(3):348–353. Copyright © 2016 by the American Society for Surgery of the Hand. All rights reserved.)

Type of study/level of evidence Therapeutic IV.

Key words Collagenase *Clostridium histolyticum*, Dupuytren disease, thumb, first webspace.

DUPUYTREN DISEASE (DD) IS A PROGRESSIVE fibromatosis of the palmar fascias of the hand and digits. Subcutaneous nodules and pitting in the palm are usually the first signs of the disease. Cords

may develop and cause flexion contractures of the fingers. Usually the deformities are located in the ulnar fingers and only in 3% on the radial side.¹ Radial involvement alone is rare.^{2,3}

Dupuytren disease pathology on the radial side of the hand is concentrated at the location of normal fascia and fibers,^{4,5} which are, according to Tubiana's⁵ description, the thenar eminence fascia, the longitudinal fibers of the superficial palmar aponeurosis, the distal transverse commissural ligament of the first web, and the proximal transverse commissural ligament (Fig. 1). Tubiana explained that the pathology caused a longitudinal fibrous cord originating on the radial side of the thenar eminence and extending into the thumb (Fig. 2). This cord may pull the metacarpophalangeal

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FIGURE 1: Palmar fascia of the radial side of the hand. A, thenar eminence fascia is thicker on the radial side of the eminence; B, longitudinal fibers of superficial aponeurosis; C, distal transverse commissural ligament of the first web; D, proximal transverse commissural ligament. (Reprinted with permission from Tubiana R. Dupuytren's disease of the radial side of the hand. *Hand Clin.* 1999;15(1):149-159.)⁵

FIGURE 2: Location of the pathologic fibrous formations on the radial side of the hand. (Reprinted with permission from Tubiana R. Dupuytren's disease of the radial side of the hand. *Hand Clin.* 1999;15(1):149-159.)⁵

(MCP) joint into radial deviation and flexion. In the longitudinal fibers of the palmar aponeurosis, the pathology can develop into a cord to the first web and flexor sheath of the thumb. This cord may produce a flexion contracture of the thumb. A distal transverse interdigital cord will be the consequence of pathology in the distal transverse commissural ligament of the first web corresponding to the natatory ligament (Grapow ligament) and can cause an adduction and retro position contracture. A transverse proximal cord in the first web, corresponding to the proximal commissural ligament, will cause a web contracture. A combination of cords can move the thumb into opposition.³ Most patients

with radial involvement experience only mild contractures and do not need treatment. However, in a minority of cases the thumb function becomes severely limited and affects activities of daily living.^{5,6}

There is a paucity of literature on the treatment of DD in the thumb and first web. Hueston⁷ and Tubiana⁵ advised wide dermofasciectomy and a full-thickness graft, especially if there is high risk for recurrence as in a diathesis.

Until recently, we usually treated contractures of the thumb less aggressively with limited fasciectomy. A PubMed search with cross-referencing did not provide us with any literature on the results of dermofasciectomy or limited fasciectomy focused on the thumb.

The use of collagenase *Clostridium histolyticum* (CCH) (Xiapex; Pfizer, Sandwich, UK) to treat DD contractures has gained popularity as a minimally invasive procedure. At least 24 hours after injection, passive extension of the digit usually causes the cord to rupture, thereby releasing the contracture. Collagenase *Clostridium histolyticum* has been tested extensively and outcomes are encouraging⁸⁻¹¹ with low complication rates and reasonable recurrence rates.¹¹ Bendon and Giele¹² conducted a pilot study on 4 subjects with 5 affected thumbs and had good results with CCH treatment. We were interested in exploring how effective CCH treatment might be for patients with radial involvement of DD. We therefore prospectively studied the results of CCH treatment in the thumb and first web space in a sample of 14 hands.

MATERIAL AND METHODS

Our study design was a prospective cohort study. We performed a power analysis for the primary study parameter (extension deficit). Values from the study by Hurst et al¹¹ were used because values specifically for the thumb are not available from the literature. The average change in range of motion from baseline in this report was 37° (99% confidence interval, 24° to 37°) after 30 days. From these data, an SD of 30° was estimated, resulting in an effect size of 1.22. We assumed an alpha of .05 and a power of 0.80. The power analysis resulted in a sample size of 9 hands. Considering dropouts, we set the target at 15 hands. We designed the study protocol according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. The ethics board of our hospital and the Central Committee on Research Involving Human Subjects approved the protocol. To be eligible for the study, subjects had to be aged 18 to 75 years and healthy

FIGURE 3: Treatment of different cords. 1, Pretendinous cord extending along the volar aspect of the proximal phalanx and ending on the radial side of the end phalanx, causing MCP and interphalangeal flexion. 2, Distal commissural cord in the first web causing adduction contracture.

enough to be able to travel the often long distance to our hospital.

Normal range of motion was defined as interphalangeal joint flexion 80° or greater, extension 10° or greater; MCP joint flexion 60° or greater, and extension 0° or greater; for the trapeziometacarpal joint: adduction 2 cm or less, radial abduction 50° or greater, and opposition 7 cm or greater.¹³ To be included in the study, subjects needed to have a contracture with a flexed position at the MCP or interphalangeal joint of at least 20° (compared with the contralateral side) caused by a palpable cord in the thumb ($n = 8$) or any adduction–opposition contracture of the thumb with palpable cords in the first web ($n = 6$) (Fig. 3).

Exclusion criteria were pregnancy or breastfeeding and having had treatment in the affected thumb before the injection. After they gave informed consent, 12 subjects (10 men and 2 women; 14 hands involved) were included over 17 months. We took a medical history concerning problems and previous treatment of the DD, comorbidity, associated diseases such as Morbus Ledderhose (plantar fibromatosis) and Peyronie (fibromatosis of the tunica albuginea of the penis), trauma and osteoarthritis in the affected hand, smoking, and intake of alcohol. In all subjects, we measured passive extension deficits on the thumb and index before and after the intervention (follow-up at 7 and 30 days and 6 months) using a standard goniometer.¹⁴ In addition, we measured the IMD, defined as the widest possible distance between the dorsal center of the

TABLE 1. Total Extension Deficits of Treated Thumbs

Measurement	Average Total Extension Deficit, degrees	SD
Before intervention, d	31	29
After intervention		
7 d	10	9
30 d	9	10
6 mo	11	13

first and second metacarpal heads in millimeters. Subjects received an injection with 0.58 mg CCH (Xiapex, Pfizer, Kent, UK), dissolved in the provided diluent in the fibrous cord and divided over 3 spots along the selected cord. The subject's treated hand was wrapped with a soft bulky dressing. Medical personnel skilled in the management of acute allergic reactions kept the subjects under observation for adverse reactions for half an hour. At least 24 hours after injection the subjects returned and were checked for adverse events. Lidocaine 1% plus adrenaline 1:100,000 field block was used for local anesthesia. The affected joints were manipulated afterward in an attempt to rupture the cords. In case of a pretendinous cord, manipulation meant passive extension of the affected joint. In case of a first web cord, often direct pressure to the cord was needed to release it. Subjects were advised to keep the thumb immobilized with a bandage for a few days and to refrain from heavy use for the first 2 weeks. They did not receive hand therapy or a night orthosis. All injections, cord ruptures, and measurements were performed by the same surgeon except for one 6-month postinjection evaluation, which was performed by a resident who was instructed regarding the assessment process. Demographical data are presented using descriptive statistics. Preintervention extension deficits of the thumb and IMD of the thumb and index finger were compared with postintervention measurements using Wilcoxon signed rank test.

RESULTS

Fourteen hands of 12 subjects with DD were included in this study. Twelve of the hands belonged to men. Average age at injection was 63 years (SD, 4.7 years). All subjects had the disease in both hands and none had previous treatment of the thumb. Ledderhose disease was present in 6 subjects. All hands except for one had been treated previously for DD located elsewhere in the hand. One day after injection, there were minor

TABLE 2. Preintervention Extension Deficits of Thumbs Compared With Postintervention Deficits

	Before Intervention Compared With 7 d After Intervention	Before Intervention Compared With 30 d After Intervention	Before Intervention Compared With 6 mo After Intervention
Z	−2.490	−2.834	−2.637
P value	.013	.005	.008

Data were analyzed using Wilcoxon signed rank test.

TABLE 3. Intermetacarpophalangeal Head Distance Between Thumb and Index Finger

Measurement	Average IMD Between Digit I and II, mm	SD, mm
Before intervention	59	11
After intervention		
7 d	62	11
30 d	65	11
6 mo	67	6

adverse events such as injection site pain,¹¹ swelling,¹² and hematoma and/or bruising.¹⁰ None of the subjects had lymphadenopathy. No serious adverse events were seen. Manipulation caused 2 skin tears. No patients had a persisting contracture for which a second injection was necessary. At 30 days after treatment, all adverse events had disappeared.

Table 1 lists the total extension deficit of the treated thumbs. Postintervention extension deficits were significantly lower than preintervention ones ($P < .05$) (Table 2). One subject had a recurrence at 6 months compared with 30 days' follow-up, with recurrence defined as an increase of 20° relative to the result achieved at 30 days or as any decrease in IMD. In this case, the subject had a recurrence with an increase in extension deficit of 30° between 30 days and 6 months.

Table 3 presents the IMDs. Except for the first postintervention measurement, the other postintervention IMDs significantly improved compared with before the intervention ($P < .05$) (Table 4). After 6 months, IMD had again significantly improved compared with 7 days after the intervention ($P = .041$; $Z = -2.047$). Analyses of IMD showed no recurrences.

Although this was not the initial purpose of our study, we performed an analysis of subgroups. The separate contributions of treatment of a pretendinous cord ($n = 8$) and a first web cord ($n = 6$) on both extension deficit and IMD were compared (Table 5). Intervention in a pretendinous cord of the thumb resulted in significant improvement ($P < .05$) of all

total passive extension deficit comparisons and almost all IMD comparisons. No significant effects on extension deficits or IMD were found after first web cord intervention. The pre- and posttreatment total extension deficits and IMD of all included subjects are listed in Appendix A (available on the *Journal's* Web site at www.jhandsurg.org).

DISCUSSION

Intervention in longitudinal cords of the thumb using CCH injection and manipulation significantly reduced the extension deficit by 20° on average. This effect occurred quickly after treatment and remained stable during follow-up of 6 months in all cases except one. In addition, the IMD significantly improved from 58 to 67 mm on average during follow-up and improved slowly. We can only speculate about the reason for this. Although the subgroups of pretendinous cord and first web cord were small, the analysis revealed notable findings. The CCH injection and manipulation had a significant effect on both extension deficits and IMD in pretendinous cords. However, treatment of the first web did not immediately affect extension deficit or IMD markedly.

Bendon and Giele¹² also studied the effect of CCH treatment in the thumb and found statistically significant improvement in a small sample of 4 patients with 5 thumbs. However, they described no analysis by type of cord.

No serious adverse events occurred in our study. Most patients had some minor adverse events including injection site pain, swelling, and hematoma and/or bruising. This is similar to the complications reported by Bendon and Giele.¹² Also, Bendon and Giele found that 40% of subjects had lymphadenopathy.

There are limitations to our study compared with the study of Hurst et al¹¹ concerning adverse events, because they treated all fingers except the thumb; nevertheless, they also found that patients injected with collagenase (204 joints) had mild and moderate adverse events (97%). Minor complications in the study of Hurst et al, such as injection site pain (66%),

TABLE 4. Comparison of Preintervention and Postintervention IMD

	Before Intervention Compared With 7 d After Intervention	Before Intervention Compared With 30 d After Intervention	Before Intervention Compared With 6 mo After Intervention
Z	−1.611	−2.043	−2.871
P value	.107	.410	.004

Data were analyzed using Wilcoxon signed rank test.

TABLE 5. Analysis per Treated Zone

Parameter	Treatment Zone		Before Intervention Compared With 7 d After Intervention	Before Intervention Compared With 30 d After Intervention	Before Intervention Compared With 6 mo After Intervention
Total extension deficit	Pretendinous cord	Z	−2.524	−2.533	−2.384
		P value	.012*	.011*	.017*
Total extension deficit	First web	Z	−0.276	−1.289	−1.473
		P value	.783	.197	.141
IMD	Pretendinous cord	Z	−2.121	−1.625	−2.271
		P value	.034*	.104	.023*
IMD	First web	Z	.000	−1.342	−1.841
		P value	1.000	.180	.066

*Indicates statistical significance ($P < .05$).

bruising (51%), and swelling (72.5%), disappeared at around 10 days. Three patients had severe adverse events: one patient had complex regional pain syndrome and 2 had ruptured tendons.

After 3 years' follow-up of joints successfully treated with CCH, Peimer et al¹⁵ found a recurrence rate (defined as an increase in flexion contracture of 20° or more in joint contractures that had been released completely) in digits 2 to 5 in 27% of MCP joints and 56% of proximal interphalangeal joints. Seven percent of those recurrences required medical or surgical intervention. We found one recurrence in our study with an increase in extension deficit of 30° between 30 days and 6 months after treatment. This period is too short to give a reliable recurrence rate. Therefore, we plan to observe our patients over a longer period. There are certainly limitations to comparing different treatment options for DD in the thumb. However, looking at the literature concerning complications and recurrence in limited fasciectomy and dermofasciectomy, we believe that treatment with CCH is a viable option for pretendinous cords in thumbs because it gives good results and is minimally invasive with minor adverse events. For example, Coert et al¹⁶ reported an overall complication incidence of 26% in 558 operations using limited fasciectomy. Various complications were described, from minor adverse events such as minor

wound infections and hematoma to serious complications such as neurovascular damage (8%). Limited fasciectomy has a recurrence rate (defined as an increase in total passive extension deficit of 30° compared with postoperative results) of approximately 21% after 5 years.¹⁷

Although the recurrence rate after dermofasciectomy (defined as the reappearance of nodules or cords) in the fingers is low, with an average of 8% in 6 years,¹⁸ recovery is more prolonged than with other surgical techniques. Complications that have few consequences in patients treated with limited fasciectomy or collagenase, such as hematoma formation, can cause major complications such as skin graft loss. Other serious complications are neurovascular damage and contracting of the grafted skin. These are rare.^{19–22} There were some limitations to our study. Because recurrence of DD in the thumb or first web would be a confounding factor, we included only subjects with primary DD in the thumb or first web in our study. Therefore, we can give results only in subjects with primary DD in the thumb and first web.

Goniometry and IMD measurements are the best available instruments to measure extension deficits, although they are not exact and may have problems with observer reliability. We maximized interobserver reliability by limiting the number of people performing

measurements to one person but were forced to have one evaluation done by a second person who was instructed regarding the assessment.

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APPENDIX A. Total Extension Deficit and IMD

Subject	Type of Cord	Total Extension Deficit (degrees)				IMD (mm)			
		Before Injection	7 d After Injection	30 d After Injection	6 mo After Injection	Before Injection	7 d After Injection	30 d After Injection	6 mo After Injection
1	First web cord	10	20	20	20	Missing	60	60	65
2	First web cord	35	25	25	20	55	Missing	60	60
3	First web cord	20	5	0	0	55	50	55	70
4	First web cord	20	10	5	0	70	70	70	70
5	First web cord	0	15	0	0	60	75	75	70
6	First web cord	0	0	0	0	70	65	70	75
7	Pretendinous cord first ray	20	15	15	15	40	50	75	60
8	Pretendinous cord first ray	50	5	10	40	50	55	60	70
9	Pretendinous cord first ray	115	20	20	15	55	55	55	60
10	Pretendinous cord first ray	35	15	5	Missing	45	45	45	Missing
11	Pretendinous cord first ray	10	0	0	0	55	60	55	60
12	Pretendinous cord first ray	40	0	0	5	60	65	85	65
13	Pretendinous cord first ray	40	0	0	0	65	70	70	70
14	Pretendinous cord first ray	40	10	25	30	80	80	75	80