Delayed manipulation after collagenase clostridium histolyticum injection for Dupuytren contracture

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Abstract

Background Collagenase clostridium histolyticum (CCH) injection for Dupuytren contracture was approved in the USA in 2010. Current FDA guidelines stipulate that finger manipulation occurs the day following injection. To investigate the safety and efficacy of delaying manipulation to 2 or 4 days following CCH injection, we conducted a prospective, randomized trial at two sites.

Methods Patients with Dupuytren contracture involving the metacarpophalangeal (MCP) joint $\geq 20^\circ$ caused by a palpable cord participated. All patients received one dose of CCH (0.58 mg/0.25 ml) and were followed for 90 days. The primary end point was the percent of patients maintaining clinical success (reduction of contracture to 0° – 5°) at 90 days post-injection. Adverse events and change in Michigan Hand Questionnaire (MHQ) score were recorded as secondary end points.

Results Thirty-seven patients enrolled; 13 were manipulated on day 1, 11 on day 2, and 13 on day 4. At 30 days after injection, the percentage of patients obtaining reduction of contracture to $<0^\circ$ – 5° extension was 92, 82, and 85 % in groups 1, 2, and 3, respectively, with no significant difference. At 90 days follow-up, the percentage of patients maintaining 0° – 5° extension was 91, 82, and 83 % in groups 1, 2, and 3, respectively, with no significant difference. Adverse events

were comparable to rates in prior studies. There were no serious adverse events. There was no statistical difference in MHQ scores between groups at any time point.

Conclusions Delaying manipulation to day 2 or 4 following CCH injection for MCP joint contractures does not increase adverse events or result in loss of efficacy.

Level of Evidence: Therapeutic, Level II.

Keywords Dupuytren contracture · Collagenase clostridium histolyticum · Delayed finger manipulation · Safety

Introduction

Dupuytren disease is a benign fibroproliferative condition of the palmar fascia wherein excessive collagen deposition may form cords, which, in turn, may progress to finger flexion contractures that often interfere with normal hand function [2]. The incidence of this disease is highest in people of northern European descent, with an estimated prevalence of 3 to 6 % among Caucasians, although it occurs in all races and ethnic groups [1]. Dupuytren disease was first described more than 400 years ago, and the mainstay of treatment has been surgical fasciectomy or fasciotomy for symptomatic contracture, performed either through open or percutaneous techniques [3].

Injectable collagenase clostridium histolyticum (CCH) was approved by the US Food and Drug Administration in 2010 and by the European Medicines Agency in 2011 as a nonsurgical alternative for the treatment of Dupuytren contracture in adults with a palpable cord [4, 5]. Collagenase clostridium histolyticum (0.58 mg) is injected into the cord identified as causing contracture of a metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joint and the finger passively manipulated into extension the following day to rupture the cord. This treatment method is based on the FDA-regulated phase 2 and 3 clinical trials previously performed [6–8] and is the

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current “on label” standard of use. Other clinical studies have also investigated finger manipulation on the day after CCH injection for cord rupture [9, 10].

Collagenase clostridium histolyticum injection is an office-based procedure that offers patients a pharmacologic treatment option in contrast to an open or percutaneous intervention. The currently approved use, however, requires two consecutive days of treatment, which may not be ideal for the surgeon or patient. Many surgeons do not have practices set up for visits on consecutive days, and patients likewise may face challenges in reserving two consecutive days for treatment. Recently, Manning et al. [11] reported on 38 patients receiving 42 CCH injections for MCP contracture who were manipulated on day 2. Ninety two percent of patients had successful reduction of contracture to $\leq 5^\circ$. The purpose of this study was to investigate the safety and efficacy of finger manipulation for cord rupture of MCP contracture at 2 or 4 days after injection with CCH in the treatment of Dupuytren contracture. We choose these timeframes seeking to identify common periods that would be convenient for both patient and surgeon. While even longer periods between injection and manipulation may be possible, for the purposes of this study, we wanted to avoid the possibility of the effect of a healing response prior to the time of manipulation.

Materials and Methods

Patients with Dupuytren contracture involving the MCP joint caused by a palpable cord participated in a multicenter, prospective, randomized trial conducted at two sites in the USA. Local institutional review boards approved the study. All patients provided written informed consent to participate in the trial and were free to withdraw at any time.

Patients

Patients were eligible for study inclusion if they were at least 18 years old and had a contracture of an MCP joint, other than the thumb, of at least 20° associated with a palpable cord. In patients with more than one eligible MCP contracture, the patient selected the finger to be treated. Exclusion criteria were prior treatment, including needle aponeurotomy, collagenase injection, fasciectomy, or fasciotomy of the affected digit, concomitant use of anticoagulant therapy (other than aspirin up to 150 mg/day), severe chronic or terminal illness that would preclude participation, allergy to clostridial collagenase, or inability to conform to the study visit schedule. Thirty-seven patients were enrolled (34 males, 3 females; mean age, 65.5 years) (Table 1).

Treatment

After informed consent was obtained, a complete medical history was recorded, as was time since onset of Dupuytren disease, Michigan Hand Outcomes Questionnaire (MHQ) [12] scores, and patient’s use of concomitant medications. Baseline finger goniometry was performed on all fingers of the affected hand.

Patients with a contracture of the MCP joint $\geq 20^\circ$ and a palpable cord were randomized to undergo finger manipulation at 1 day (group 1), 2 days (group 2), or 4 days (group 3) after injection. Patients were stratified based on contracture severity to either low severity ($\leq 50^\circ$ contracture) or high severity ($>50^\circ$ contracture). A 1:1:1 randomization scheme was used for each severity group to prevent any group from having a disproportionate number of patients with either more or less severe contractures. Randomization was done with a computer-generated random numbers table employing random block sizes from 4 to 8.

All patients received one dose of CCH (0.58 mg/0.25 mL diluent) injected into the cord that was causing the contracture, per manufacturer’s guidelines. All injections were given by one of three fellowship-trained hand surgeons. After injection, hands were wrapped in a soft, bulky dressing and patients instructed to keep the hand elevated and immobile for the remainder of the day. Patients were also instructed to avoid use of the treated finger and to keep the bandage in place and dry until the assigned follow-up visit for the finger manipulation procedure. Prior to finger manipulation, local anesthesia (either bicarbonate-buffered [1 mL] 1 % lidocaine injection [9 mL] or a 1:1 mixture of 1 % lidocaine and 0.5 % bupivacaine, based on investigator preference) was administered. On the day of finger manipulation, adverse events and whether the cord spontaneously ruptured were recorded, the extension procedure performed (regardless of occurrence of spontaneous rupture), and post-manipulation range of motion measured. After manipulation, patients wore an extension splint during sleep for up to 4 months and performed home range-of-motion exercises.

Patients were followed at 10, 30, and 90 days after injection. At each visit, finger goniometry, MHQ scores, and adverse events were recorded. Measurements were performed by either a physician extender with training and experience in goniometry or a fellowship-trained hand surgeon from outside the investigator’s department to avoid bias. The primary end point was the percentage of patients who maintained clinical success (as defined in the CORD 1 study [8]) as a reduction of contracture to 0° – 5° of extension at 90 days after injection. Secondary endpoints were adverse events and change in Michigan Hand Questionnaire score. Kruskal-Wallis and Pearson chi-square tests compared continuous and categorical variables, respectively.

Table 1 Baseline demographics and clinical characteristics

Characteristic	Group 1 (n=13)	Group 2 (n=11)	Group 3 (n=13)	P value
Age, mean (SD)	63.9 (10.3)	67.0 (6.4)	65.5 (10.2)	0.6662
Gender, n (%)				
Female	0 (0)	2 (18)	1 (8)	0.2660
Male	13 (100)	9 (82)	12 (92)	
Hand, n (%)				
Left	2 (15)	5 (45)	9 (69)	0.0212
Right	11 (85)	6 (55)	4 (31)	
Finger, n (%)				
Little	7 (54)	7 (64)	7 (54)	0.9100
Long	1 (8)	1 (9)	1 (8)	
Ring	5 (38)	3 (27)	5 (38)	
Contracture (degrees), mean (SD)	49.6 (18.3)	45.0 (20.0)	48.7 (19.1)	0.7407
Flexion (degrees), mean (SD)	89.8 (7.8)	91.8 (4.1)	92.3 (5.6)	0.6085
MHQ score, mean (SD)	71.7 (22.1)	77.9 (19.2)	82.5 (16.5)	0.4079

MHQ Michigan Hand Questionnaire

Results

Of the 37 patients enrolled, 13 underwent finger manipulation on day 1 (group 1), 11 on day 2 (group 2), and 13 on day 4 (group 3). There was no significant difference among groups in gender ($P=0.266$) or finger involved ($P=0.91$). There was a significant difference in hand involved, with group 1 having 11 right hands and 2 left hands, group 2 having 6 right hands and 5 left hands, and group 3 having 4 right hands and 9 left hands ($P<0.05$) (Table 1). There were no significant differences among the groups regarding mean baseline values in contracture, flexion, or MHQ scores (Table 1). Three patients had a spontaneous rupture before their assigned day of manipulation. All three occurred in patients in the day 4 group, and all underwent formal manipulation due to the presence of residual contracture.

At 30 days after injection, the percentage of patients who obtained clinical success (0° – 5° contracture) was 92 % in group 1, 82 % in group 2, and 85 % in group 3 (Table 2). At the 90-day follow-up, the percentage of patients achieving the primary end point, maintenance of clinical success, was 91 % in group 1, 82 % in group 2, and 83 % in group 3, with no significant difference among groups (Table 2). The mean

($\pm$ SD) reduction in contracture from baseline to day 90 follow-up was 48.8° ($\pm 16.6^{\circ}$), 42.4° ($\pm 20.9^{\circ}$), and 44.4° ($\pm 17.3^{\circ}$) in groups 1, 2, and 3, respectively. Baseline contracture (low vs high severity) did not influence the outcome at 90 days. From baseline to day 90, MHQ scores improved from 72 to 93 in group 1, from 78 to 94 in group 2, and from 83 to 88 in group 3. There was no statistical difference in MHQ scores among groups at any time point, although there was a trend toward higher scores in patients with clinical success at day 90.

Adverse events are shown in Table 3 and are comparable with rates seen in previous studies [7–10]. The most common adverse events were swelling ($n=32$), bruising in finger/hand ($n=26$), and pain ($n=11$). There were four skin tears and one case of transient numbness (duration, 2 days). There were no serious adverse events.

Discussion

To date, the majority of literature on CCH injection for Dupuytren contracture has been limited to studies that follow the FDA-approved instructions outlining finger manipulation

Table 2 Clinical success 30 and 90 days after injection, stratified by group

Characteristic	Group			P value
	Group 1 (day 1)	Group 2 (day 2)	Group 3 (day 4)	
Clinical success, n/n (%) ^a (contracture 0° – 5° 30 days after injection)	11/12 (92)	9/11 (82)	11/13 (85)	0.4167
Clinical success, n/n (%) ^b (contracture 0° – 5° maintained to 90 days after injection)	10/11 (91)	9/11 (82)	10/12 (83)	0.8109

^a One patient had missing data on day 30

^b Three patients had missing data on day 90

Table 3 Adverse event profile for delayed manipulation after CCH injection for Dupuytren contracture

Adverse event	Frequency No. of patients (% of group)			Overall %	Duration (days)
	Group 1	Group 2	Group 3		
Swelling—finger/hand	13 (100)	9 (82)	10 (77)	86	6.06±3.39
Bruising—finger/hand	9 (69)	8 (73)	9 (69)	70	8.05±4.57
Pain—finger/hand	1 (8)	4 (36)	5 (38)	27	6±4.43
Blood blister	3 (23)	0	2 (15)	14	14±2.83
Lymphadenopathy	3 (23)	2 (18)	0	14	4.25±2.50
Skin tear	2 (15)	2 (18)	0	11	8.33±0.57
Itching—finger/hand	1 (8)	3 (27)	0	11	2.33±1.15
Armpit pain	0	1 (9)	0	3	11
Bruising—armpit	0	0	1 (8)	3	9
Numbness	0	0	1 (8)	3	2
Itching in armpit	0	0	1 (8)	3	2
Pain in palm	0	1 (9)	0	3	49

CCH collagenase clostridium histolyticum

for cord rupture on the day after injection. The rationale for a 24-h delay before finger manipulation in clinical trials was to allow time for sufficient collagen lysis of the treated cord. Additionally, the adverse event profile during clinical studies was of great importance, and thus a patient visit on the next day was preferable to ensure safety [7–10].

Requiring consecutive treatment days may be a burden for both surgeon and patient. Additionally, the swelling and pain associated with CCH injection is usually present by the day following injection, and then abates over the following 1 to 2 weeks. More time between injection and manipulation allows the severity of these side effects to diminish [8].

Although our study used a small cohort of patients, the data indicate that a delay of 2 or 4 days vs 1 day in finger manipulation for cord rupture after CCH injection showed a high degree of clinical success (reduction to 0°–5° contracture) at 90 days post-injection, with no significant difference in efficacy. Improved MHQ scores were seen in each of the CCH treatment groups, paralleling reduction in contracture.

Most importantly, the safety profile of patients treated in this study was comparable and consistent with the many clinical trial studies that eventually led to FDA approval [7–10].

Spontaneous ruptures can occur at any point between the time of injection and manipulation. As might be expected, we found that the patients with the greatest delay in manipulation, at 4 days, had the highest number of spontaneous ruptures. Though we did not see spontaneous rupture in the day 1 and day 2 cohorts, we have certainly noted these to happen at these time points in our clinical practice. In this study, skin tears only occurred in the patients manipulated on day 1 or day 2, despite making sure that no group had a disproportionate number of high-severity patients. Though the numbers were not sufficient to find a statistical difference, this trend supports

the potential benefit of allowing the amount of swelling to diminish prior to manipulation.

The main limitation of the study is the small patient cohort. Because of this, though we found no statistically significant difference in efficacy or MHQ score between groups, it is possible that there was a difference, and our study was underpowered to find it. Another limitation is that PIP joints were not included in this study and, as such, require further investigation to determine whether delayed finger manipulation after CCH injection is safe and effective for that joint. Furthermore, it may be likely that time points beyond 4 days for finger manipulation may be effective as well. However, it is difficult to know without further study when the enzymatically degraded cord might begin to consolidate and reorganize, making rupture more difficult. Future studies might be directed at defining when exactly this process may occur and how long manipulation can be delayed with reliable cord rupture and a high degree of safety.

This study showed that there is no significant difference in efficacy 90 days after CCH injection when finger manipulation for cord rupture is delayed until day 2 or day 4 after CCH injection. Delaying manipulation can be performed safely, without an increase in adverse events. Patients treated successfully with CCH injection for Dupuytren contracture after delayed manipulation showed improvement in their MHQ scores, demonstrating improved hand function with reduction of contracture.

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Conflict of Interest F. Thomas D. Kaplan is a consultant of Auxilium Pharmaceuticals and received research support for this study.

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Gregory A. Merrell declares no conflicts of interest.

Raymond Pahk declares no conflicts of interest.

Statement of Human and Animal Rights The study protocol was approved by local institutional review boards, and the research was carried out in compliance with the Declaration of Helsinki as currently amended.

Statement of Informed Consent All participants provided written informed consent and were free to withdraw at any time. Informed consent was obtained from all individual participants included in this study.

Clinical Trials Registration This study was registered on ClinicalTrials.gov. The identifier is NCT01226121. URL is <http://clinicaltrials.gov/ct2/show/NCT01226121>.

References

1. Badalamente MA, Hurst LC. Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg [Am]*. 2007;32(6):767–74.
2. Badalamente MA, Hurst LC, Hentz VR. Collagen as a clinical target: nonoperative treatment of Dupuytren's disease. *J Hand Surg [Am]*. 2002;27(5):788–98.
3. Black EM, Blazar PE. Dupuytren disease: an evolving understanding of an age-old disease. *J Am Acad Orthop Surg*. 2011;19(12):746–57.
4. Chung KC, Pillsbury MS, Walters MR, Hayward RA. Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. *J Hand Surg [Am]*. 1998;23(4):575–87.
5. Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N. Injectable collagenase clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. *J Hand Surg [Am]*. 2010;35(12):2027–38.
6. Hurst L. Dupuytren's contracture. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozl JA, editors. *Green's operative hand surgery*. 6th ed. Philadelphia: Churchill Livingstone; 2011. p. 141–58.
7. Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med*. 2009;361(10):968–79.
8. Leclercq C. Epidemiology. In: Tubiana R, Leclercq C, Hurst LC, Badalamente MA, Mackin EJ, editors. *Dupuytren's disease*. London: Martin Dunitz Ltd; 2000. p. 53–8.
9. Manning CJ, Delaney R, Hayton MJ. Efficacy and tolerability of Day 2 manipulation and local anesthesia after collagenase injection in patients with Dupuytren's contracture. *J Hand Surg Eur. Vol.*, May 29 2013 (Online First)
10. Witthaut J, Jones G, Skrepnik N, Kushner H, Houston A, Lindau TR. Efficacy and safety of collagenase clostridium histolyticum, a non-surgical treatment for adults with Dupuytren's contracture: short-term results from two open-label studies, in the US (JOINT I) and Australia and Europe (JOINT II). *J Hand Surg [Am]*. 2013;38(1):2–11.
11. Xiaflex® (collagenase clostridium histolyticum) [prescribing information]. Malvern, PA: Auxilium Pharmaceuticals, Inc.; December, 2013.
12. Xiapex® (collagenase clostridium histolyticum) [prescribing information]. Windsor, UK: Auxilium UK Limited; April, 2013.