Prospective Randomized Controlled Trial Comparing 1- Versus 7-Day Manipulation Following Collagenase Injection for Dupuytren Contracture

Dayne T. Mickelson, MD, Shelley S. Noland, MD, Andrew J. Watt, MD, Kathleen M. Kollitz, BS, Nicholas B. Vedder, MD, Jerry I. Huang, MD

**Purpose** To compare the efficacy, tolerance, and safety of manual manipulation at day 7 to day 1 following collagenase *Clostridium histolyticum* (CCH) injection for Dupuytren contracture.

**Methods** Eligible patients were randomized to manipulation at day 1 versus day 7 following CCH injection. Preinjection, premanipulation, postmanipulation, and 30-day follow-up metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint contractures were measured. Pain scores were recorded at each time point. Data were stratified per cohort based on primary joint treated (MCP vs PIP). Means were compared using paired and unpaired t-tests.

**Results** Forty-three patients with 46 digits were eligible and were randomized to 1-day (22 digits) and 7-day (24 digits) manipulation. For MCP joints, there were no significant differences in flexion contractures between 1- and 7-day cohorts for initial (47° vs 46°), postmanipulation (0° vs 2°), or 30-day follow-up (1° vs 2°) measurements. Premanipulation, the residual contracture was significantly lower in the 7-day group (23° vs 40°). For PIP joints, there were no significant differences between 1- and 7-day cohorts for initial (63° vs 62°), premanipulation (56° vs 52°), postmanipulation (13° vs 15°), or 30-day (14° vs 16°) measurements. There were no significant differences in pain or skin tears between the 2 groups. No flexor tendon ruptures were observed.

**Conclusions** The effectiveness of CCH in achieving correction of Dupuytren contractures was preserved when manipulation was performed on day 7, with no differences in correction, pain, or skin tears. These data suggest that manipulation can be scheduled at the convenience of the patient and surgeon within the first 7 days after injection. (*J Hand Surg Am.* 2014; 39(10):1933–1941. Copyright © 2014 by the American Society for Surgery of the Hand. All rights reserved.)

**Type of study/level of evidence** Therapeutic I.

**Key words** Collagenase *Clostridium histolyticum*, Dupuytren contracture, follow-up, injection, timing.
Progressive Dupuytren contractures have traditionally been treated through surgical interventions including needle aponeurotomy, segmental fasciotomy, limited fasciectomy, and radical dermatofasciectomy with skin grafting. However, with surgical treatment, patients often experience a prolonged recovery and risk complications including infection, wound problems, swelling, stiffness, nerve injury, and complex regional pain syndrome.\(^1\)\(^-\)\(^3\)\(^-\)\(^5\) Reported recurrence rates vary from 5% to 50%.\(^3\)\(^-\)\(^5\) Initially reported in 1996, collagenase \textit{Clostridium histolyticum} (CCH) is a purified mixture of 2 bacterial collagenases (AUX-I and AUX-II) from \textit{Clostridium histolyticum} that causes degradation of the collagen within the diseased Dupuytren cord.\(^7\) Several open-label and observational studies in addition to 2 double-blind placebo-controlled Phase III U.S. Food and Drug Administration (FDA) trials (Collagenase Option for the Reduction of Dupuytren’s [CORD I & CORD II]) have been conducted\(^7\)\(^-\)\(^12\) CORD I demonstrated a metacarpophalangeal (MCP) joint contracture reduction of 41\(\%\) and a proximal interphalangeal (PIP) contracture reduction of 29\(\%\) after CCH treatment compared with placebo (4\(\%\) and 5\(\%\) reduction, respectively).\(^8\) Consequently, CCH has emerged as a safe, effective, minimally invasive treatment for Dupuytren contracture.

Approved by the FDA for clinical use in February 2010, CCH is marketed in the United States as Xiaflex (Auxilium Pharmaceuticals, Malvern, PA).\(^13\) Current practice protocol consists of a CCH injection into 3 contiguous areas of the primary cord along the palm and digit. The patient then returns to the office or clinic 24 hours later to have the affected finger extended and the cord ruptured.\(^14\) This manipulation can be painful and carries a 13\(\%\) risk of skin tearing.\(^7\) The CORD I and II phase 3 trials, as well as all subsequent therapeutic studies, have followed this standard one-day manipulation protocol.\(^7\)\(^-\)\(^12\)

Because of scheduling issues, doctors are known to delay digit manipulation after CCH injection. Case series have reported no apparent difference between outcomes when manipulation is delayed.\(^15\)\(^-\)\(^17\) This aligns with our early anecdotal experience as we opted to delay the manipulation until clinic the following week. We have subjectively noted decreased edema and bruising, equivalent efficacy, and improved patient satisfaction. The purpose of this prospective, randomized controlled trial was to determine the effectiveness and possible side effects of postponing manipulation from day 1 to day 7 after CCH injection for Dupuytren contracture. We hypothesized that manipulation on day 7 would have similar efficacy and incidence of skin tears compared with manipulation on day 1.

Materials and Methods

Study design

This study was a prospective, randomized controlled trial. Patients were enrolled after meeting inclusion criteria (palpable cord with \(>20^\circ\) flexion contracture in any MCP or PIP joint). Subjects were randomized to receive manipulation on either day 1 or day 7 following CCH injection. Enrollment packets were labeled in advance with day 1 and day 7 stickers in equal distribution placed within the packet. The treating physician removed enrollment packets from a binder at random on the day of injection in a blinded fashion. Patients with more than one finger involved could have another digit injected after completion of initial treatment protocol. The second digit was enrolled and randomized separately. In patients with both MCP and PIP joint involvement, the treatment was first directed at the more severely contracted joint.

The primary endpoint was the degree of residual joint contracture of the primary joint 30 days after CCH injection. Based on the criteria in the CORD I and CORD II study, clinical success was defined as less than 5\(\%\) residual contracture at 30-day follow-up. The study’s secondary outcome measures included pain score, skin tear rate, premanipulation and postmanipulation joint contracture, and clinical improvement (as defined in the CORD trials as \(\geq 50\%\) reduction in joint contracture after 30 d relative to baseline).

All eligible patients were provided with informational materials and completed a written informed consent prior to beginning treatment. The subjects’ deidentified relevant health information and subjective and objective clinical study data were collected and entered into a secure database. The data were subsequently extracted for analysis. Our institution’s review board and human subjects division reviewed and approved the study.

Patient population

Eligible patients who presented for Dupuytren contracture treatment and met inclusion criteria between July 2012 and December 2013 at one institution were offered enrollment in the study. Subjects were eligible if they were healthy; were older than 18 years; had a distinctly palpable cord; and had an MCP or a PIP joint contracture, or both, of at least 20\(\circ\). Exclusion criteria consisted of patients with a...
history of collagen vascular disorder, a prior hypersensitivity reaction to collagenase, a neuromuscular disorder affecting the hand, or a previous treatment of the affected joint within 3 months of the study.

Assessment

A health questionnaire was administered at the initial clinic visit that included the patient’s health history, family history, and Dupuytren contracture treatment history. Data were collected at their initial clinical visit, their injection visit, their manipulation visit, and their 1-month follow-up visit (Fig. 1).

Standard goniometric measurements of the MCP and PIP joint flexion contractures were recorded for the affected digit in maximum active extension. Measurements of the PIP joint were performed with the MCP in a flexed position. These measurements were taken at the maximum active extension position at regular time points: preinjection, premanipulation, immediate postmanipulation, and 30-day follow-up. The attending physician performed all measurements.

Pain was logged on a standard 10-point visual analog scale (VAS) at the time of injection, just prior to manipulation, and at the time of manipulation. Subjects were monitored for adverse responses to injection and manipulation, including lymphadenopathy, allergic reaction, skin tear, and tendon rupture.
Injection and manipulation

On injection day, 0.58 mg of CCH was reconstituted per standard protocol. After obtaining consent, equal volumes of CCH were injected at 3 contiguous locations along the Dupuytren cord a few millimeters apart. Care was taken to inject directly into the cord and no deeper than 2 mm to avoid injection into the flexor tendon. For PIP joint contractures, injections were placed no more than 4 mm distal to the proximal digital flexion crease to minimize risk of flexor tendon injection. The 2 treating attending physicians, who are both board-certified hand surgeons with extensive experience with CCH injections, performed all injections and manipulations.

The subject then returned either 1 or 7 days after CCH injection depending on randomization. Interval history and premanipulation goniometric measurements were taken. All patients received manipulation regardless of premanipulation goniometric measurement. After obtaining consent, a digital nerve block in the palm were performed using 1% lidocaine. Gentle manipulation of the digit was performed with passive extension. Postmanipulation goniometric measurements were then taken. The patient was then referred to therapy for passive and active range of motion exercises, edema control, and fitting of a custom hand-based extension orthosis for nighttime use. If there was a skin tear, the wounds were covered with petroleum gauze and a gauze roll dressing. Under the supervision of a hand therapist, the patient performed daily home dressing changes. The patients were evaluated by the therapist twice weekly for wound care and range of motion exercises until the tear had fully healed. For PIP joint contractures, additional therapy visits were recommended, which have been demonstrated to improve contracture correction. Activity modification was recommended for the first week with no heavy lifting or gripping with the treated hand. Nighttime hand-based extension orthosis fabrication was recommended for 3 months.

Data analysis

The cohorts were stratified according to the primary joint (MCP vs PIP) treated. The chronologically collected mean contracture angles, pain scores, and skin tears were calculated. This data were compared using 2-tailed, paired and unpaired t-tests as appropriate, with an alpha set to 0.05.

RESULTS

A total of 46 digits in 43 patients were enrolled between July 2012 and December 2013. Three patients had a second digit enrolled. These subjects were randomized to 1-day (n = 22 digits) or 7-day (n = 24 digits) manipulation. Three patients did not complete 30-day follow-up but were included in final analysis of data gathered through the day of manipulation (Fig. 1). The study population consisted of 35 men and 8 women with mean age of 63 years and similar characteristics between the 2 groups (Table 1), except for the number of women. The most commonly affected digit was the little finger (n = 26; 57%) followed by the ring finger (n = 14; 30%). These cohorts were stratified into the primary joint treated: MCP joint (1-d, n = 12; 7-d, n = 13) and PIP joint (1-d, n = 10; 7-d; n = 11).

MCP joint treatment

Mean goniometric measurements and ranges were calculated for initial, premanipulation, postmanipulation, and 30-day follow-up MCP joint contractures in both the 1-day and the 7-day groups (Appendix A, available on the Journal’s Web site at www.jhandsurg.org). Near-full clinical correction (≤ 5°) of MCP joint contractures prior to manipulation was found in 4 of 13 digits in the 7-day group. This was not observed in the patients in the one-day manipulation group. Mean contracture reduction was similar between the 1-day (46°) and the 7-day (44°) groups (P = .74). Contracture correction was maintained at 30-day follow-up in both manipulation groups (Fig. 2). Clinical success was defined within the CORD trials as a contracture of 5° or less at 30 days postinjection. With this definition, our MCP joint clinical success was 91% for both the 1-day and the 7-day groups (10 of 11 subjects who returned for evaluation at 30 days in both groups). Clinical improvement (correction ≥ 50% as defined by the CORD trial) was 100% in both the 1-day and the 7-day MCP joint groups.

PIP joint treatment

Mean goniometric measurements and ranges were calculated for initial, premanipulation, postmanipulation, and 30-day follow-up PIP contractures in both the 1-day and the 7-day groups (Appendix B, available on the Journal’s Web site at www.jhandsurg.org). Mean contracture reduction was similar between the 1-day (50°) and the 7-day (46°) groups (P = .66). Contracture correction was maintained at 30-day follow-up in both manipulation groups (Fig. 3). Severe PIP joint contractures of 70° or greater were present in 9 of the 21 joints treated. Our clinical success (contracture ≤ 5° at 30-d follow-up) for PIP joint contractures was 40% (4/10) for the
1-day group and 36% (4/11) for the 7-day group. By the CORD trial criterion of clinical improvement (correction ≥ 50% at 30-d follow-up), our clinical improvement was 100% for the 1-day and 91% for the 7-day PIP joint groups.

**Pain and complications**

There were no significant differences in VAS score injection pain or manipulation pain between the 1-day and the 7-day groups (Fig. 4). The one-day patients reported slightly more premanipulation pain.

There were 6 skin tears in the 1-day group and 9 skin tears in the 7-day group (relative risk for 7 d, 1; 95% confidence interval [CI] 0.6–3.2). Within the one-day cohort, there were 3 tears for MCP joint and 3 for PIP joint contractures. Within the 7-day cohort, 3 tears were observed in MCP joint and 6 in PIP joint contractures (Fig. 5). All skin tears had healed uneventfully by the follow-up at 30 days. There were no flexor tendon ruptures in either group. There were no allergic reactions.

**DISCUSSION**

In this prospective, randomized controlled trial, we compared the clinical outcomes of patients manipulated at day 1 versus day 7 after CCH injection. This deviates from the manipulation at 24 hours following CCH injection protocols used in published clinical trials and observational studies, as well as the recommendation from the manufacturer and the approval from the FDA. Studies suggest that the CCH enzyme activity is confined to the local injection area and is active for less than 24 hours. The FDA-approved protocol was derived from this

---

**TABLE 1. Cohort Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1 d</th>
<th>7 d</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digits treated</td>
<td>22</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>65 (50–82)</td>
<td>64 (43–85)</td>
<td>.88†</td>
</tr>
<tr>
<td>Sex</td>
<td>M, 20; F, 1</td>
<td>M, 15; F, 7</td>
<td>.05‡</td>
</tr>
<tr>
<td>Hand dominance</td>
<td>R, 19; L, 2</td>
<td>R, 19; L, 3</td>
<td>.99†</td>
</tr>
<tr>
<td>Family history</td>
<td>11</td>
<td>8</td>
<td>.23‡</td>
</tr>
<tr>
<td>Previous fasciotomy in treated digit</td>
<td>2</td>
<td>2</td>
<td>.99‡</td>
</tr>
<tr>
<td>Previous needle aponeurotomy in treated digit</td>
<td>5</td>
<td>1</td>
<td>.90‡</td>
</tr>
<tr>
<td>Previous collagenase injection in treated digit</td>
<td>0</td>
<td>0</td>
<td>.99‡</td>
</tr>
</tbody>
</table>

*Comparison of study subject characteristics between 1-d and 7-d manipulation cohorts.
†t test.
‡Fisher exact test.

**FIGURE 2:** MCP joint is the primary joint treated. Mean contractures between cohorts at the 4 time points of the study.
scientific basis as the period when the cord is presumably most susceptible.13 However, many doctors delay manipulation for up to 7 days.

Manning et al15 reported the outcomes of 45 patients who underwent manipulation 48 hours after injection. Contracture improvements were similar to those reported in prior studies with greater than 90% reduction in MCP joint (n = 38) and 55% reduction in PIP joint (n = 8) contractures at 3- and 14-week follow-up. Hentz et al16 described success when the interval to manipulation was lengthened from 1 day (n = 25) to 7 days (n = 25) with comparable MCP joint corrections in 1-day (47° to 11°) and 7-day (46° to 9°) patients. Similar PIP joint outcomes were observed between 1-day (56° to 25°) and 7-day (53° to 16°) patients. In addition, spontaneous cord ruptures were more common in the 7-day group (58% vs 7% for the MCP joint; 33% vs 0% for the PIP joint), although the specific definition of spontaneous rupture was not defined.

For the treatment of MCP joints, this study found no difference in 30-day outcomes between the 1-day and the 7-day manipulations. However, at the time of manipulation, there was a significantly higher autodissolution effect within the 7-day cohort compared with the 1-day cohort. This was corroborated by the findings of other studies that noted at least partial correction of the injected finger without manual manipulation.15,16 Although all subjects were manipulated in this study, 31% had already reached near full extension (≤ 5°) upon their return visit. Manipulation was performed even in patients with partial or full extension to ensure complete rupture of the cord, because sometimes a palpable cord was still present.

Similarly, for the treatment of PIP joint contractures, there was no difference in 30-day outcomes
between the 1-day and the 7-day manipulation. There were no PIP joint contractures that corrected themselves without manipulation. This may be related to contracture of the volar plate and collateral ligaments. Therefore, even with cord rupture, most patients do not have spontaneous correction without manipulation of the PIP joint.

Based on the criterion for clinical success in the CORD studies, there was no significant difference between our cohorts. In comparison with the CORD outcomes, our primary MCP joint contracture improvement was also greater with a similar rate of clinical success (Fig. 7). We attribute these improved outcomes to the injection of local anesthesia prior to manipulations, which allowed the manipulation to be painless and more forceful. Local anesthetic injection was not part of the CORD protocols to avoid confounding the results with either the mechanical effect of the needle or of the injected volume of fluid on the cord.

Skin tears occur after 9% to 19% of manipulations. Hentz reported an increased number of skin tears with 7-day (3 of 25, 12%) versus 1-day (0 of 25, 0%) manipulation. The risk for skin tears

**FIGURE 5:** Skin tear frequency between cohorts. One-d and 7-d cohorts stratified based on primary joint treated. MCP vs PIP. RR, relative risk.

**FIGURE 6:** MCP joint outcomes compared with CORD I and CORD II trial outcomes at 30 days. Mean total change in contracture (°), percentage of contracture reduction, and percentage that achieved clinical success (as defined within the CORD trials as a contracture ≤ 5° at 30 d after injection).
increased with severity of contracture, specifically at the PIP joint. With PIP joints, we observed a higher rate of skin tears in both the 1-day (3 of 10 = 30%) and the 7-day (6 of 11 = 55%) groups. This is likely due to the increased number of severe PIP joint contractures of 70° or greater treated (9 of 21 PIP joints). With local anesthesia, our manipulations may also have been more aggressive compared with previously published reports. All tears healed uneventfully by 30 days with standard outpatient wound care. Practitioners must educate patients regarding the risk of a skin tear and its treatment.

We hypothesized that manipulation would be better tolerated at day 7 by allowing time for the swelling and digit tenderness to improve. There was a statistically significantly lower pain score in the 7-day group at premanipulation (VAS score 0.6 vs 1.4; \( P = .03 \)); however, the clinical relevance is trivial at these pain levels. We found no difference in VAS pain score during manipulation between the cohorts, because a digital nerve block was performed prior to manipulation. Although only anecdotal, 3 of the patients randomized to the 7-day group were happy with their results and refused randomization for treatment of a second digit, instead requesting a 7-day manipulation.

Limitations of this study include the its small study population collected from a single institution. A post hoc power analysis for a power of 0.8 determined that 1,005 patients would have to be enrolled to find a difference between the groups for the MCP joint and 500 patients would have to be enrolled for the PIP joint. Furthermore, this study could not be conducted in a blinded fashion. The use of local anesthetic in this trial probably allowed for the surgeon to apply more pressure for a longer period of time than in other studies, which may have led to improved outcomes than previously reported. Also, the use of anesthetic for manipulation likely confounded manipulation pain score comparison.

This study’s results suggest that, when treating Dupuytren contracture, the safety and effectiveness of manipulation after CCH injection is preserved at day 7. Delaying manipulation from 1 day to up to 7 days, based on the convenience of the patient and surgeon, is a feasible option when counseling and scheduling patients for CCH treatment of their Dupuytren contracture.

REFERENCES


### APPENDIX A. MCP Primary Joint Contracture Results

<table>
<thead>
<tr>
<th>MCP Primary Joint Treated</th>
<th>1-d Cohort (Mean [range])</th>
<th>7-d Cohort (Mean [range])</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of digits</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Initial contracture</td>
<td>47° (20°–80°)</td>
<td>46° (30°–75°)</td>
<td>.94</td>
</tr>
<tr>
<td>Premanipulation contracture</td>
<td>40° (20°–70°)</td>
<td>23° (0°–75°)</td>
<td>.04</td>
</tr>
<tr>
<td>Postmanipulation contracture</td>
<td>0° (0°–0°)</td>
<td>2° (0°–15°)</td>
<td>.14</td>
</tr>
<tr>
<td>30-d follow-up contracture*</td>
<td>1° (0°–10°)</td>
<td>2° (0°–10°)</td>
<td>.75</td>
</tr>
<tr>
<td>Initial premanipulation contracture (automatic rupture proxy)</td>
<td>6°</td>
<td>23°</td>
<td>.03</td>
</tr>
<tr>
<td>Initial 30-d contracture* (overall improvement)</td>
<td>46°</td>
<td>44°</td>
<td>.74</td>
</tr>
</tbody>
</table>

*Three patients lost to 30-d follow-up were excluded from analysis (1 from 1-d cohort [n = 11]; 2 from 7-d cohort [n = 11]).

### APPENDIX B. PIP Primary Joint Contracture Results

<table>
<thead>
<tr>
<th>PIP Primary Joint Treated</th>
<th>1-d Cohort (Mean [range])</th>
<th>7-d Cohort (Mean [range])</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of digits</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Initial contracture</td>
<td>63° (33°–110°)</td>
<td>62° (30°–105°)</td>
<td>.91</td>
</tr>
<tr>
<td>Premanipulation contracture</td>
<td>56° (10°–110°)</td>
<td>52° (20°–90°)</td>
<td>.70</td>
</tr>
<tr>
<td>Postmanipulation contracture</td>
<td>13° (0°–45°)</td>
<td>15° (0°–40°)</td>
<td>.81</td>
</tr>
<tr>
<td>30-d follow-up contracture</td>
<td>14° (0°–35°)</td>
<td>16° (0°–45°)</td>
<td>.67</td>
</tr>
<tr>
<td>Initial premanipulation contracture (auto rupture proxy)</td>
<td>7°</td>
<td>10°</td>
<td>.48</td>
</tr>
<tr>
<td>Initial 30-d contracture (overall improvement)</td>
<td>50°</td>
<td>46°</td>
<td>.66</td>
</tr>
</tbody>
</table>