Collagenase Clostridium Histolyticum Injections Can Be an Effective Alternative to Surgical Intervention in Moderate to Severe Dupuytren’s Contracture

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Collagenase Clostridium Histolyticum Injections Can Be an Effective Alternative to Surgical Intervention in Moderate to Severe Dupuytren’s Contracture

Abstract
Background: Dupuytren’s contracture is a common debilitating fibroproliferative disease of the hand. The current standard of care for moderate or severe Dupuytren’s is surgical fasciectomy. However, while surgery yields a significant initial correction of the contracture, the recurrence rate is as high as 71% bringing into question the efficacy of surgery and whether it is worth the surgical risk. Collagenase Clostridium histolyticum (CCH) injections were approved by the FDA in February 2010 for the treatment of Dupuytren’s contracture. This review evaluates the current literature that directly compares the efficacy of CCH injections to surgical fasciectomies.

Methods: An exhaustive literature search using MEDLINE-Ovid, Web of Science, and CINAHL was conducted. The following search terms were used: “Dupuytren’s contracture,” “collagenase,” and “fasciectomy.” The search was further narrowed to include only English-language articles. Inclusion criteria consisted of studies evaluating patients who initially present with a contracture of at least 30° and articles directly evaluating the post interventional contracture degrees between CCH injections and fasciectomies. Studies were excluded if their follow-up was less than 3 months and if multiple interventions were attempted during the study. The studies were then evaluated for their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Guidelines.

Results: Two studies were included in this systematic review, meeting both the inclusion and exclusion criteria. One case-control retrospective study followed 142 patients with Dupuytren’s contracture and found at latest follow-up that 46% of metacarpophalangeal (MCP) joints treated with CCH injections and 68% of MCP joints treated with fasciectomy maintained joint contracture. Another propensity score matched study evaluated 132 subjects and found that there was no significant residual contracture at MCP at latest followup between fasciectomy and CCH injection groups. Fasciectomies did slightly better at the proximal interphalangeal (PIP) joint compared to CCH injections.

Conclusion: CCH injections are a viable non-surgical option in the treatment of moderate to severe Dupuytren’s contracture. Surgical fasciectomies are the current standard of care, but are subject to high scrutiny due to the high level of recurrence that occurs post-procedurally, the relatively high risk of major adverse events, and increased incidence of comorbidities found in the population with Dupuytren’s contracture. It is difficult to discern how CCH injections compares to surgical fasciectomies, but early research, such as the aforementioned discussed, suggest they are strong alternatives based on relative efficacy, patient tolerance, and favorable safety profile. Further research will be needed to elucidate the clinical importance of CCH injections in the treatment of Dupuytren’s contracture.

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Collagenase Clostridium Histolyticum Injections Can Be an Effective Alternative to Surgical Intervention in Moderate to Severe Dupuytren’s Contracture

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A Clinical Graduate Project Submitted to the Faculty of

The School of Physician Assistant Studies

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Hillsboro, OR

For the Masters of Science Degree, August 13, 2016

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|| Biography ||

[Redacted for privacy]
Abstract

Background:
Dupuytren’s contracture is a common debilitating fibroproliferative disease of the hand. The current standard of care for moderate or severe Dupuytren’s is surgical fasciectomy. However, while surgery yields a significant initial correction of the contracture, the recurrence rate is as high as 71% bringing into question the efficacy of surgery and whether it is worth the surgical risk. Collagenase Clostridium histolyticum (CCH) injections were approved by the FDA in February 2010 for the treatment of Dupuytren’s contracture. This review evaluates the current literature that directly compares the efficacy of CCH injections to surgical fasciectomies.

Methods:
An exhaustive literature search using MEDLINE-Ovid, Web of Science, and CINAHL was conducted. The following search terms were used: “Dupuytren’s contracture,” “collagenase,” and “fasciectomy.” The search was further narrowed to include only English-language articles. Inclusion criteria consisted of studies evaluating patients who initially present with a contracture of at least 30° and articles directly evaluating the post interventional contracture degrees between CCH injections and fasciectomies. Studies were excluded if their follow-up was less than 3 months and if multiple interventions were attempted during the study. The studies were then evaluated for their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Guidelines.

Results:
Two studies were included in this systematic review, meeting both the inclusion and exclusion criteria. One case-control retrospective study followed 142 patients with Dupuytren’s contracture and found at latest follow-up that 46% of metacarpophalangeal (MCP) joints treated with CCH injections and 68% of MCP joints treated with fasciectomy maintained joint contracture. Another propensity score matched study evaluated 132 subjects and found that there was no significant residual contracture at MCP at latest follow-up between fasciectomy and CCH injection groups. Fasciectomies did slightly better at the proximal interphalangeal (PIP) joint compared to CCH injections.

Conclusion:
CCH injections are a viable non-surgical option in the treatment of moderate to severe Dupuytren’s contracture. Surgical fasciectomies are the current standard of care, but are subject to high scrutiny due to the high level of recurrence that occurs post-procedurally, the relatively high risk of major adverse events, and increased incidence of comorbidities found in the population with Dupuytren’s contracture. It is difficult to discern how CCH injections compares to surgical fasciectomies, but early research, such as the aforementioned discussed, suggest they are strong alternatives based on relative efficacy, patient tolerance, and favorable safety profile. Further research will be needed to elucidate the clinical importance of CCH injections in the treatment of Dupuytren’s contracture.

Keywords:
Dupuytren’s contracture, collagenase, fasciectomy
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Table 1: Characteristics of Reviewed Studies and GRADE profile

MCP……………………………………………………………………………….. Metatarsophalangeal
PIP………………………………………………………………….. Proximal Interphalangeal
CCH……………………………………………………………………….. Collagenase Clostridium Histolyticum
FDA………………………………………………………………………. Federal Drug Administration
GRADE……………… Grading of Recommendations Assessment, Development and Evaluation
Collagenase Clostridium Histolyticum Injections Can Be an Effective Alternative to Surgical Intervention in Moderate to Severe Dupuytren’s Contracture

BACKGROUND

Dupuytren’s contracture is a common and disabling fibroproliferative condition of the hand. This disease most often occurs in elderly males, with a mean diagnosed age of 55 years, and has a high prevalence in those with Northern European descent. Two million people are believed to have the condition in the United Kingdom alone.

Pathologically, Dupuytren’s contracture results in fibroblastic proliferation and uninhibited type III collagen deposition. The etiology of Dupuytren’s disease, however, is largely unknown. There is strong research that suggests an autosomal dominant trait with incomplete inheritance involving genes encoding a Wnt signaling pathway, which promotes cellular proliferation. Other research finds a strong correlation between those with diabetes, smoking, and heavy alcohol intake.

Deformities of the normal anatomy determine where the greatest contractures will occur. The skin pitting, normally seen earlier in the disease progression, is the result of involvement of the small vertical fibers. Abnormal development of the pretendinous band will result in metacarpophalangeal joint (MCP) contracture. Involvement of the lateral digital sheet causes flexion at the proximal interphalangeal (PIP) joint, while irregularity at the spiral cord results in both PIP and MCP contracture.

Those who seek medical attention for Dupuytren’s contracture often complain of difficulty with daily activities such as shaking hands, combing their hair, or catching their hand on their pocket. The current standard of care for moderate to severe Dupuytren’s contracture is surgical fasciectomy. While surgery yields a significant initial correction
of contracture and improved functionality, recurrence rates have been reported to be as high as 71%. Additionally, patients with Dupuytren’s contracture often have existing comorbidities (eg, advanced age, smokers, diabetes) that complicate surgery and/or make surgery a suboptimal option. Approximately 15% of cases of fasciectomies have associated major complications including: digital nerve injury (3.4%), digital artery injury (2%), infection (2.4%), and complex regional pain syndrome (5.5%).

Collagenase Clostridium histolyticum (CCH) injections are a new, nonsurgical alternative to the treatment of Dupuytren’s contracture. CCH consist of 2 collagenase proteins produced and isolated from Clostridium histolyticum that cleave the triple helical structure of collagen molecules. CCH injections were approved by the FDA in the United States for the treatment of Dupuytren’s contracture in February 2010 after multiple prospective, multicenter clinical trials demonstrated its short-term efficacy compared to placebo. When comparing the efficacy of CCH injections to the current standard of care (surgical fasciectomies), can CCH injections truly be a viable nonsurgical option for the treatment of Dupuytren’s contracture?

**METHODS**

An exhaustive literature search using MEDLINE-Ovid, Web of Science, and CINAHL was conducted. The following search terms were used: “Dupuytren’s contracture,” “collagenase” and “fasciectomy.” The search was further narrowed to include only English-language articles. Inclusion criteria consisted of patient’s initially presenting with a contracture of at least 30°, articles directly comparing the post interventional contracture degrees between CCH injections and fasciectomies. Studies
were excluded if their follow-up was less than 3 months and if multiple interventions were attempted during the study. The studies were then evaluated for their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Guidelines.  

RESULTS

The search generated 27 articles. Applying the aforementioned inclusion and exclusion criteria resulted in 2 articles. The first article, a case-control retrospective study reviewed the electronic records at a single academic hand surgical center from January 2009 through January 2013. The second, a propensity score-matched study found patients from one of seven practices in the Netherlands from August 2011 to March 2014 through a prospectively maintained database. See Table 1.

Muppavarapu et al

This case-control retrospective study aimed to compare the efficacy of collagenase injections with fasciectomy in the treatment of Dupuytren’s contracture. The electronic medical records were reviewed at a single academic hand surgical center from January 2009 through January 2013 by 3 surgeons who had previously participated in the CORD-2 trial and utilized a standardized data collection form. Primary outcome measurements was the resolution of joint contracture of 0-5° deficit of full extension. Secondary outcomes included measurements of the magnitude of residual flexion contracture and adverse events following each intervention. Statistical analysis was performed with the R statistical programming language using two sample t tests continuous data and chi-square test for categorical data.
A total of 142 patients were identified from the medical records, 81 underwent CCH injections while 61 underwent fasciectomies. Fourteen were excluded due to having secondary procedures performed. 1-year follow up data was available for 117 of the remaining 128 patients: 44 patients (94 joints) underwent fasciectomies and 73 patients (100 joints) underwent CCH injections. In the collagenase group, 51 out of the 100 joints met the primary endpoint at early follow-up. Additionally, 25 of those 51 (49%) joints continued to meet the primary endpoint goal at latest follow-up. In the fasciectomy group, 66 of the 94 (70%) joints met the primary endpoint at early follow-up. 56 of those 94 (60%) joints continued to meet the primary endpoint goal at latest follow-up. Individual analysis found that MCP joints responded more positively compared to PIP joints with both CCH injections and fasciectomies. Analysis of secondary outcomes found the mean residual joint contracture was less in the fasciectomy group compared to the CCH injection group at latest follow up (28.4° vs. 11.8°).¹⁵

The article also discussed adverse events between the two groups. Over 70% of the patients in the CCH injection group reported mild adverse effects including local edema, ecchymosis, and pain. Skin tearing occurred in 18% of patients following manual manipulation. No infections were reported. The fasciectomy group reported 1 case of digital neurovascular injury (2.2%), which required microsurgical primary repair. Two cases of deep wound infection were also reported; both of which resulted in subsequent irrigation, debridement, and oral antibiotics.¹⁵

The authors concluded that fasciectomies were more likely to have better correction of Dupuytren’s contracture at 1-year follow up. They also determined that both interventions had poorer results at the PIP joint compared to the MCP joint. They
theorized that surgical fasciectomy allowed for more complete excision of the cord tissue and resulted in slower contracture recurrence. The authors further went on to say that CCH injections remained a viable, non-operative treatment due to the fact that they were generally well tolerated by patients, had a more favorable safety profile, and allowed patients to return to work/activity sooner.\textsuperscript{15}

\textbf{Zhou et al}

The purpose of this study\textsuperscript{16} was to directly compare the early clinical results of CCH injections and limited fasciectomies with the use of propensity scoring in order to avoid confounding variables. Patients were gathered from August 2011 to March 2014 amongst 7 practice sites in the Netherlands using a prospectively maintained database\textsuperscript{16}.

CCH injections were administered according to the manufacturer’s instruction and dosage was limited to 0.20 mL and 0.25 mL. Treated fingers were manually manipulated 24-72 hours after the administered injection. Limited fasciectomy was performed with tourniquet exsanguination and loupe magnification. Cords were approved by Bruner type incisions with Z-plasties\textsuperscript{16}.

Originally, 397 patients were found for this study, which resulted in 218 being eligible after exclusion criteria. From this group, 66 CCH injection patients and 66 limited fasciectomy patients were considered matched through propensity scores\textsuperscript{16}.

At the MCP joint, no significant difference was found between the CCH injection group and limited fasciectomy groups residual contracture (13° vs. 6°, p=0.095). At the PIP joint, the degree of residual contracture was slightly better with limited fasciectomy (25° vs. 15°, p=0.010). Again this study found that both interventions performed better at the MCP vs. PIP\textsuperscript{16}. 
This study also included the Michigan Hand Outcomes Questionnaire as a measure for patient satisfaction as a secondary outcome. CCH was found to have significantly larger improvements than limited fasciectomies in overall satisfaction, activities of daily living, and work performance; fasciectomies only performing better in overall hand appearance.\textsuperscript{16}

All major adverse events were found to be in the fasciectomy group. Three events of tenosynovitis were reported and required further intervention as well as one example of nerve injury. The CCH injection group reported high levels of local mild adverse events: peripheral edema (74%), contusion (64%) and extremity pain (26%)\textsuperscript{16}.

The authors concluded that CCH injections were a viable option compared to limited fasciectomy at both the PIP and MCP joint. The authors had stated that patients who were willing to sacrifice maximal contracture correction for quicker recovery rate and avoidance of surgery would likely be happier with a CCH injection. They continued to state that their research is limited due to the length of follow-up and more long-term follow-up for recurrence would be need to better understand the efficacy of CCH injections\textsuperscript{16}.

**DISCUSSION**

Both studies\textsuperscript{15,16} found that CCH injection recipients were found to have more residual contracture on follow-up compared to surgical fasciectomy, however, Zhou et al\textsuperscript{15,16} found a more prominent statistically significant difference in contracture compared to the Muppavarapu et al. study\textsuperscript{15,16}. Additionally, both found that fasciectomies and CCH injections both performed worse at residual contracture at the PIP joint as compared to the MCP joint. The authors surmised that the recurrence following the CCH injections
was overall understanding because it simply disrupts the collagen cord and does not address the disease process itself, as opposed to open fasciectomy, in which more complete and precise excision is possible. Despite CCH injections performing worse in residual contracture compared to surgical fasciectomy, both studies concluded that CCH injections were a viable non-surgical option in moderate to severe Dupuytren’s Contracture. While patients in the CCH injection groups experience more frequent local reactions, it was overall tolerated well and had a favorable safety profile. Zhou et al speculated that the CCH injection group scored better in multiple categories in their Michigan Hand Outcomes Questionnaire, which indicated that hand function returned quicker with CCH injections compared to surgical fasciectomy.

Further research in CCH injections suggests its viability in the clinical setting. Early long-term evaluation of recurrence by the CORDLESS study finds that CCH injections show similar recurrence rates to surgical fasciectomy at 3-year and 5-year follow-ups. Both of these studies utilized the manufacture’s guidelines on how to administer the CCH injections, namely one injection per cord at each encounter, but newer research indicates that there is little risk involved for the patient with multiple injections and would require further investigation to determine if CCH injection efficacy is affected. Lastly, research in the United Kingdom showed that the current administration of CCH injections could be as high as 3 times more cost effective than surgical fasciectomy.

Several limitations were identified in these studies during appraisal. Both were retrospective case control studies and inherently have limitations as compared to randomized controlled trials. Secondly, each study had a limited population size: n=132.
in Zhou et al study\textsuperscript{16} and n=194 in the Muppavarapu et al. study\textsuperscript{15}. The length of follow-up was too short in the context of discussing Dupuytren’s contracture considering that the current standard of care, surgical fasciectomy, has a potential recurrence rate as high as 71\%.\textsuperscript{7} Zhou et al\textsuperscript{16} addresses this concern and state their deliberate intent to address early clinical outcomes because so few studies have compared CCH injections to surgical fasciectomies in their initial efficacy and associated risks. Additionally, this article’s findings could be confounded due to patients with both primary and recurrent disease in their population. Finally, several authors disclosed that they had been prior consultants to Pfizer and Sobi, two European manufactures of injectable collagenase, which inherently brings to question the quality of their research. The article states that support was received from Pfizer only in the form of injections that were provided for free. The Muppavarapu et al\textsuperscript{15} study had no standardized protocol for post intervention care including, hand splinting and hand therapy, creating an unknown variable in the results presented.

While these studies are both retrospective studies with inherent limitations and a small population size, they indicate that CCH injections may potentially be a viable tool in the treatment of Dupuytren’s contracture. Further randomized controlled trials with blinded clinical evaluators would be needed to further clarify the true efficacy of CCH injections compared to surgical fasciectomy.

**CONCLUSION**

CCH injections are a viable non-surgical option in the treatment of moderate to severe Dupuytren’s contracture. Surgical fasciectomies are the current standard of care,
but are subject to high scrutiny due to the high level of recurrence that occurs post-procedurally, the relatively high risk of major adverse events, and increased incidence of comorbidities found the population with Dupuytren’s contracture.$^{6-8}$ It is difficult to discern how CCH injections compares to surgical fasciectomies, but early research, such as the aforementioned discussed, suggest they are strong alternatives based on relative efficacy, patient tolerance, and favorable safety profile. Further research will be needed to elucidate the clinical importance of CCH injections in the treatment of Dupuytren’s contracture.
References


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<sup>a</sup>Did not account for post procedural splinting and hand therapy
<sup>b</sup>Small sample size
<sup>c</sup>Previous authors have consulted with manufacturing companies previously