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# **Is Collagenase Clostridium Histolyticum a Safe and Effective Treatment for Adult Patients with Dupuytren's Contracture?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not collagenase clostridium histolyticum is a safe and effective treatment for adult patients with Dupuytren's contracture.

**STUDY DESIGN:** Review of two double-blind, placebo-controlled randomized controlled trials and one cross-sectional study. All of these studies are published in English between 2009-2013.

**DATA SOURCES:** Two double-blind, placebo-controlled randomized controlled trials and one cross-sectional study found using PubMed.

**OUTCOMES MEASURED:** Each randomized controlled trial measured the ability to meet the primary end point and all secondary endpoints, percent decrease in degree of contracture, increase in range of motion, patient satisfaction, and recording of adverse events which played a significant role in patient quality of life.

**RESULTS:** Hurst et al and Gilpin et al showed a significant increase in range of motion and decrease in the flexion contracture after the use of collagenase clostridium histolyticum compared to the placebo. The NNT for Hurst et al was 2 while the NNT for Gilpin et al was 3. There were significantly more adverse effects in the collagenase group than placebo group such as contusion and injection site hemorrhage or pain. Hay et al found surgery was made more difficult in 4 out of 15 (26.7%) cases compared to the other 11 out of 15 (73.3%) cases in which surgery was not made more difficult.

**CONCLUSIONS:** Based on these three studies, collagenase clostridium histolyticum is a safe and effective treatment for adults with Dupuytren's contracture. The studies exhibited significant improvement in range of motion and decreasing the flexion contractures involved in Dupuytren's.

**KEY WORDS:** Collagenase clostridium histolyticum, Dupuytren's contracture

## INTRODUCTION

Dupuytren's contracture is a disorder in which collagen is produced in excess amounts and is deposited in the palmar aspect of the hands surrounding the tendons. With time, thick cords form and lengthen down the hand which leads to flexion contractures. These flexion contractures greatly limit the hand's ability to function.<sup>1</sup> This paper evaluates two double-blind, placebo-controlled trials and a cross-sectional study comparing the safety and efficacy of collagenase clostridium histolyticum in adult patients with Dupuytren's contracture.

Dupuytren's contracture is relevant to the physician assistant profession and to patients because of its incidence, cost, and effect on a patient's quality of life. The incidence of Dupuytren's contracture is 4% in the United States<sup>2</sup> and 3-6% of whites globally.<sup>1</sup> The cost for the fasciectomy surgical procedure which has historically been the standard of care treatment for Dupuytren's contracture is \$2102.56 while the cost for the collagenase clostridium histolyticum injection is \$1418.04, which makes the injection form of treatment cost 33% less than the fasciectomy.<sup>3</sup>

While the underlying etiology of Dupuytren's contracture is unknown, genetics are thought to play a role since a positive family history is common in patients with Dupuytren's contracture.<sup>2</sup> Recurrence is a common process with Dupuytren's contracture no matter the treatment. Recurrence usually occurs as a slow process over a few years.

There are different treatment modalities for Dupuytren's contracture. Dupuytren's contracture can be treated via needle aponeurotomy, open fasciectomy/fasciotomy surgical procedures, or via collagenase clostridium histolyticum injection.<sup>4</sup> Currently, the standard of care for Dupuytren's contracture is an open fasciectomy. Collagenase clostridium histolyticum is

being proposed as a new treatment because it is less invasive, carries less risk than the surgical option, and is more cost-effective than an open fasciectomy.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not collagenase clostridium histolyticum is a safe and effective treatment for adult patients with Dupuytren's contracture.

## **METHODS**

The population in the 2 randomized, double-blind, placebo-controlled trials and 1 cross-sectional article utilized in this review includes adult patients with Dupuytren's contracture. The intervention for the treatment group was 0.58 mg collagenase clostridium histolyticum injection. The comparison used in patients who were in the control group was a placebo injection of 10mM tris plus 60mM sucrose. The outcomes measured were the safety and efficacy of collagenase clostridium histolyticum which were measured by the ability to meet the primary and all secondary endpoints, increase in range of motion, recording of adverse events, and surveys on the distortion of anatomy completed by surgeons who performed open fasciectomy procedures on recurrent Dupuytren's cords after previously receiving collagenase clostridium histolyticum. All of these have a significant effect on the quality of life for patients.

Keywords used in searches for these articles on PubMed were Dupuytren's disease, clostridial collagenase, Dupuytren's contracture, collagenase clostridium histolyticum, and Dupuytren's. The articles chosen were published in English. Inclusion criteria used for selection of the patients in these studies were healthy males and female over age 18 with Dupuytren's contracture, women who were either postmenopausal or used contraception,

metacarpophalangeal (MCP) contractures between 20° and 100° or proximal interphalangeal (PIP) contractures between 20° and 80°, and the inability to place affected finger and palm flat on a table at the same time. Exclusion criteria included women who were breastfeeding or pregnant, people with bleeding disorders, recent stroke, previous treatment to the affected digit within 90 days, use of a tetracycline derivative within 14 days, anticoagulant within 7 days, allergy to collagenase, or anyone with chronic muscle, neurologic, or neuromuscular disorder that affects the hands. The author searched the articles via PubMed and selected them based on their relevance to the safety and efficacy of collagenase clostridium histolyticum and if the articles included outcomes that matter to patients. The statistics reported or used in the articles were relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), confidence interval (CI), and p-values. Table 1 displays the above mentioned information.

**Table 1- Demographics & Characteristics of included studies**

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Hurst <sup>1</sup> (2009)	Double blind RCT	308	62.7 +/- 9.5	Patients over 18, women who were either postmenopausal or used contraception, MCP contractures between 20° and 100° or PIP contractures between 20° and 80°, inability to put finger and palm flat on table at same time	Pregnant or breastfeeding women, bleeding disorders, recent stroke, previous treatment within 90 days of affected finger, use of tetracycline derivative within 14 days of study, use of anticoagulant within 7 days of study, allergy to collagenase, patients with chronic muscle, neurologic, or neuromuscular disease to hands	2	0.58 mg collagenase clostridium histolyticum plus 0.25 mL sterile diluent for MCP joints or 0.20 mL sterile diluent for PIP joints

Gilpin <sup>4</sup> (2010)	Double blind RCT	66	63.8 +/- 9.0	Patients over 18, women who were either postmenopausal or used contraception, MCP contractures between 20° and 100° or PIP contractures between 20° and 80°, inability to put finger and palm flat on table at same time	Pregnant or breastfeeding women, bleeding disorders, recent stroke, previous treatment within 90 days of affected finger, use of tetracycline derivative within 14 days of study, use of anticoagulant within 7 days of study, allergy to collagenase, patients with chronic muscle, neurologic, or neuromuscular disease to hands	2	0.58 mg collagenase clostridium histolyticum + lyophilized tris + sucrose
Hay <sup>5</sup> (2013)	Cross sectional	15	n/a	Adult patients with Dupuytren's contracture recurrence after a previous collagenase clostridium histolyticum injection	Adult patients with Dupuytren's contracture with no prior treatment with collagenase clostridium histolyticum	0	n/a

## OUTCOMES MEASURED

The outcomes measured include ability to meet the primary end point and all secondary endpoints, percent decrease in degree of contracture, increase in range of motion, and recording of adverse events. The primary end point was a reduction of the joint contracture to 0-5° of full extension by day 30 post-injection. Secondary end points were two different times used to compare recurrence of the contracture. These two times were 30 days after the first injection and 30 days after the last injection.<sup>1,4</sup>

Changes in range of motion were measured by using the finger goniometry technique. These angles were measured during screening prior to starting the treatments, during treatment, and 90 days after treatment. To monitor safety and adverse events, patients were monitored for 60 minutes after the injection. In addition, their vital signs were monitored before injection, for 60 minutes following injection, on days 1, 7, 30, and 90. Blood and urine samples were obtained at screening, 30 and 90 days after injection.<sup>1</sup>

## RESULTS

Hurst et al<sup>1</sup> and Gilpin et al<sup>4</sup>, both double-blind placebo-controlled randomized controlled trials evaluated the safety and efficacy of collagenase clostridium histolyticum on Dupuytren's contractures by comparing experimental groups to control groups. The experimental groups received the collagenase clostridium histolyticum injection into the affected anatomy whereas the control groups received a placebo injection into the affected anatomy.

Hay et al<sup>5</sup>, a cross sectional study examined the distortion of anatomy in the area collagenase clostridium histolyticum was injected in patients who had recurrence of Dupuytren's contracture after receiving the injection. The study gathered information by surveying surgeons performing the open fasciectomy on these patients who received the collagenase clostridium histolyticum injection previously.

**Table 2. Efficacy of collagenase clostridium histolyticum in the treatment of Dupuytren's contracture**

Study	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)	P-value	Confidence Interval (CI)
Hurst <sup>1</sup> (2009)	8.41	0.572	2 patients	<0.001	95% (primary end point) 99%



					(secondary end point)
Gilpin <sup>4</sup> (2010)	8.25	0.396	3 patients	<0.001	n/a
Hay <sup>5</sup> (2013)	n/a	n/a	n/a	n/a	n/a

**Table 3. Comparison of MCP and PIP range of motion (ROM) before and after treatment**

Study	MCP ROM before treatment	MCP ROM after treatment	PIP ROM before treatment	PIP ROM after treatment
Hurst <sup>1</sup> (2009)	43°	84°	46°	75°
Gilpin <sup>4</sup> (2010)	40°	80°	41°	73°
Hay <sup>5</sup> (2013)	n/a	n/a	n/a	n/a

Hurst et al<sup>1</sup> evaluated the efficacy in numerous ways. The collagenase group met the primary and secondary end points significantly more than the placebo group ( $p < 0.002$ ). In addition, contractures were returned to 0-5° of full extension in 64% of joints in the collagenase group compared to 6.8% in the placebo group. Most of the joints in the collagenase group that did not meet the primary or secondary end points did not receive all of the injections. The most common reason for this was that there was no palpable cord present. Table 3 illustrates the change in range of motion before and after treatment with collagenase clostridium histolyticum. A median of 56 days was required to attain the primary end point. Out of all the joints that met the primary end point, none had recurrence by day 90.<sup>1</sup>

Additionally, 96.6% of patients who received the collagenase injection experienced at least 1 adverse effect compared to 21.2% in the placebo group. Significantly more injection and manipulation-related events such as contusion, injection site hemorrhage, injection site pain, pain in upper extremity, tenderness, ecchymosis, injection site swelling, pruritis, skin laceration, LN enlargement and pain on palpation, lymphadenopathy, erythema, blister, injection-site pruritis and axillary pain were noted in the collagenase group ( $p < \text{or equal to } 0.02$ ). Most were mild to moderate in severity and resolved without intervention within a median of 10 days. Of

note, 20 patients in experimental group and 2 in placebo group experienced severe reactions such as peripheral edema, injection site pain or hemorrhage, contusion, tenderness, or tendon rupture. There were no deaths or nerve injuries reported.<sup>1</sup> Therefore, the NNT was calculated as 2 (Table 2), which means that for every 2 patients treated with collagenase clostridium histolyticum, one more patient will have improvement of their condition compared to the control.

In the 12 month double-blind phase of Gilpin et al<sup>4</sup>, the collagenase-injected group experienced significantly reduced contractures compared to the placebo group (44.4% reduction vs 4.8% reduction,  $p < 0.001$ ). In the experimental group, it took a mean of 57 days to reach the primary end point and a mean of 1.5 injections. Most of the joints in the collagenase group that did not meet the primary end point did not receive 3 injections into the affected cord, most often because there was “no palpable cord to inject.”<sup>4</sup> When analyzing data from the entire 12 month study, 134 Dupuytren's cords were injected with collagenase. From those, 62 were MCP joint cords and 72 were PIP joint cords. Additionally, 42 of the 62 (67.7%) MCP joints and 26 of 72 (36.1%) PIP joints had a reduction in contracture after the last injection.<sup>4</sup>

Recurrence was defined in the study as an increase in joint contracture to 20° or greater in the presence of a palpable cord at any time during the study in joints that had a reduction in contracture to 0° to 5° of normal. No joint met these criteria by the end of the study, which lasted for 12 months.<sup>4</sup>

Gilpin et al<sup>4</sup> measured safety by noting the adverse events experienced by the patients. All (100%) of the patients who got the collagenase injection reported at least one adverse effect compared to 8 out of 21 (38%) patients in the placebo group. Patients who were injected with collagenase had significantly higher rates of edema, contusion, extremity pain, injection site pain

or hemorrhage, and lymphadenopathy compared to the placebo group ( $p < 0.05$ ). Most adverse effects were mild or moderate and resolved within a median of 8-10 days. One serious adverse effect experienced by a patient was a flexion pulley rupture. No arterial, nerve, or tendon injuries were reported during the 12 month study.<sup>4</sup> The NNT was calculated as 3 (Table 2) which means that for every 3 patients treated with collagenase clostridium histolyticum, one more patient will have improvement in their condition compared to the control.

Hay et al presented the results as continuous data in the form of 5 grades which represented the level of difficulty in performing open surgical procedures on patients who received the collagenase clostridium histolyticum injection previously. Grade 1 was defined as easier than a primary operation. Grade 2 was equivalent to a primary operation in difficulty. Grade 3 was harder than a primary operation, grade 4 was equivalent to a revision operation, and grade 5 was harder than a revision operation. Out of 15 cases, 9 were rated as grades 1 or 2 of difficulty. Additionally, 2 cases were grade 4 difficulty and 4 cases were rated as grade 5 difficulty.<sup>5</sup>

For ease of understanding, these results were converted to dichotomous data in this review. The data was converted into the following two groups: surgery was made more difficult as a result of the collagenase clostridium histolyticum and surgery was not made more difficult as a result of the collagenase clostridium histolyticum injection. Surgery was made more difficult in 4 out of 15 (26.7%) cases compared to the other 11 out of 15 (73.3%) cases in which surgery was not made more difficult from the collagenase injection. The respondents described the findings of anatomy in the 4 cases which were more difficult. The anatomy was described as “thick” and “hard” scars that made dissecting difficult.<sup>5</sup>

## DISCUSSION

Collagenase clostridium histolyticum is FDA approved for the treatment of Dupuytren's contracture and for men age 18 and older, Peyronie's disease.<sup>6</sup> Often any new product requires an extended period of time for health care providers to integrate it into their practice. Subsequently, it is much easier to find a healthcare provider who uses collagenase clostridium histolyticum in an urban setting compared to a rural area due to the prevalence of physicians. This is improving with time. In addition, while collagenase clostridium histolyticum is more affordable than the open fasciectomy, it is still expensive if insurance fails to cover it or if a patient is uninsured. This is another potential barrier to care. The sponsor of clostridium collagenase histolyticum, Auxilium Pharmaceuticals, offers a co-pay reimbursement program and a patient assistance program which may help deflect some of the cost if a patient qualifies. It is important to note that collagenase clostridium histolyticum is contraindicated in patients who have a history of hypersensitivity to collagenase. Additionally, since these studies were performed on adults age 18 and over, it is not known if collagenase clostridium histolyticum is safe to use in patients under age 18.<sup>6</sup>

Gilpin et al<sup>4</sup> highlights the importance of continued follow-up over the next several years with patients in the study to monitor the affected cord. Hurst et al<sup>1</sup> expressed the importance in assessing patient compliance with wearing custom fitted splints after the injection every night for up to 4 months. Hay et al<sup>5</sup> noted the importance of evaluating more patients but explained there are a limited number of patients who have undergone surgery after receiving collagenase injections which limited their study. Hay et al<sup>5</sup> also noted the potential of subjectivity in the responses from the healthcare providers they surveyed as well as the subjectivity of noting distortion of anatomy during the surgeries performed.

## **CONCLUSION**

Based on this systematic review of the chosen studies, collagenase clostridium histolyticum is a safe and effective treatment for adult patients with Dupuytren's contracture. The data in these studies represents the efficacy and safety of collagenase clostridium histolyticum. Future areas of study in long-term follow up would be beneficial to monitor continued patient satisfaction and recurrence. Additionally, it would be beneficial to include larger sample sizes in future studies.

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