

Treatment of Single Cords in Dupuytren Disease with Collagenase *Clostridium Histolyticum*: Study of a Cohort with Follow-up at 1 Year

Tratamiento de cuerdas únicas en la enfermedad de Dupuytren con colagenasa de *Clostridium histolyticum*: estudio de una cohorte con seguimiento a 1 año

Ignasi Manent Bistué¹ Sonia Suau Mateu² Ana Maria López Louzao¹ Pier Claudio Caputo¹
 Víctor Antonio Rodríguez Roiz¹ Ignasi De Villasante Jirón¹ Montserrat Del Valle Jou²

¹Residency in Traumatology and Orthopaedics, Fundació Hospital de l'Esperit Sant, Universitat de Barcelona, Santa Coloma de Gramanet, Barcelona, Spain

²Hand Surgery Unit, Fundació Hospital de l'Esperit Sant, Universitat de Barcelona, Santa Coloma de Gramanet, Barcelona, España

Address for correspondence Ignasi Manent Bistué, MD, Residente de Traumatología y Ortopedia, Fundació Hospital de l'Esperit Sant, Universitat de Barcelona, Avenida Mossèn Pons i Rabadà, s/n, 08923, Santa Coloma de Gramanet, Barcelona, España (e-mail: ignasi.manent@gmail.com).

Rev Iberam Cir Mano 2018;46:34–39.

Abstract

Objective The purpose of the present work was to assess the effectiveness of collagenase *Clostridium histolyticum* in patients with Dupuytren disease with single cords and assess the recurrence rate in the first year after the treatment.

Material and Methods In this classic cohort study, a total of 53 patients (50 of them male) with a mean age of 68 years were studied who had been diagnosed with Dupuytren disease located in the metacarpophalangeal joint, in single cords, with more than 40° of extension loss. They were given an injection of collagenase *C. histolyticum* and later manipulation under locoregional anesthesia. The loss of extension was evaluated after a week and at the 1st, 3rd, 6th and 12th months. The effectiveness was analyzed with basis on the results of the Student t-test for paired data, as well as those of the effect size (ES) test.

Results An important and statistically significant correlation was found for the loss of cord extension in the metacarpophalangeal joint ($t = 32.113$; $p < 0.01$; $ES = 4.11$; standardized response mean [SRM] = 4.15).

Conclusion Collagenase is an injectable treatment, which is not very aggressive compared with surgery and is effective for the loss of extension in the metacarpophalangeal region secondary to single cord in Dupuytren disease during the first year.

Keywords

- ▶ collagenase
- ▶ *clostridium histolyticum*
- ▶ injection
- ▶ extension
- ▶ dupuytren disease

Resumen

Objetivo Valorar la efectividad de la colagenasa de *Clostridium histolyticum* en los pacientes con enfermedad de Dupuytren con cuerdas únicas y valorar el índice de recidivas a lo largo del primer año.

Método En este estudio de cohortes clásico se estudió un total de 53 pacientes (50 varones), con una edad media de 68 años, con el diagnóstico de enfermedad de Dupuytren localizada en la articulación metacarpofalángica, en cuerdas únicas con más de 40° de pérdida de extensión. Fueron sometidos a la inyección de colagenasa de *Clostridium histolyticum* y posteriormente manipulación bajo anestesia locoregional. La pérdida de extensión fue evaluada a la semana y al primer, tercer, sexto y doceavo meses. La efectividad se analizó en base al test T-student para datos apareados y el tamaño del efecto (ES).

Resultados Se objetivó una importante corrección estadísticamente significativa de la pérdida de extensión para cuerdas en articulación metacarpofalángica [$t = 32.113$; $p < 0.01$; $ES = 4.11$; $SRM = 4.15$].

Conclusión La colagenasa es un tratamiento inyectable, poco agresivo en comparación a la cirugía y efectivo durante el primer año para la pérdida de extensión en región metacarpofalángica, secundaria a las cuerdas únicas en enfermedad de Dupuytren.

Palabras-clave

- ▶ colagenasa de *clostridium histolyticum*
- ▶ inyección
- ▶ extensión
- ▶ enfermedad de dupuytren

Introduction

Until 2010, the treatment for Dupuytren disease was predominantly surgical, with medical treatment usually not effective (vitamins A and E,¹ colchicine, steroid injections,² radiotherapy,³ verapamil, nifedipine,⁴ etc). In 2010, the Food and Drug Administration (FDA) and subsequently, in 2011, the European Medicine Agency (EMA) approved the use of collagenase *Clostridium histolyticum* (CCH) for patients with palpable single cords, since it was found to be effective in phases 2 and 3 of clinical trials when compared with placebo,^{5,6} releasing the cords obtained through aponeurotomy.⁷ The benefits of CCH in the treatment of Dupuytren disease have been demonstrated in clinical trials, which have led to its widespread use in the United States and in some countries of the European Union over the last few years,⁸⁻¹⁰ being used in the treatment of palpable single cords.

Through imaging tests, such as magnetic resonance imaging, the changes in the fascia caused by CCH, which include the discontinuity of the fascia, a decrease in thickness and a decrease in the intensity of the signal, are translated into images.¹¹ Many of the current results on the effectiveness of CCH in the metacarpophalangeal joint are still in the short and medium term following the injection, and recurrences of the loss of extension of around 7% at 12 months of follow-up are described,¹² and up to 39% at the 5-year follow-up.¹³ In spite of this, recurrences can be effectively treated with multiple injections of CCH at separate times.¹⁴ Likewise, the treatment of Dupuytren disease with CCH could be an alternative to surgically treated extension loss, in which patients have undergone a failed fasciectomy.^{15,16}

The aim of this study is to evaluate the effectiveness of CCH to treat palpable single cords with metacarpophalangeal joint involvement in patients with Dupuytren disease during

the first year after injection, and the development of possible secondary complications. The protocol used in our center is also described.

Material and Methods

Study Population

All the patients who attended our clinic between 2012 and 2016 were included in the study. Recruitment was performed exclusively by M.d.V. and was performed based on patients referred to our center's hand surgery unit from the primary care service of Santa Coloma de Gramanet.

We recruited a maximum of 21 patients per year, due to a restriction required by our center's scientific committee, fulfilling the following criteria:

- a) presence of unilateral or bilateral Dupuytren disease with involvement of a single radius,
- b) loss of extension greater than 40° in the affected joint,
- c) without the presence of associated joint stiffness and
- d) over the age of 18

The exclusion criteria were: breastfeeding, pregnancy, blood coagulation disorders, recent myocardial infarction, previous treatment of the joint 90 days before starting the study, use of anticoagulants 7 days before the beginning of the study, use of tetracycline derivatives 14 days before the beginning of the study and allergy to CCH or hypersensitivity to any of the excipients included in the section.

None of the patients who were included in the sample had previously received treatment for Dupuytren disease.

Individuals were included in the cohort consecutively.

Clinical Design

This is a classic cohort study with measurements before and at 1 year posttreatment.

Intervention

The patients included in the study signed the normal informed consent for the intervention, including a specific consent authorizing treatment with CCH.

All patients were evaluated regarding the degree of loss of extension of the affected radius, confirming that this was due to a cord corresponding to the entity of Dupuytren, and later CCH was injected into the cord, in the metacarpophalangeal zone. In each cord, 0.25 mL of a solution obtained from the dissolution of 0.58 mg of enzyme with 0.39 mL of solvent mixture (water, calcium chloride dihydrate and sodium chloride) was injected. All patients were seen after 24 hours in the same center for digital manipulation after the application of local anesthesia to median and ulnar nerves in the wrist with 10 ml of lidocaine at 2%. All patients wore a nighttime passive extension finger splint for 1 month, with an option of wearing it for another 2 months as support.

The patients were monitored after 1 week of digital manipulation, and then again at 4 weeks, and at 3, 6 and 12 months.

Instruments and Measurements

The main variable of our study was the loss of extension achieved in the joints affected by palmar retraction at the end of the first year after treatment, measured in degrees. As a secondary variable, the appearance of adverse effects in the course of the treatment with the technique was studied.

To measure the loss of extension, a standard manual goniometer was used. Both before the treatment and in all the follow-up visits, the loss of extension was always assessed by the same observer in all the individuals of the sample, placing the manual goniometer in the dorsal region of the joint studied in the maximum extension position tolerated and placing it on the metacarpal and proximal distal region of the first phalanx.

Cutaneous wounds, regional lymph nodes and tendon ruptures were considered complications.

Statistical Analysis

For the statistical analysis, descriptive statistics were used to represent the demographic characteristics of the sample, the results of the main and secondary variables. Using the Shapiro-Wilk test, the normality of the sample was studied. To assess the statistical significance of the differences observed in the main variable before and after the injection, the Student t-test was used for paired data with a level of significance of 0.05. We defined the null hypothesis (H_0) as no existing differences in the extension deficit before and after 1 year of CCH injections, and the alternative hypothesis (H_1) being the cases in which differences did exist in the deficit of joint extension before and after 1 year of the injection.

The effect size (ES) was calculated for the loss of extension in the first follow-up, after 1 year, in relation to that prior to treatment with the following formula: $ES = X_{cambio}/DS_{pre}$, in which X was the mean of the change after the first year of treatment in relation to that prior to treatment, and DS was the standard deviation before treatment. The effect size was

considered low if the result was lower than 0.5, medium if it was between 0.5 and 0.8, and high if it was greater than 0.8.¹⁷ Likewise, the standardized response mean (SRM) was calculated with the formula $SRM = X_{cambio}/DS_{cambio}$, in which Xcambio was the mean of the change after the first year of treatment in relation to that prior to treatment, and DS cambio was the standard deviation of the differences after the first year of treatment in relation to those prior to treatment.

For statistical analysis, the Statistical Package for Social Sciences (SPSS) v20 software (IBM Corp., Armonk, NY, USA) was used.

Results

The sample was initially composed of a total of 57 individuals, of which 4 dropped out during follow-up, with a total of 53 completing follow-up, of which 50 were male (94.34%) and 3 were female (5.66%), in whom a total of 60 joints were treated. The mean age (standard deviation) was 67.97 (7.58) years. In seven patients, both hands were treated for single cords. **Table 1** summarizes the demographic characteristics of the sample studied.

The mean (standard deviation) of the degrees of loss of metacarpophalangeal extension before CCH injection was

Table 1 Baseline characteristics of the cohort studied

Gender	N* (%)
→Male	50 (94.34)
→Female	3 (5.66)
Age	Mean (SD)**
	67.97 (7.58)
Dominant hand	N (%)
→Right	52 (98.11)
→Left	1 (1.89)
Treated hand	N (%)
→ Right	33 (55.00)
→ Left	27 (45.00)
Treated radius	N (%)
→ 4° radius	33 (55.00)
→ 5° radius	24 (40.00)
→ 3° radius	3 (5.00)
Risk factors of Dupuytren	N (%)
→ Tobacco use	24 (45.28)
→ Alcohol consumption	11 (20.75)
→ Diabetes mellitus	19 (35.84)
→ Concomitant neoplasia	16 (30.19%)
→ Ledderhose disease	2 (3.77%)
→ Peyronie disease	1 (1.89%)
→ Epilepsy under treatment	1 (1.89%)

Abbreviation: SD, Standard deviation.

Note: *N: Sample size for each of the sample characteristics.

Table 2 Results of the loss of extension before the treatment and at the end of follow-up

	Mean	SD	95%CI	
Loss of extension (pre-treatment)	51.92	12.35	48.52	55.32
Loss of extension (1 year)	1.16	3.10	0.31	2.01
Change difference (pre-1 year)	50.75	12.24	47.38	54.12
ES	4.11			
SRM	4.15			

Abbreviations: 1 year, measurement after one year of treatment; ES, effect size = mean change/SD pre-treatment; 95%CI, confidence interval within 95% of the mean; pre-1 year, change in loss of extension from pre-treatment to 1 year later; pre-treatment, measurement before treatment; SD, Standard deviation; SRM, standardized response mean = mean change/SD of the change.

Notes: Loss of extension in degrees. Effects of ES or SRM treatment > 0.8 are considered a clinically significant improvement. Note that the 95%CI of the average of the change does not include the “zero” that constituted the null hypothesis ($H_0 = 0$) so it was concluded that the average of the change was significant ($t = 32.11, p < 0.01$).

51.92° (12.35). The treatment caused significant improvement in the loss of joint extension. In the control performed 12 months after the CCH injection, the mean (standard deviation) of degrees of extension loss in the metacarpophalangeal joint was 1.16° (3.10). The differences resulted in a statistically significant improvement ($t = 32.11, p < 0.01$). The effect size (ES) obtained in the progression of the sample in the first year of the study was high (> 0.8). The SMR was also high. The statistical study is summarized in ►Table 2.

All patients experienced a decrease in the extension defect compared with before the manipulation, and 59 of the treated joints (98.34%) showed no relapse at the annual

check-up. In our cohort, a relapse was experienced with a 20° loss of extension at the annual check-up.

Four of the joints treated (6.66%) with the injection experienced spontaneous stretching before performing manipulation under anesthesia in the operating room.

►Fig. 1 shows progression during the first year for the mean extension loss for the metacarpophalangeal joint.

Of the 60 joints treated, 34 (56.66%) suffered complications. In the first month check-up, 100% of these complications had already resolved spontaneously.

In our series, no allergic reaction was reported, nor did we find flexor tendon ruptures. The adverse reactions recorded in our series are summarized in ►Table 3.

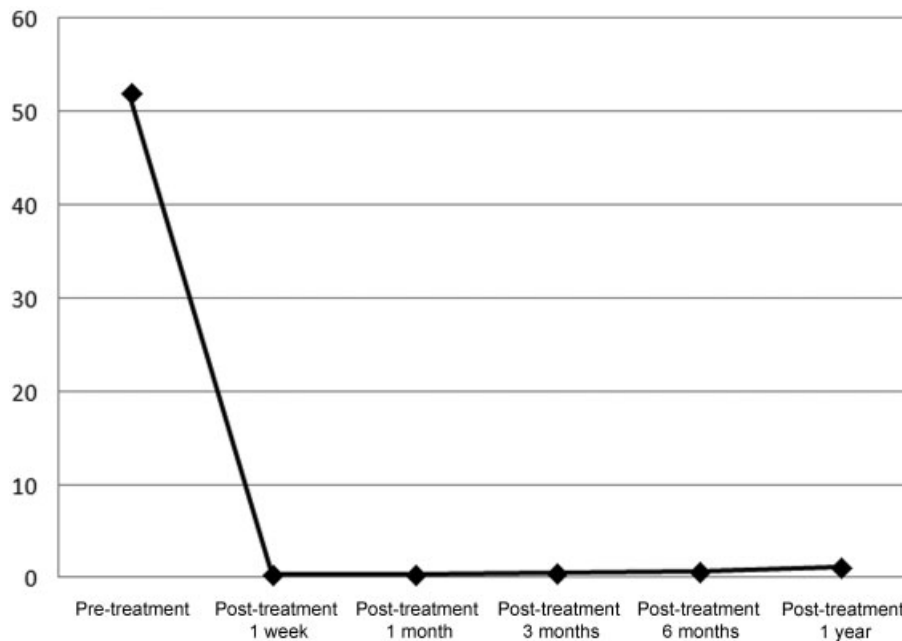


Fig. 1 Evolution of the average degree of joint contracture for metacarpophalangeal joint in the first year of follow-up. Foot of figure: in the ordinates the numbers represent the average in degrees of loss of extension on the metacarpophalangeal joint in the cohort studied. The abscissa specifies the different moments in which measurements were made (from the moment of diagnosis to evolution at the end of the year of follow-up). \bar{x} of degrees of loss of pre-treatment extension: 51.92°. \bar{x} of degrees of loss of extension to the first week: 0.42°. \bar{x} of degrees of loss of extension to the first month: 0.42°. \bar{x} of degrees of loss of extension at 3 months: 0.5°. \bar{x} of degrees of loss of extension at six months: 0.67°. \bar{x} of degrees of loss of extension at 1 year: 1.17°.

Table 3 Complications observed after collagenase *Clostridium histolyticum* injection

Complication	N (%)
→Cutaneous wounds	31 (51.66%)
→Regional adenopathy	3 (5.00%)
→Ruptured tendon	0 (0.00%)

Note: * The incidence with which the studied cohort suffered the aforementioned complications is presented.

Discussion

All individuals in the cohort in which our study is based experienced a decrease in the loss of extension that was maintained during the first year, and only one cord treated with CCH experienced a recurrence after 1 year, presenting a loss of extension of 20°. All the complications that we experienced were minor and were resolved conservatively and without sequelae in the first month after the injection. These results are consistent with those of Syed et al,¹⁸ with a cohort for cords with exclusively metacarpophalangeal involvement, obtaining a recovery in the extension deficit of more than 40° on average. All the adverse effects described in the Syed et al¹⁸ study were resolved, on average, within 10 days, completely and spontaneously.

In our study, 98.34% of the patients experienced a complete remission of the disease at the time of traction that remained without evident recurrence until the follow-up visit a year later, which is consistent with the Hurst et al⁵ CORD I study, in which 306 patients were monitored for 3 months and in which 0% of recurrences were described; it also appears to be consistent with the Gilpin et al⁶ study, in which 66 patients are monitored over 12 months and a 0% recurrence is also described. Recurrences may increase over time, as longer follow-up studies. such as Peimer et al,¹³ show recurrence rates of 35% in a follow-up of 623 patients at 3 years and 47% at 5 years. Watt et al¹⁹ followed 8 patients for 8 years after CCH injection and showed recurrence in 75% of the cases.

In our series, we did not observe any serious complication, but the frequency of minor complications was high. Despite this, progression with local treatment was excellent in all patients. Patients with palpable fascial cords attached to the skin may have an increased risk of skin lesions as a result of the pharmacological effect of CCH and the extension procedure of the finger on the skin at the site of the cord being treated.

The main strength of our study is the very close monitoring that was performed in the sample, showing that 1 year after the CCH injection, recurrences are rare and practically non-existent. It also highlights the large sample size monitored and the low drop-out rate, which was 6.6%. Other studies on CCH, such as the CORDLESS study by Peimer et al,¹³ had drop-out rates at follow-up of 32.22%, or the Scherman et al²⁰ study, in which they experienced a drop-out rate of 7.5% at the 1-year follow-up after the CCH injection.

Another strong point inherent in the study's inclusion criteria is the admission of only the cords that were considered to be the most serious, including only those with more than 40° loss of extension.

The main weakness of our study was the follow-up time: 12 months seems to be little when compared with other studies that are currently underway and more so when it has already been shown that there are recurrences. Another weak point is intrinsic to the patients' own exclusion criteria: only patients with single cords have been included in the study, making it impossible to study the efficacy of CCH in cords that affect multiple radii.

In our work, no study was performed on the reliability of measurements of the contractures studied with manual goniometer, in addition to which all measurements were made by the same physician (thus eliminating the inter-observer error). However, although the differences are usually minor, measurement errors can also occur in the same observer.²¹

Another weak point of our work is not having used a *patient reported outcome* instrument to compare the health perceived by the patient concerning the contracture before and after treatment.

Conclusion

Collagenase *C. histolyticum* is an effective product during the first year for treatment of metacarpophalangeal joint extension loss secondary to single fibrous cords in patients with Dupuytren disease.

Ethical Approval

The study was approved by our center's Clinical Research Ethics Committee.

Conflicts of Interest

The authors have no conflicts of interests to declare.

References

- Rayan GM. Nonoperative treatment of Dupuytren's disease. *J Hand Surg Am* 2008;33(07):1208-1210
- Ketchum LD, Donahue TK. The injection of nodules of Dupuytren's disease with triamcinolone acetonide. *J Hand Surg Am* 2000;25(06):1157-1162
- Betz N, Ott OJ, Adamietz B, Sauer R, Fietkau R, Keilholz L. Radiotherapy in early-stage Dupuytren's contracture. Long-term results after 13 years. *Strahlenther Onkol* 2010;186(02):82-90
- Rayan GM, Parizi M, Tomasek JJ. Pharmacologic regulation of Dupuytren's fibroblast contraction in vitro. *J Hand Surg Am* 1996;21(06):1065-1070
- Hurst LC, Badalamente MA, Hentz VR, et al; CORD I Study Group. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med* 2009;361(10):968-979
- 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.e1
- Starkweather KD, Lattuga S, Hurst LC, et al. Collagenase in the treatment of Dupuytren's disease: an in vitro study. *J Hand Surg Am* 1996;21(03):490-495

- 8 Arandes JM. Aponeurotomía enzimática (Enzymatic Aponeurotomy). *RICMA* 2014;42(01):3–8
- 9 Muppavarapu RC, Waters MJ, Leibman MI, Belsky MR, Ruchelsman DE. Clinical outcomes following collagenase injections compared to fasciectomy in the treatment of Dupuytren's contracture. *Hand (NY)* 2015;10(02):260–265
- 10 Pérez-Giner R, Aguilera L. Resultado precoz del tratamiento de la enfermedad de Dupuytren mediante inyección de colagenasa. (Early outcome of the treatment of Dupuytren's disease by collagenase injection). *RICMA* 2015;43(01):13–19
- 11 Crivello KM, Potter HG, Moon ES, Rancy SK, Wolfe SW. Does collagenase injection disrupt or digest the Dupuytren's cord: a magnetic resonance imaging study. *J Hand Surg Eur Vol* 2016;41(06):614–620
- 12 Hurst LC, Badalamente M, Smith T. Author's reply: Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med* 2009;361:2578–2580
- 13 Peimer CA, Blazar P, Coleman S, Kaplan FTD, Smith T, Lindau T. Dupuytren's contracture recurrence following treatment with collagenase clostridium histolyticum (CORDLESS [Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study]): 5-year data. *J Hand Surg Am* 2015;40(08):1597–1605
- 14 Bear BJ, Peimer CA, Kaplan FTD, Kaufman GJ, Tursi JP, Smith T. Treatment of recurrent Dupuytren contracture in joints previously effectively treated with Collagenase Clostridium histolyticum. *J Hand Surg Am* 2017;42(05):391.e1–391.e8
- 15 Bainbridge C, Gerber RA, Szczypa PP, et al. Efficacy of collagenase in patients who did and did not have previous hand surgery for Dupuytren's contracture. *J Plast Surg Hand Surg* 2012;46(3-4):177–183
- 16 Gaston RG, Larsen SE, Pess GM, et al. The efficacy and safety of concurrent collagenase clostridium histolyticum injections for 2 dupuytren contractures in the same hand: a prospective, multi-center study. *J Hand Surg Am* 2015;40(10):1963–1971
- 17 Pallant J. *SPSS Survival Manual: A Step by Step Guide to Data Analysis using SPSS for Windows*. 3rd ed. England: McGraw Hill; 2007
- 18 Syed AM, Mcfarlane J, Chester T, et al. Clinical efficacy and cost-effectiveness of Clostridium histolyticum collagenase injections in a subpopulation of Dupuytren's contracture patients. *Eur Orthop Traumatol* 2014;5(03):311–316
- 19 Watt AJ, Curtin CM, Hentz VR. Collagenase injection as nonsurgical treatment of Dupuytren's disease: 8-year follow-up. *J Hand Surg Am* 2010;35(04):534–539, 539.e1
- 20 Scherman P, Jenmalm P, Dahlin LB. One-year results of needle fasciotomy and collagenase injection in treatment of Dupuytren's contracture: A two-centre prospective randomized clinical trial. *J Hand Surg Eur Vol* 2016;41(06):577–582
- 21 Kim SG, Kim EK. Test-retest reliability of an active range of motion test for the shoulder and hip joints by unskilled examiners using a manual goniometer. *J Phys Ther Sci* 2016 28(03):722–724