

# Clostridium histolyticum as first-line treatment of Dupuytren's disease

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## ABSTRACT

**INTRODUCTION:** The optimal minimal invasive treatment for Dupuytren's contractures (DC) remains debated. The aim of this study was to evaluate the effect of *Clostridium histolyticum* collagenase after 1-4 years of follow-up. The outcomes of this study were 1) overall improvements in degrees from baseline to follow-up; 2) contraction recurrence defined as an extension deficit above 20°, and 3) Hurst endpoint defined as an extension deficit below 5°.

**METHODS:** All patients treated with *C. histolyticum* collagenase at the Regional Hospital Horsens from 2013 to 2016 with a minimum of one year of follow-up due to DC were included. The range of motion of the affected finger joint was measured before and immediately after injection and at follow-up. Specific information regarding known comorbidities to DC was acquired.

**RESULTS:** A total of 112 metacarpophalangeal (MCP) and 47 proximal interphalangeal joints were included. Total improvement in the range of motion for MCP and proximal interphalangeal joints were 43° and 16°, respectively. The recurrence rate was 9% for MCP joints and 70% proximal interphalangeal joints. 73% of MCP joints and 9% of proximal interphalangeal joints achieved the Hurst endpoint. 92% of the patients were willing to repeat treatment.

**CONCLUSIONS:** Collagenase is a viable first-line treatment for MCP joint contractures. However, results are inferior in the proximal interphalangeal joint.

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Dupuytren's contracture (DC) is a chronic, progressive disease that involves the palmar fascia of the hand. As the disease progresses, rigid cords are formed in the palm of the hand causing flexion contractures primarily of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints [1, 2].

Treatment of DC remains a challenge due to frequent recurrence. Surgery is the mainstay treatment, but is not without complications, and is associated with high recurrence rates [3]. Minimal invasive procedures such as percutaneous needle fasciotomy (PNF) [4] and *Clostridium histolyticum* collagenase (Xiapex in

Europe/Xiaflex in the US) [5] have been increasingly used in recent years. However, both have recurrence rates that exceed those of surgery [6]. Nevertheless, studies have shown that minimal invasive procedures are often preferred by the patient and the surgeon alike owing to the simplicity of the procedure and the patient's early return to activities of daily living after the procedure [7, 8].

In 2009, *C. histolyticum* collagenase was introduced into clinical practice following a Food and Drug Administration approval, with promising efficacy results compared with placebo [5]. In 2013, *C. histolyticum* collagenase treatment was introduced at Regional Hospital Horsens by one dedicated hand surgeon who had received a standard introduction programme by the manufacturer.

The aim of this study was to evaluate the effectiveness of a single-shot *C. histolyticum* collagenase treatment at a regional hospital in non-selected patients with a least one year of follow-up (FU). The following outcomes were evaluated: 1) overall improvements in degrees from baseline to FU in MCP and PIP joints; 2) contraction recurrence – defined as extension deficit (ED) above 20° (indication for treatment at our centre) and 3) Hurst endpoint defined as an ED below 5° [5].

## METHODS

Between January 2013 and May 2016, a total 189 patients received *C. histolyticum* collagenase at our hospital. Patients were invited to attend clinical FU during 2017 if the *C. histolyticum* collagenase treatment had been done in a DC cord that had not previously been treated (Figure 1). A total of 119 patients (63%) were evaluated involving 112 MCP joints and 47 PIP joints (Table 1). In all, 17 patients (19 digits) had treatment at both the MCP joint and the PIP joint in the same finger, but not simultaneously. The other 93 MCP joints and 28 PIP joints were at different digits and were treated independently. The mean FU was 2.5 years (95% confidence interval (CI): 1.0-4.1). One hand surgeon (LS) performed all treatments as outpatient procedures. All patients were referred to our centre by a primary care physician and received the treatment free of cost within the national public healthcare service system. Among DC patients treated at our hospital in

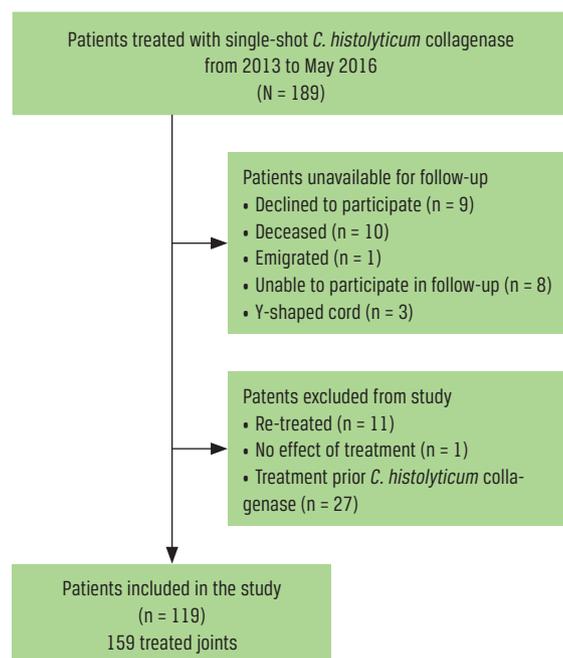
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**FIGURE 1**

Description of patients included in the study. One patient with a proximal interphalangeal joint contracture was excluded from the study due to lacking effect of the treatment. Only minimal clinical sign after *Clostridium histolyticum* collagenase injection at the day of manipulation was seen, and the joint was not extendable. Hence, the conclusion was either ineffectiveness of the *C. histolyticum* collagenase injection or the extension deficit of the finger was due to arthrogenic causes.



the study period, *C. histolyticum* collagenase was performed in two-thirds, whereas one-third of patients either preferred surgery or the DC cord was not suitable for enzymatic treatment according to the manufacturer's guidelines. Indication for *C. histolyticum* collagenase was a palpable Dupuytren's cord with an active ED of 20° or above in a finger PIP or MCP joint.

*C. histolyticum* collagenase was administered ac-

ording to the manufacturer's guidelines in MCP and PIP joints, and manipulation was performed the day after injection. All patients were recommended to use a night extension splint for three months. The active ED was measured with a goniometer before injection, after manipulation and at FU. Specific information regarding known comorbidities to DC was acquired (diabetes mellitus, drugs, smoking and type of employment).

**Data analysis**

Parametric data were presented as means with 95% CIs and non-parametric and categorical data were presented as medians with 25%-75% interquartile range (IQR).

Uni- and multivariate regression analyses were performed to identify potential predictors of outcome among selected baseline variables (sex, age, family history, smoking and diabetes mellitus). Only ring and little fingers were included in the regression analyses. Patients who were excluded or who were not available for FU were not included in analysis.

*Trial registration:* The study was registered with ClinicalTrials.gov (NCT03331926) and approved by the Danish Data Protection agency (1-16-02-43-17). Under current national legislation, a formal ethics approval was not necessary.

**RESULTS**

The baseline median ED was 50° (IQR: 40-60°, range: 20-90°) for MCP joints and 55° (IQR: 40-65°, range: 20-90°) for PIP joints. The median ED after manipulation was 0° (IQR: 0-0°, range: 0-10°) for MCP and 0° (IQR: 0-10°, range: 0-50°) for PIP joints. At FU, the median ED was 0° (IQR: 0-10°, range: -10-75°) for MCP joints and 40° (IQR: 20-55°, range: 0-80°) for PIP joints. After manipulation, the overall mean reduction in ED was 50° (95% CI: 47-52°) in MCP joints and 47° (95% CI: 42-52°) in PIP joints. At FU, the overall mean reduction in ED was 43° (95% CI: 39-47°) in MCP joints and 16° (95% CI: 9-22°) in PIP joints. Contraction recurrence was seen in ten (9%) MCP joints and in 33 (70%) PIP joints. The Hurst endpoint was maintained at FU in 82 (73%) MCP joints and in four (9%) PIP joints. Complete correction of ED (ED = 0°) was maintained in 76 (68%) of the MCP joints and in two (5%) of the PIP joints at FU.

Regression analysis identified no correlations between the selected predictor variables in any of the reported outcomes. One patient described minor cold intolerance to the treated finger; no other major adverse events, such as nerve injuries; complex regional pain syndrome or tendon ruptures were identified at FU. A total of 27 patients (17%) had a skin rupture that healed without infections or problems. At FU, 119 pa-

**TABLE 1**

Baseline demographic and clinical data for 119 patients treated with a single-shot *Clostridium histolyticum* collagenase. Mean age at treatment was 68 (95% CI: 67-69) years.

	n (%)		
	total	MCP (N = 112)	PIP (N = 47)
Males	97 (82)	-	-
Family disposition	54 (45)	-	-
Bilateral affection	101 (85)	-	-
Currently smoker	29 (24)	-	-
Alcohol consumption <sup>a</sup>	95 (80)	-	-
Diabetes mellitus	17 (12)	-	-
Antiepileptic medicine	4 (3)	-	-
<i>Affected finger by joint treated</i>			
Index	-	1 (1)	3 (6)
Middle	-	5 (4)	3 (6)
Ring	-	49 (44)	13 (28)
Little	-	57 (51)	28 (60)

CI = confidence interval; MCP = metacarpophalangeal joint; PIP = proximal interphalangeal joint.

a) Defined as > 0 U/wk irrespective of sex.

tients (92%) were willing to repeat treatment, irrespective of the clinical results obtained.

## DISCUSSION

We found that *C. histolyticum* collagenase is effective for DC in MCP joints with a low recurrence rate after 1-4 years of FU; however, with inferior results in PIP joints.

Our findings are comparable to those reported in existing literature evaluating *C. histolyticum* collagenase in large, standardised series. The three-year CORDLESS study [6] identified a maintained low recurrence in 65% of the treated joints, similar to our study, and the highest recurrence rate was recorded for PIP joints (56%) compared with MCP joints (27%). Evaluating the same population, the CORDLESS five-year study identified successful treatment in 53% of the joints, again with a poorer outcome in PIP than MCP joints [9].

The direct cost of *C. histolyticum* collagenase is higher than the cost of PNF. A randomised controlled trial with two-year FU in 50 PIP joints [10] failed to show a superior effect of *C. histolyticum* collagenase compared with PNF with a contracture recurrence of 83% in the *C. histolyticum* collagenase group, similar to the 70% found in our study.

In a single-blinded, prospective study, 69 MCP joints treated with *C. histolyticum* collagenase were compared with 71 MCP joints treated with PNF. At the one-year FU, 90% of the joints in both groups maintained full extension [11]. A randomised, controlled trial with one-year FU of 86 rays (81 MCP joints and 38 PIP joints) found no significant difference in outcomes [12]. Further long-term randomised studies with joint cost-effectiveness analysis of minimal invasive treatments of DC are needed before an in-depth differentiation between *C. histolyticum* collagenase and PNF is possible. As such, which treatment to apply in DC is optimally made by the surgeon and patient in a shared decision after discussing the advantages and drawbacks? In general, patients are satisfied with *C. histolyticum* collagenase; and if recurrence occurs, 92% of the patients in our sample were willing to repeat their *C. histolyticum* collagenase procedure, which has also been reported previously [13].

Adverse events to *C. histolyticum* collagenase are progressively described in the literature. We observed no major adverse events (infections, tendon ruptures, or complex regional pain syndrome) in our study. Tears of the skin are common after manipulation. In our study, skin tears were seen in 17% of the cases, which is comparable to reports from other studies [10, 14].

The cause of DC is multifactorial. Gender [15], age [16], inheritance [17], smoking [18], diabetes [19] and manual labour [20] have all been associated with



A 66-year-old male with needle fasciectomy of the fifth finger proximal interphalangeal (PIP) joint in 2014. Recurrence after one year. *Clostridium histolyticum* collagenase in 2015, recurrence after two years, and now involving both the fourth and fifth PIP joints.

DC. We evaluated known risk factors, trying to identify possible predictors for recurrence in general and per joint, but none were found to be significantly associated with outcome in our sample.

We recognise that our study has limitations. A total of 43 patients were excluded or not available for FU, and 27 patients had received previous treatment before referral to our institution. Our cohort thus consists of a sample of DC patients undergoing *C. histolyticum* collagenase treatment for the first time. Eleven patients were excluded and thus not evaluated in our study as they had already received further treatment for DC between the baseline treatment and the planned FU. Theoretically, this could decrease the rate of success for a single-shot *C. histolyticum* collagenase to 16%  $((10 + 11)/(119 + 11))$  contracture recurrence in MCP joints and to 83%  $((33 + 11)/(42 + 11))$  contracture recurrence in PIP joints.

Unquestionably, recurrence of DC remains a challenge. Yet, the definition of recurrence after treatment of DC is unclear in the literature. There is no apparent consensus as to whether ED should be evaluated by passive or active finger motion, and whether to use a dichotomous limit of 0°, 5° or 20° of ED as failure, or a continual degree of reduction. We measured an active ED, and hence we expect that our results are more conservative than those of studies evaluating passive ED.

The FU period varies from one to four years. As DC is a progressive disease, the rate of contracture recurrence could increase with an increase in the minimum FU period. Only one surgeon performed the treatments. The surgeon had no previous experience in the use of *C. histolyticum* collagenase besides the standardised introduction programme provided by the manufacturer. However, we see this as strength to the study, and as a true description of the effectiveness of *C. histolyticum* collagenase in a non-selected everyday series of patients.

This study confirms that *C. histolyticum* collagenase is an effective and safe treatment for DC and shows that *C. histolyticum* collagenase is valuable as a first-line procedure in MCP joints, but with inferior results in PIP joints, at 1-4 years of FU.

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**CONFLICTS OF INTEREST:** Disclosure forms provided by the authors are available with the full text of this article at [Ugeskriftet.dk/dmj](http://Ugeskriftet.dk/dmj)

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