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Prospective Study

Long-term assessment of collagenase treatment for Dupuytren's contracture: A 10-year follow-up study

Passiatore M *et al.* 10-year follow-up of collagenase in Dupuytren

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Abstract

BACKGROUND

Enzymatic fasciotomy with collagenase clostridium histolyticum (CCH) has revolutionized the treatment for Dupuytren's contracture (DC). Despite its benefits, the long-term outcomes remain unclear. This study presented a comprehensive 10-year follow-up assessment of the enduring effects of CCH on patients with DC.

AIM

To compare the short-term (12 wk) and long-term (10 year) outcomes on CCH treatment in patients with DC.

METHODS

A cohort of 45 patients was treated with CCH at the metacarpophalangeal (MCP) joint and the proximal interphalangeal (PIP) joint and underwent systematic re-evaluation. The study adhered to multicenter trial protocols, and assessments were conducted at 12 wk, 7 years, and 10 years post-surgery.

RESULTS

Thirty-seven patients completed the 10-year follow-up. At 10 years, patients treated at the PIP joint exhibited a 100% recurrence. However, patients treated at the MCP joint only showed a 50% recurrence. Patient satisfaction varied, with a lower satisfaction reported in PIP joint cases. Recurrence exceeding 20 degrees on the total passive extension deficit was observed, indicating a challenge for sustained efficacy. Significant differences were noted between outcomes at the 7-year and 10-year intervals.

CONCLUSION

CCH demonstrated sustained efficacy when applied to the MCP joint. However, caution is warranted for CCH treatment at the PIP joint due to a high level of recurrence and low patient satisfaction. Re-intervention is needed within a decade of treatment.

Key Words: Collagenase; Xiapex; Dupuytren disease; Dupuytren recurrence; long term follow-up

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Core Tip: Collagenase has shown efficacy in the treatment of Dupuytren's contracture. While its short-term effectiveness is well-documented in the existing literature, there is an absence of studies addressing the long-term outcomes of collagenase treatment of Dupuytren's contracture. The objectives of this study were to compare the short-term and long-term (10 years) outcomes and to assess the satisfaction with the treatment in 45 subjects enrolled in a phase 3 study in 2012.

INTRODUCTION

Patients with Dupuytren's contracture (DC), also known as palmar fibromatosis, experienced a significant breakthrough for treatment in the early 21st century. This advancement was marked by the introduction of the enzymatic fasciotomy technique, which is a novel approach involving the infiltration of the fibrous cord with collagenase derived from *Clostridium histolyticum* (CCH)^[1]. In contrast to traditional surgical procedures, enzymatic fasciotomy is a less invasive alternative^[2-4]. However, the long-term outcomes of this innovative technique are unknown due to its recent introduction and the scarcity of studies with extended follow-up periods^[5].

There is a growing trend of re-assessing patients who underwent enzyme fasciotomy^[2,3]. Notably, it has been observed that some individuals treated with this technique have not experienced sustained long-term benefits. In 2012, our institution enrolled 45 patients into a phase 3 study to receive CCH for the treatment of DC with palpable cord manifestations. A comprehensive 7-year follow-up revealed a recurrence

of the disease, particularly among patients who were treated at the proximal interphalangeal (PIP) joint. Additionally, there was evidence of recurrence in patients who were treated at the metacarpophalangeal (MCP) joint^[3]. The aim of this study was to compare the outcomes observed at 12 wk post-treatment with those documented over a 10-year follow-up period.

MATERIALS AND METHODS

This study was part of a multicenter trial aligned with the Ministry of Health Decree of May 8, 2003 and was carried out at the Unit of Orthopaedics and Surgery of the Hand at the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome (Ethics Committee Protocol P/488-857-872-1041-1113/CE/2012)^[3]. Initiated in January 2012, the study involved 45 patients receiving CCH injection for the treatment of DC with palpable cord manifestations. The primary focus was to evaluate the long-term (10 years) clinical outcomes following CCH treatment in individuals diagnosed with DC.

Inclusion and exclusion criteria

The inclusion and exclusion criteria of the prospective study are listed in Table 1. Within the framework of the present investigation, all individuals who had been previously subjected to a comprehensive review during the 7-year follow-up were systematically contacted. Those re-examined at 10 years after treatment underwent assessments encompassing both goniometric and clinical parameters.

Treatment

The surgery procedure was conducted by experienced hand surgeons injecting the appropriate drug quantity into the affected cords. A sterile dressing was applied, and patients were told to refrain from finger extension. The following day, a forced extension disrupted the pathologic cord, and a thermoplastic splint was applied for 7 d continuously followed by 12 h each day for an additional 7 d. Evaluations were

conducted before treatment and 7 d after the procedure by the surgeon and a physiotherapist. The 10-year follow-up was conducted by the same treating surgeon.

Data collection and follow-up

Passive extension deficit (PED) and total PED (TPED) measurements were recorded before treatment and 12 wk, 7 years, and 10 years after treatment. Additionally, the recurrence rate of the disease at 7 years after treatment was assessed. Recurrence was characterized as a postoperative angular deformity exceeding 20° in at least one of the treated joints accompanied by the presence of a detectable cord^[6]. Recurrence could be accompanied by a loss of hand function necessitating further intervention. The overall satisfaction of participants was appraised using a 10-point scale known as the General Satisfaction Index administered during the 10-year follow-up visit.

In light of recent advancements in patient-reported outcome measures, our patients underwent evaluation utilizing the Michigan Hand Questionnaire (MHQ)^[7] and the Unité Rhumatologique des Affections de la Main Scale (URAM Scale)^[8].

End points

The primary endpoint of the study was assessment of the long-term efficacy and the occurrence of significant disease recurrence at the 10-year follow-up. The secondary outcomes included evaluating sustained functionality at the 7-year follow-up and assessing general satisfaction with the received treatment.

Statistical analysis

The presented data encompassed mean values and standard deviations, with precision limited to a single decimal digit. Parametric data were subjected to comparative analysis using the Student's *t* test, while non-parametric data underwent analysis *via* the Mann-Whitney test or Wilcoxon test. Significance levels were set at $P < 0.05$. The statistical analyses were conducted using GraphPad Software Prism 8 for Mac (La Jolla, CA, United States).

RESULTS

For the initial study, 45 patients (38 males and 7 females) were enrolled. At the 7-year follow-up, 3¹ patients required surgical treatment before completing the established follow-up due to an unsatisfactory clinical result. Two patients died and did not complete the 7-year follow-up assessment. At the 10-year follow-up, an additional 2 patients did not complete the assessment. Therefore, 37 patients were included in the current study. Patients were categorized by treatment in the MCP joint or in the PIP joint.

Patients treated at the MCP joint

There were 31 patients treated at the MCP joint (10-year PED: 11.5 ± 11.4 ; range: 0-30). Nine patients (29.0%) had a recurrence on the treated joint (Table 2). Seventeen patients (54.8%) had a worse TPED due to recurrence of disease by PIP joint involvement (10-year TPED: 25.8 ± 10.9 ; range: 0-50). Overall patient satisfaction was 6.7 ± 1.7 . The mean MHQ score was 80 ± 21 . The mean URAM score was 59 ± 19 . A statistically significant difference was observed when comparing the outcomes at the 7-year² follow-up and at the 10-year follow-up for PED ($P = 0.00222$) and TPED ($P < 0.00001$).

Patients treated at the PIP joint

There were 6 patients treated at the PIP joint (10-year PED: 41.7 ± 5.2 ; range: 35-50). All patients experienced recurrence at the treated joint (Table 3). All patients had a worse TPED due to recurrence of the disease by PIP joint involvement (10-year TPED: 56.7 ± 8.2 ; range: 50-70). Overall patient satisfaction was 5.0 ± 0.6 . The mean MHQ score was 70 ± 15 . The mean URAM score was 63 ± 16 . The sample size ($n = 6$) did not meet the criteria for the Wilcoxon test to approximate normality. Therefore, accurate computation of a P value was not feasible.

DISCUSSION

This investigation represents one of the longest follow-up studies demonstrating the efficacy of enzymatic fasciotomy. It should be noted that during this follow-up study, collagenase was removed from the European market^[9] but not due to safety or efficacy issues. The data from this 10-year follow-up, along with data from the 7-year follow-up^[3], has revealed novel findings for the use of collagenase in the treatment of DC. Our results mostly align with trends observed in other studies with shorter follow-up periods^[3,10-12].

Previous studies with extended follow-ups have already reported instances of disease recurrence. Zhang *et al*^[10] documented a recurrence rate of 80% and the necessity for re-intervention in 53% of cases after a minimum of 5 years of follow-up. Similarly, Göransson *et al*^[12] reported a 5-year recurrence rate of 50% that was accompanied by high patient satisfaction. Our previous study, evaluating the population 7 years after treatment^[3], revealed that 86.7% of PIP joint-treated patients and 65.6% of MCP joint-treated patients experienced recurrence of the contracture. Notably, 86.7% of patients concluded treatment after a single collagenase injection despite subsequent recurrences^[3].

Our analysis adhered to the international consensus definition of recurrence^[6], which revealed that 54.8% of patients exhibited a deterioration of more than 20 degrees of TPED in the MCP joints. According to this criterion, 100% of patients treated at the PIP joint experienced a recurrence. Additionally, if we included patients with 20 degrees of TPED (the lower limit of recurrence definition), the recurrence rate would reach 67.7%. Notably, no patient exhibited a TPED of zero at the 10-year follow-up. In addition, our evaluation did not account for the potential activation of the disease in untreated fingers.

The recurrence is likely due to DC pathophysiology and the nature of CCH treatment. While CCH enables cord lysis, it does not eliminate a substantial portion of pathological aponeurosis, which allows the persistence of pathological collagen. There is limited evidence suggesting that CCH induces inflammatory stimulation, potentially activating the generation of further pathological collagen^[4].

Despite these challenges, patients generally express satisfaction with the treatment, particularly when applied to the MCP joint. Conversely, patients treated at the PIP joint exhibited lower satisfaction levels, necessitating further treatment in most cases.

Given our findings, we would recommend collagenase treatment for palpable cords at the MCP joint if it were currently available. We also recommend cautioning patients about the potential for recurrence. Conversely, we do not recommend CCH application at the PIP joint due to low patient satisfaction, the high recurrence rate, and the need for re-intervention within 10 years.

Our study had some limitations, including result disparities between the MCP joint and PIP joint, and a 17.6% loss to follow-up from the initial sample of 45 patients. The deterioration observed in this case series underscores the importance of re-evaluating cases beyond the typical 5-year follow-up.

CONCLUSION

The use of CCH in treating DC is recommended when applied to palpable cords at the MCP joint. The benefits of the treatment are the non-invasiveness and the rapid postoperative recovery. However, patients should be informed of the risk of recurrence.

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PRIMARY SOURCES

1

Rocco De Vitis, Marco Passiatore, Andrea Perna, Silvia Careri, Vitale Cilli, Giuseppe Taccardo. "Seven-year clinical outcomes after collagenase injection in patients with Dupuytren's disease: A prospective study", Journal of Orthopaedics, 2020

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