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Original article

Adverse effects associated with collagenase clostridium histolyticum in Dupuytren disease: A prospective study

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ABSTRACT

Background: Collagenase clostridium histolyticum is now recognized as a viable treatment for Dupuytren disease. The high rate of adverse effects reported in patients continues to spark debate and raise questions about the true frequency of effects and their associated mechanisms of action.
Hypothesis: To investigate whether outcomes of CCH treatment are related to the number of adverse effects experienced. To evaluate short-term clinical outcomes in a series of patients.
Material and methods: Prospective single-center cohort study. The Primary End Point for effectiveness at 30 days was deficit of 0°–5°. Adverse effects were evaluated during CCH injection, removal of the dressing prior to finger extension, and finger extension. To investigate the relationship between adverse effects and treatment effectiveness, we analyzed the association between number of effects and clinical outcome at 30 days.
Results: A total of 208 injections were evaluated. The mean baseline contracture was 32.11°. Ninety-four patients (45.2%) had a mild contracture. Treatment was effective at 30 days in 194 of the injections (93.3%). The rate of effectiveness per joint was 93.5% for metacarpophalangeal joints ($n = 129$) and 92.9% for proximal-interphalangeal joints ($n = 65$). In total, 734 adverse effects were reported (mean, 3.53). No statistically significant associations were identified between disease severity and secondary effects. Variance analysis showed statistically significant differences in patients with severe contractures (mean, 3.91; 95% CI 3.57–4.25), and in patients with proximal-interphalangeal contractures (mean, 4.17; 95% CI 3.76–4.59).
Conclusions: We found no relationship between number of adverse effects and treatment effectiveness at one month following CCH injection.
Level of proof: IV, cohort prospective study.

1. Introduction

Collagenase clostridium histolyticum (CCH) is now recognized as a viable treatment for Dupuytren disease (DD), alongside surgery and needle aponeurotomy [1,2]. However, many questions remain on its use. The high rate of adverse effects reported in patients with DD treated with CCH continues to spark debate and raise questions about the true frequency of effects and their associated mechanisms of action [3]. Although most adverse effects are short-lived and are generally mild or moderate [4], rates of up to 100% have been described in some series [5–10], and some authors see this as worrying [11]. Severe adverse effects are rare [3] and have mostly been described in isolated clinical reports [12–14].

Adverse effects associated with the use of CCH have usually been evaluated using the same method as that used in the CORD trials [4,5], which essentially consists of listing the effects observed. These effects occur in the immediate period following the injection of CCH and include local or regional inflammatory events and immune-mediated events (with varying degrees of lymphadenitis) along the arm. In the vast majority of cases, they resolve spontaneously [3].

The aim of this study was to investigate whether outcomes of CCH treatment at one month are related to the number of adverse effects experienced or whether they are more closely related to other factors, such as cord thickness, degree of flexion, and finger involved. A secondary objective was to evaluate short-term clinical

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outcomes of CCH treatment in a series of patients treated on at our hospital and compare these results with those published to date.

2. Materials and methods

We performed a prospective single-center cohort study of consecutive DD patients treated with CCH between July 7, 2011 and March 2, 2017. All the patients signed an informed consent form agreeing to both treatment and inclusion in the study. The study was approved by the ethics committee and the Spanish Agency of Medicines and Medical Devices (AEMPS) (JPJ-COL-2015-01).

The inclusion criteria were a contracture angle of $\geq 20^{\circ}$ [4] in a metacarpophalangeal (MCP) and/or proximal-interphalangeal (PIP) joint on one or both hands, involvement of one or two digits [15], and absence of declared allergies to either CCH or local anesthetics. Patients with DD affecting the thumb or the distal interphalangeal joint were not included, according to the product data sheet. Where applicable, antiplatelet treatment was interrupted 7 days before the injection and oral anticoagulants were temporarily switched to low-molecular-weight heparins. Both the CCH injection and the finger extension procedures were performed according to a previously described protocol [15].

Procedures were performed by two orthopedic surgeons in all cases. The injection volumes were 0.25 mL for MCP joints and 0.20 mL for PIP joints (total dose, 0.58 mg). Finger extension was performed 24–48 hours after CCH injection. During this time, the injection site was covered with an occlusive dressing. Wrist block was achieved at the moment of extension using one injection of 10 mL mepivacaine 2% with one or two punctures at the proximal crease of the wrist to block the medial and cubital nerves. Sensory block was assessed by pinprick testing at two different sites [16].

The Primary End Point for treatment effectiveness at 30 days was assessed using the CORD criterion of an extension deficit of 0°–5° [4]. Treatment effectiveness was assessed using degree of passive extension deficit. Adverse effects were evaluated on three occasions: during CCH injection (pain rating), during removal of the dressing prior to finger extension, and during finger extension. The adverse effects contemplated are listed in Table 1, together with their definition, moment of assessment, and measurement method. Pain was assessed using a numerical rating scale (NRS) where patients rate intensity of pain on a scale of 0 (no pain) to 10 (worst imaginable pain). A score of 0 is equivalent to no pain, while scores of 1–3, 4–6, and 7–10 correspond to mild, moderate, and severe pain, respectively [17]. Scores of 3 or higher were considered to indicate pathological pain. A reduction in pain of at least 1.3 points was considered to be clinically significant [18].

To investigate the relationship between adverse effects and treatment effectiveness, we analyzed the association between number of effects and clinical outcome at 30 days. We chose this time point, as spontaneous extensions have been observed up to 1 month after CCH injection [4]. We then analyzed the association between treatment outcome and degree of contracture based on the severity criteria applied in the CORD trials, in which MCP and PIP contractures of $< 50^{\circ}$ and $< 40^{\circ}$ respectively are considered mild.

Qualitative data are expressed as means (SD) or medians (interquartile range [IQR]) depending on whether the data were normally or non-normally distributed. Quantitative variables were compared using the *t* test or the nonparametric Wilcoxon test. Dichotomous variables were analyzed using the chi^2 test, the Pearson test, or the Fisher exact test as appropriate. Qualitative variables with more than two categories were analyzed using trend tests, and correlations between variables were investigated using Pearson or Spearman correlation coefficients. All variables were previously evaluated as modifying or confounding factors according to the criteria proposed by Maldonado and Greenland [19].

3. Results

Over the 6 years analyzed, 151 patients received 208 CCH injections. The mean age of the patients was 66.05 (SD: 8.632) years and the vast majority (87.4%) were male. Demographic and clinical characteristics are summarized in Table 2.

Table 1
Adverse effects associated with CCH: definitions, moment of assessment, and measurement method.

Adverse effect	Moment of assessment	Definition	Measurement method
Injection pain	During injection	Pain experienced during CCH injection	Numerical rating scale (0–10)
Lymphadenopathy	Removal of dressing before finger extension	Presence of lymphadenitis, epitrochlear or axillary pain, or palpable epitrochlear or axillary lymph nodes	Observation (Yes/No)
Pruritus	Removal of dressing before finger extension	Itching, evaluated by asking the patient directly	Subjective (Yes/No)
Injection site pain	Removal of dressing before finger extension	Gentle palpation of injection site; considered positive if the patient expressed pain verbally or through gestures or removed his/her hand	Observation (Yes/No)
Edema/swelling	Removal of dressing before finger extension	Presence of swelling/inflammation without signs of bleeding	Observation (Yes/No)
Ecchymosis/hematoma	Removal of dressing before finger extension	Presence of bruising or hematological remains due to the inflammatory process without broken skin	Observation (Yes/No)
Blood blisters	Before/after finger extension	Intact blood-filled blisters	Observation (Yes/No)
Skin laceration	After finger extension	Open skin wound of any size resulting from the procedure	Observation (Yes/No)
Pain during manipulation	After finger extension	Pain during cord extension with anesthetic block	Numerical rating scale (0–10)

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