INTRODUCTION

Collagenase clostridium histolyticum (CCH) enzyme infiltration is a minimally invasive treatment method for Dupuytren’s disease, which has emerged in recent years as an alternative to traditional surgery (selective aponeuroectomy). Its use has steadily increased since its introduction in 2010. Zhao et al report an increase of Dupuytren’s procedures by 36% in the United States (from 50,287 to 68,318) between 2007 and 2013. However, the yearly number of surgical treatments decreased by 13.9% in the same period, and the number of collagenase procedures rose consistently from 4112 in 2010 to 18,626 in 2013. CCH has established itself as a safe, effective, and minimally invasive treatment compared with fasciectomy, with increased benefits to MCPJs. Recurrences occur with CCH as well as with traditional surgery, the main predictors of which have been identified; long-term studies have demonstrated a rate of recurrence comparable to fasciectomy. CCH use has been extended also to palmar nodules and to repeat injections (up to three times as per the description by Costas et al).

CCH treatment is always indicated and preferable to surgery when a palpable retracting cord is present.
Although both surgical and injective treatments are effective in the long term, a wider use of the enzyme had been spreading worldwide due to a number of advantages, that is, the absence of hospitalization, surgery, scar, physiotherapy,\(^5\) until the marketing authorization’s holder requested its withdrawal from the European Medical Market, for commercial reasons (insufficient sales in the extra-US market), not related to safety profile or inefficacy of the medication, with effect from January 1, 2020.\(^13\)

Indications and protocol of administration of CCH are strictly regulated by governmental authorities in the pharmacological field, that is, Food and Drug Administration in the USA,\(^12\) and, until withdrawal, the European Medicines Agency in the European Union\(^15\) and the Italian Drug Administration Agency in Italy (Agenzia Italiana del Farmaco).\(^16\) However, import of the medication is practiced by European surgeons, under their direct responsibility, after notification of the use to the local health institutions.

The use of a CCH dose different than the standard 0.58 mg has been described in the literature.\(^1\) Furthermore, the treatment of multiple digits in the same hand simultaneously has been proven to be possible and safe.\(^2\)

When using the standard dose of CCH (0.58 mg), the remaining 0.32 mg are usually discarded.

To date, a single cord in a single digit should be injected according to guidelines, which are strictly based on the initial study protocols that first explored and confirmed safety and efficacy of this drug.\(^2\)

In the present study, an original modality of use with a smaller dosage has been experienced and preliminarily evaluated, thereby verifying the hypothesis that cord rupture can be achieved even when underdosing the standard CCH treatment. This consisted of utilizing the remainder of the vial, after traditional use, to inject an additional cord affecting another digit (multicord technique). Safety and efficacy of this application have been evaluated.

**METHODS**

This study conforms to the Declaration of Helsinki, was approved by the local institutional review board, and was reported according to the STROBE statement. All patients consecutively accessing the first author’s clinical department who had Dupuytren’s contracture with a positive tabletop test and a palpable cord were offered CCH treatment between December 2018 and December 2019. Patients with Dupuytren’s disease with at least two independent pathological cords, causing deformity of two digits, were considered, with their written consent, for an original use of the medication. The innovative treatment consisted of simultaneous injection of the two cords with a single vial. Patients were neither randomized nor blinded to the treatment they received. Inclusion and exclusion criteria are illustrated in Table 1 and consisted of at least one cord affecting a metacarpophalangeal joint and another independent cord affecting another metacarpophalangeal joint. Independency of the second cord from the first one was defined as the absence of any connection between the two and a distance of at least 2 cm. This criterion was verified through both palpation and ultrasound scan. The distance of 2 cm was arbitrarily determined as a reasonable distance capable of keeping two supratendinous cords separated, between two adjacent digits, to limit the bias deriving from local diffusion of the CCH or weakening effect on the collagen structure of very adjacent cords. The worse of the affected metacarpophalangeal joints was the first treated, with the prescribed 0.58-mg dose, at the standard recommended dilution for metacarpophalangeal joints (0.90 mg in 0.39 ml of provided solvent) as shown in Video 1. (See Video [online], which displays digit manipulation after simultaneous injection of full dose to ring finger and lesser dose to thumb, right hand in a 62-year-old man.) In case the patient had another less retracted cord in the other hand, this was also treated with the smaller 0.32-mg dose.

According to the protocol, only 0.58 mg is to be infiltrated. Since the drug is dispensed in vials of 0.90 mg, the injection of the remaining 0.32 mg that would otherwise remain unused was used for the additional independent cord.

All cords treated with the 0.58-mg dose were compared with cords treated with a 0.32-mg dose of CCH.

The main endpoints considered were the perioperative variations of passive extension deficit (PED) and range of motion (ROM), both expressed as degrees at 24 hours (after manipulation), 1 month, and 12 months. Complications were also compared. Pain was evaluated through a visual analogue scale (VAS) ranging from 1 to 10 (VAS go from 0–10, not 1–10) within 48 hours of the injection. A 1–10 patient satisfaction questionnaire was administered. This was an “ad-hoc survey,” with all the limitations and biases that may derive from this type of survey as thoroughly described by Santesso et al.\(^17\) Patients were retrospectively included in the study after signing an informed consent. The study was conducted in full respect of the Declaration of Helsinki. No registration or formal

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**Table 1. Inclusion and Exclusion Criteria**

| Inclusion Criteria |
|--------------------|
| 1. Dupuytren’s disease with contracture |
| 2. MP contracture with palpable cord |
| 3. Second MP contracture with palpable cord |
| 4. Absence of palpable and untrasoundographic connection between the two cords |
| 5. Distance of at least 2 cm between the two cords |

| Exclusion Criteria |
|--------------------|
| 1. Allergy to CCH |
| 2. Recurrent disease |
| 3. Already treated disease |
| 4. Absence of palpable cords |

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**Takeaways**

**Question:** Is underdosing collagenase from 0.58 to 0.32 mg equally effective in enzymatic cordotomy for Dupuytren’s disease?

**Findings:** Through a comparative case series, analyzing the improvement of passive extension deficit, no disadvantage emerged if a dose of 0.32 mg is used instead of 0.58 mg.

**Meaning:** Underdosing collagenase is equally effective in the treatment of Dupuytren’s disease.
approval by the local ethical committee was necessary as per indication of the local institutional review board, since the modification in the scheme of CCH use has already been described both in terms of dose and the number of cords and/or fingers to be simultaneously treated. Moreover, in the current study, the medication was underdosed compared with original prescriptions.

**Statistical Analysis**

Data were statistically analyzed to find any possible significance in the comparison of the two groups, cords treated with the standard dose, and cords treated with the lesser dose. The PED variation at each time point (24 hours, 30 days, and 12 months) compared with the baseline was analyzed both as a continuous variable (relative change respect to the baseline) and as a categorical variable considering the relative variation from baseline (at least a reduction of 50%) and the achieving of a level between 0 degrees and 5 degrees. Continuous variables were described as mean ± standard deviation (SD) and compared between groups using the Student t test. Categorical variables were reported as frequency (percentage) and compared between groups using the Fisher exact test.

Statistical analyses were performed using STATA version 11.2 (StataCorp, Tex.).

**RESULTS**

A total of 26 patients (29 hands) were included in the study, of whom 25 were men and one was a woman; all were White. Of these, nine patients had two independent cords within one hand, and 17 patients had a single cord. In three patients with bilateral Dupuytren’s disease, an additional less retracted cord was found in the other hand and treated with the 0.32-mg dose. Therefore, in nine patients, two cords in the same hand were treated, each in a single independent digital ray (total 18 cords in 18 digits); in 17 patients, a single cord was injected, and within this group, three patients received the additional smaller dose of 0.32 mg on the milder cord affecting the other hand. In total, 35 digits were injected, 23 with 0.58 mg and 12 with 0.32 mg.

The mean preinjection PED was 54 degrees (30–140 degrees) in the 0.58-mg group and 33 degrees (30–70 degrees) in the 0.32-mg group.

As summarized in Table 2 and Figure 1, the 0.32-mg dose is sufficient to cause the lysis of a cord with similar results compared to the greater conventional dose of 0.58 mg, in terms of all considered endpoints, with no statistically significant difference ($P > 0.05$). Complications and patient satisfaction are also comparable with the two doses. The only indicator that varied between the two doses was the mean reduction of PED at 24 hours. This endpoint is more relevant with the 0.32-mg dose, and this result is statistically significant ($P < 0.05$), as illustrated in Figure 2. No recurrence occurred in either of the two groups. Figures 3 and 4 illustrate one case. A simultaneous injection was performed to two independent cords within a single hand (left hand), with the standard 0.58-mg dose to the ring finger and the 0.32-mg dose to the proximal interphalangeal joint of the little finger.

**DISCUSSION**

This study shows that altering the original prescriptions of Hurst’s protocol would appear to be possible due to the safety and efficacy of results.

A limitation of this study is the nonrandomized design and the small number of participants. Furthermore, the lesser dose is almost always used in the same hand in which another dosage of 0.58 mg has been injected, which might be a bias in case of drug diffusion, although the exclusion of cords in close vicinity (<2 cm) or connection mitigates this bias. In addition, even though the 0.32-mg amount was injected into cords that were apparently unconnected and far apart within the same hand, this might be uncertain. In fact, due to the intricate web of cords that Dupuytren’s contracture causes, even cords that seem to be far apart may have some sort of deep, palpable, undetectable connection or vicinity, which would bias the intention to treat only independent cords.

The release of a single cord, particularly in case of adjacent digits, may cause the correction of both digits or at least positively influence the release of the adjacent

| Table 2. Comparison between Collagenase 0.58 and Collagenase 0.32 |
|----------------|----------------|
| **Collagenase 0.58** | **Collagenase 0.32** | **P** |
| N° of PED reduced to 0°–5° within 30 d (%) | 19 (83) | 10 (83) | 0.651 |
| N° of PED reduced by at least 50% within 30 d (%) | 25 (100) | 12 (100) | 0 |
| Mean reduction of PED in % within 30 d (SD) | 90 (15) | 86 (15) | 0.470 |
| N° of PED reduced by at least 50% within 24h (%) | 9 (22) | 6 (26) | 0.068 |
| Mean reduction of PED in % within 24h (SD) | 59 (13) | 40 (12) | 0.051 |
| Mean increase of ROM in % within 30 d (SD) | 67 (25) | 56 (33) | 0.262 |
| Mean increase of ROM in % within 24h (SD) | 67 (25) | 55 (33) | 0.262 |
| N° of PED reduced to 0°–5° within 12 mo (%) | 20 (87) | 10 (83) | 0.643 |
| N° of PED reduced by at least 50% within 12 mo (%) | 20 (87) | 10 (83) | 0.643 |
| Mean increase of ROM in % within 12 mo (SD) | 72 (25) | 68 (26) | 0.288 |
| Bleeding N (%) | 0 | 0 | 0 |
| Skin necrosis N (%) | 6 (27) | 5 (42) | 0.460 |
| Pain expressed as a 1–10 VAS (SD) | 2.7 (1.5) | 2.8 (1.1) | 0.960 |
| Infection N (%) | 0 | 0 | 0 |
| Parasthesias N (%) | 0 | 0 | 0 |
| Mean global satisfaction from 1 to 10 (SD) | 8.9 (0.9) | 9.0 (0.7) | 0.650 |
| Recurrence at 24 mo | 0 | 0 | 0 |

Categorical variables are reported as frequencies. Continuous variables are reported as mean ± SD.
digit, and this bias has not been completely neutralized in this study.

All cords included in this study series affected the metacarpophalangeal cord to improve the homogeneity of the study population. However, the release force cannot apply exclusively to single digits, and this can be another bias limiting this study. Notwithstanding, outside of the present study, interphalangeal joints with Dupuytren’s retraction were also effectively treated with the lesser 0.32-mg dose, and no recurrence has occurred so far.

Atroshi et al.\textsuperscript{18} already described a change of therapeutic dosage, overdosing the injection compared with the original protocol, with equal safety and efficacy. Gaston et al.\textsuperscript{19} and Cook et al.\textsuperscript{20} successfully proposed simultaneous injections into two sites at the full dose. The treatment was approved by the Food and Drug Administration in 2014. However, Gaston et al.\textsuperscript{19} report a greater risk of adverse events with two injections.

In terms of cost-effective analysis, Sefton et al.\textsuperscript{21} demonstrate the cost-effective superiority of injection over fasciectomy. Similarly, Smeraglia et al.\textsuperscript{22} in their review, have reported the validity of this treatment compared with traditional surgery.

According to their article, the use of collagenase at regular doses and schemes (according to original prescriptions) is cost-effective, with savings between 29\% and 70\% compared with surgical fasciectomy. An additional saving both compared with surgery and with the in-label dosage of CCH is obtained with our proposed technique. As per manufacturer’s prescription, an additional independent

Fig. 1. Diagram comparing the increase of ROM between the two doses (0.58 vs 0.32 mg). No statistically significant difference is found for any timeframe.

Fig. 2. Diagram comparing the mean reduction (%) of PED within 24 hours in case of collagenase 0.58 vs 0.32 mg. The outcome is improved by the use of the lesser dose, and the result is statistically significant ($P = 0.031$).
cord would require an additional new vial; the amount saved with the suggested dosage is the entire cost of a vial; there is no evidence, at least from the presented limited case series, that the proposed lesser dosage would be less effective for the therapeutic purpose of enzymatic lysis of a Dupuytren’s cord.

Previous studies showed the safety and effectiveness of similar protocols. Grandizio et al. injected the two affected joints (metacarpophalangeal and proximal interphalangeal joints) of a single digital ray with one vial. Coleman et al. injected more than one joint, each with a single separate vial. Verheyden simultaneously injected multiple cords at two sites with differing doses, which do not correspond to the repeatedly unconventional fixed dose we describe in this study. Coleman et al. described a simultaneous injection to two cords within the same hand, but both injections utilized the standard 0.58-mg dose. The literature does not mention any study describing the use of a fixed, lower than conventional dose to treat a cord, as demonstrated by the present study.

An interesting finding, which has to be explored in future studies, is to determine the minimum dosage to be prescribed to obtain the effect. An interesting starting point for future research is the increased performance of the lesser dose in the current study at the 24-hour timescale. The mean reduction of PED is more relevant with the 0.32-mg dose, and this result is statistically significant ($P < 0.05$). As Table 1 shows, other endpoints appear to be improved with the 0.32-mg dose, although these results are not statistically significant. A possible role of biochemically induced edema might explain why lower amounts of enzyme are associated with an apparent advantage in the early hours after injection, compared with higher and possibly more proedematous doses.

The option to use the spare dose of CCH (0.32 mg) has been proven to be feasible, safe, and effective, as even with 0.32 mg the pathologic cord is enzymatically treatable and can be mechanically interrupted exactly as with the standard 0.58-mg dose.

In conclusion, a 0.32-mg dosage of CCH is at least equally safe and equally effective as the standard 0.58-mg quantity, when utilized to inject an additional cord in the same patient. Further research is necessary to confirm these preliminary but promising results.
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