SCIENTIFIC ARTICLE

Pain Associated With Treatment of Dupuytren Contracture With Collagenase *Clostridium histolyticum*

Rafael Sanjuan-Cerveró, MS,*† Francisco J. Carrera-Hueso, PhD,‡ Pedro Vazquez-Ferreiro, MD,†§ Narjis Fikri-Benbrahim, PhD,‖ Nuria Franco-Ferrando, MD,* Clayton A. Peimer, MD¶

Purpose The primary objective of this study was to quantify the degree of pain associated with collagenase Clostridium histolyticum (CCH) injection and to determine whether it is related to other factors in the intervention.

Methods A prospective study of 135 patients was performed to evaluate pain at 3 points during treatment: (1) after CCH injection, using a numerical rating scale (NRS), (2) a binary (positive/negative) assessment before manipulation 24 hours after CCH and after removing the bandage, and (3) after joint manipulation performed with wrist block anesthesia.

Results The average NRS for pain during infiltration was 4.7. Pain was present before manipulation in 52.6% of patients. Pain from manipulation showed an average NRS score of 3.6. The amounts of pain at CCH infiltration, pain after 24 hours, and pain from the manipulation were correlated because patients who experienced pain during CCH infiltration were more likely to report experiencing pain during manipulation.

Conclusions Collagenase *Clostridium histolyticum* injection for treating Dupuytren contracture can be a painful process. There is a clear relationship between a patient's level of pain during injection of CCH and the likelihood that the patient will experience pain during manipulation, even with the use of local anesthesia. *(J Hand Surg Am. 2017;42(2):e109–e114. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Prognostic IV.

Key words Collagenase *Clostridium histolyticum*, Dupuytren disease, injection, extension, pain.

Online Only

DUPUYTREN CONTRACTURE (DC) IS a chronic fibroproliferative disease, traditionally treated surgically.[1] Collagenase *Clostridium histolyticum* (CCH) is considered an alternative to surgery[2] and its use is increasing.[3] Estimates from the United Kingdom project an increase in the number of cases of DC as the population both ages and lives with more comorbidity[4]; therefore, CCH may be an important treatment option because of its minimally invasive nature.

We perform CCH injection according to the protocol of Hurst et al,[5] which established areas safe for

*From the *Orthopedics and Traumatology Service, Hospital de Denia, Dénia, Alicante; the †University of Granada, Granada; the ‡Pharmacy Service, Hospital Dr Moliner, Porta Coeli s/n Serra, Valencia; the §Ophtalmologic Department, Hospital Virxen da Xunqueira, Cee, A Coruña; the ‖Academic Center in Pharmaceutical Care, University of Granada, Granada, Spain; and the ¶College of Human Medicine, Michigan State University, East Lansing; and the UP Health System—Marquette/Duke-LifePoint, Marquette, MI.*

Received for publication June 25, 2016; accepted in revised form November 23, 2016.

C.A.P. had past financial involvement with Auxilium Pharmaceuticals.

No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

Corresponding author: Rafael Sanjuan-Cerveró, MS, Orthopedics and Traumatology Service, Partida Beniadla s/n, Denia 03700, Alicante, Spain; e-mail: rafael.sanjuan@marinasalud.es.

0363-5023/17/4202-0014$36.00/0
http://dx.doi.org/10.1016/j.jhsa.2016.11.032

avoiding damage to tendons. Other studies advocate small changes in the CCH injection technique in order to improve treatment effectiveness and patient comfort.[6–8] These include anesthetizing the treatment area immediately before infiltration[8] because many patients report intense pain with needle insertion and during enzyme injection.

In 2002, Badalamente et al[9] published their phase 2 studies in which they advised administering a local anesthetic before manipulating the cord 24 hours after injection. Since the U.S. Food and Drug Administration allowed the use of anesthetic for manipulation in 2010, its use has become routine.[10] Anesthetizing the area makes it easier to manipulate the cord and decreases the number of attempts that must be made in order to rupture the cord, although the anesthetic does not have any influence on the final outcome of treatment.[3] Currently, there is no uniformly defined protocol for the use of anesthetic during the manipulation. However, several studies have not considered anesthesia necessary or recommended it when CCH is administered, even though patients report considerable pain at injection.[2,5,11] Given that pain at infiltration and during manipulation is one of the most common complaints associated with treatment with CCH,[2,5,11] some practitioners take preventive measures to control it. There have been few studies of the relationships between such pain and demographic characteristics or other factors related to DC. Knowledge of these factors could help decrease pain incidence. Patients vividly recall the pain at enzyme injection and that "pain memory" could influence their decision not to complete treatment. A patient satisfaction survey recently has shown that 23% of the patients would not repeat treatment with CCH because of concerns about pain associated with the procedure.[12]

The objective of this study was to quantify the pain associated with CCH injection and determine whether this pain is associated with other factors related to DC or its treatment.

MATERIALS AND METHODS

The study sample consisted of all patients who were diagnosed with DC with involvement of 1 or 2 rays, in at least 1 hand, and who were treated with CCH. Treatment decisions were based on palpating the DC fascial cord with a positive Hueston test.[13] Patients were admitted to the study according to the protocol authorized by the hospital's research committee, and all patients signed the pertinent informed consent.[14]

Included were patients diagnosed with DC with a contracture of 20° or in the metacarpophalangeal and/or proximal interphalangeal joints in 1 finger (except the thumb) and who were 18 years of age or older. No distal interphalangeal joints were treated during this study. Patients with contraindications to CCH or allergy to local anesthetics were excluded. Patients undergoing treatment with antiplatelet medications stopped their medication 7 days before CCH infiltration. Patients on oral anticoagulants were temporarily changed to a low-molecular-weight heparin.

All injections were completed according to product specifications,[5,15,16] but with a modification to the injection technique[6] as described later. The CCH injections, wrist blocks, and manipulations were performed by 2 different orthopedic surgeons (R.S-C. and N.F-F.).

The volume of injection for metacarpophalangeal joints was 0.25 mL and for PIP joints was 0.20 mL, for a total dose of 0.58 mg of CCH. The hand was first disinfected with alcohol chlorhexidine and then injected in 3 different locations along the cord using a monoblock needle in order to avoid product leakage between the needle and the syringe. In each case, the injections were made perpendicular to the longitudinal axis of the cord. After injection, patients quantified the pain they experienced using a verbal numerical rating scale (NRS). Bandages were applied and the patients were asked to keep their hands elevated, refraining from use as much as possible. Oral analgesics (acetaminophen 650 mg, ibuprofen 600 mg, or metamizole 575 mg every 8 hours) were taken as needed for pain.[10] After injection, patients were monitored for 15 minutes for any signs of hypotension, vasovagal syncope, or allergic reaction.

Manipulation took place 24 hours after infiltration in all cases. The bandage was removed, and the site checked for signs of inflammation or pain. The pain assessment was considered positive if, upon exerting light pressure on the infiltrated area, there was verbal confirmation of pain. Next, a wrist block was performed on all patients using 10 mL of 2% mepivacaine spread over the median and ulnar nerves. Manipulation was performed once the effectiveness of the block was confirmed by the absence of pain when the fingertip was pricked with a pin. After manipulation, pain experienced by the patient during the manipulation process was recorded using the same verbal NRS.[17]

Numerical rating scale scores ranged from 0 (no pain) to 10 (worst imaginable pain), with pain scores categorized as follows: 0, no pain; 1 to 3, slight; 4 to 6, moderate; and greater than 6, very serious or intense.[17] Pain was considered "present" in scores greater than 3 on the NRS. All clinical and demographic variables