JOURNAL OF PLASTIC SURGERY AND HAND SURGERY
2022, VOL. 56, NO. 1, 23–29
https://doi.org/10.1080/2000656X.2021.1901723

ARTICLE

Can collagenase effectiveness in Dupuytren's contracture be improved by using ultrasound-guided Injection? A comparative study

Luis Aguilella[a], Rosana Pérez-Giner[b], Victoria Higueras-Guerrero[c], Elena Belloch-Ramos[c], María Cuenca-Torres[d] and Eva Llopis-San Juan[c]

[a]Department of Orthopaedic Surgery, Hospital Universitario de La Ribera, Alzira, Valencia, Spain; [b]Department of Orthopaedic Surgery, Hospital Virgen de los Lirios, Alcoy, Alicante, Spain; [c]Department of Radiology, Hospital Universitario de La Ribera, Alzira, Valencia, Spain; [d]Research Unit, Hospital Universitario de La Ribera, Alzira, Valencia, Spain

ABSTRACT

The objective of this study was to compare the effectiveness of ultrasound-guided injection of collagenase Clostridium histolyticum (CCH) in patients with Dupuytren's contracture (DC), with the standard injection. We hypothesised that the ultrasound-guided Injection of CCH is more effective than the standard injection. A prospective cohorts study in patients with DC was done. We treated consecutively 47 fingers with the standard injection and 43 with the ultrasound-guided. Patients in both groups had the same inclusion criteria. The degrees of contracture of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints were measured before treatment and after three months. We compared the effectiveness of each type of injection in respect to obtaining a complete finger extension and to the percentage of improvement in each finger and in each joint. With ultrasound-guided injection, complete finger extension was obtained in 54% of cases and an 81% mean percentage of correction of the finger contracture; with standard injection 49% and 77%, respectively. In the MCP joint, the mean percentage of correction was 92.5 % in the ultrasound-guided Injection group and 84% in the standard injection group. In the PIP joint, it was 75.1% in the ultrasound-guided injection group and 65.3% in the standard injection group. These results showed no statistical significance. Hand surgeons must balance the possible benefits of the ultrasound-guided injection with the complexity and resources needed to perform the technique.

ARTICLE HISTORY
Received 23 July 2020
Revised 12 January 2021
Accepted 27 February 2021

KEYWORDS
Clostridium hystolyticum; collagenase; Dupuytren's contracture; Dupuytren's disease; ultrasound-guided injection

Introduction

The treatment of Dupuytren's contracture (DC) by means of injection of collagenase Clostridium histolyticum (CCH) into the cords is a pharmacological treatment, not surgical, which is widely used. Its effectiveness and safety was demonstrated initially in CORD I and CORD II clinical trials [1,2], as well as in JOINT I and JOINT II, and in POINT X open-label multicentre studies [3,4]. The CORDLESS study [5,6] provided information on the evolution at short and medium term of a large number of patients. Currently, many hand surgeons have adopted this therapeutic modality as one more tool in the treatment of DC.

The injection of CCH is habitually done through clinical examination, palpating the cord selected for the treatment and injecting a dose of 0.58 mg of collagenase, distributed at three points, into the cord. This common practice arises some doubt in respect to its precision. It is not possible to be absolutely sure that we are injecting in the centre of the cord, unless we use some complementary technique. This problem could be solved by guiding the needle with ultrasound imaging. Ultrasound imaging makes it possible for us to check that the point of the needle is exactly in the centre of the cord at the moment of injection, which theoretically would lead us to expect greater effectiveness of the treatment.

The objective of this study was to compare the effectiveness of ultrasound-guided injection of CCH in patients with DC, with the effectiveness of standard injection, which is used in common practice. We hypothesised that ultrasound-guided injection of CCH is more effective than standard injection.

Material and methods

Study population

Patients with DC who presented a palpable cord, primary or recurrent [1,7], causing a metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) contracture greater than 20° in any of the fingers, were included in the study. Those with involvement of the thumb were excluded [1]. Recruitment was carried out at the out-patients clinic by the same surgeon in all cases (LA).

This study was approved by the Ethics Committee for Clinical Research of our hospital. Informed consent of all participating patients in the study was obtained.

Clinical design

A classical cohorts study was designed, with prospective longitudinal follow-up of two consecutive groups of patients. Group A,

CONTACT Luis Aguilella luis.aguilella@comv.es Department of Orthopaedic Surgery, Hospital Universitario de La Ribera, Alzira, Valencia, Spain
Supplemental data for this article can be accessed online at https://doi.org/10.1080/2000656X.2021.1901723

the unexposed cohort, included 40 patients with 47 cases (each finger treated was considered as a case). A standard injection of CCH was made to this group. Group B, the exposed cohort, were treated after group A, and included 43 patients with 43 cases. The group B patients received an ultrasound-guided injection of CCH. During the period of treatment of group B, no patient was allocated to group A. The same inclusion criteria and the same dose of 0.58 mg of CCH were used in all cases in both groups.

The selection of the point of injection, a relevant aspect in those patients who presented involvement of two joints of the same finger, was performed depending on the characteristics of the cords of the affected finger. In those patients where there was involvement of only one joint, MCP or PIP, the injection was made directly on the cord responsible for the contracture. However, when there was the involvement of two joints, to determine which cord was best suited for injection, in order to obtain the better clinical result with a single injection, the MCP hyperflexion manoeuvre was used, which highlights the dynamism in Dupuytren's contracture described by Rodrigues [8]. If the performance of this manoeuvre (Figure 1) substantially improved the contracture of the PIP joint, which demonstrated its dependence on the pretendinous cord, then the injection was performed on that cord. If no reduction in the contracture of the PIP joint with the MCP hyperflexion manoeuvre was observed, which demonstrated its dependence on a phalangeal central or lateral cord, we opted to inject in the most affected joint. In this case, the patient was warned of the possibility of having to receive a second injection in order to extend the other joint. The total dose of CCH for each case was administered fractioned in three contiguous points of the same cord.

The standard injection was done in the normal way. The ultrasound-guided injection was performed in all of the cases by a radiologist using an 18 MHZ superficial stick type probe placed in the axial plane. The needle point was ultrasound-guided until it was situated in the centre of the cord (Figure 2), where one-third of the dose of CCH was injected. This same process was repeated in two other contiguous points of the cord, thus completing the total dose of CCH.

Post-injection protocol was identical in both groups. At 24–48 h following the injection, the rupture of the cord manoeuvre was carried out, under local anaesthesia, and all of the patients were recommended to use a nocturnal splint during three months.

Instruments and measurements

The degrees of contracture of the MCP and PIP joints were measured using a goniometer before the treatment and at three months evolution. The effectiveness of each modality of injection was compared in respect to obtaining complete correction in each finger and in each joint. In concordance with other studies [1], a contracture equal to or less than 5°, passively measured, was accepted as complete correction. The percentage of

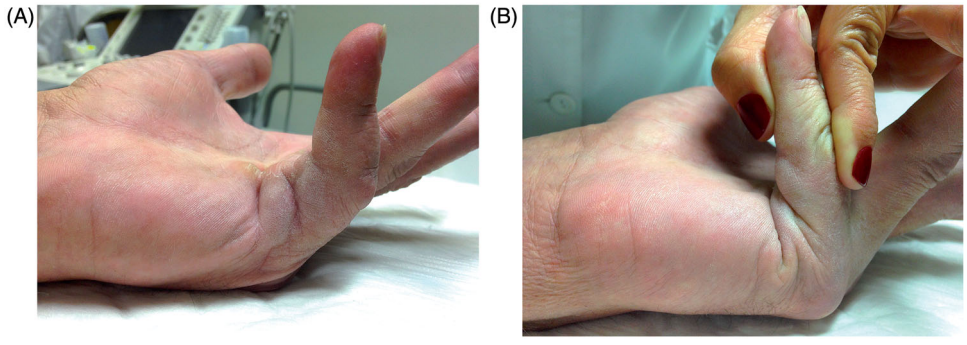


Figure 1. Fifth finger of the left hand affected by DC, with involvement of MP and PIP joints (A). Correction of contracture of PIP joint is noted when effecting maximum passive flexion of the MP joint (B).

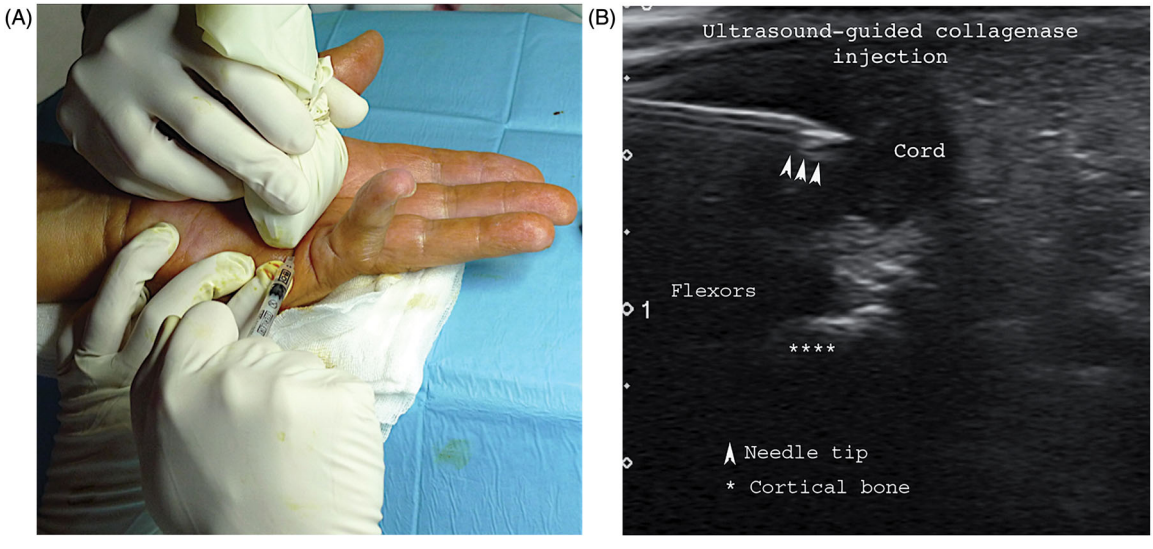


Figure 2. Ultrasound-guided Injection of one cord (A). The needle can be directed with precision toward the centre of the cord (B).

Table 1. Clinical data of the patients treated in both groups. The quantitative variables are expressed using means and standard deviations.

	Standard injection	Ultrasound-guided Injection
No. cases	47	43
Age	64.3 (SD 8.6)	65 (SD 9.1)
Sex	45 M / 2 W	40 M / 3 W
Finger affected	23, 5th / 21, 4th / 3, 3rd	24 5th / 15 4th / 2 3rd / 2 2nd
Hand affected	18 right / 29 left	19 right / 24 left
Total initial contracture	64.1° (SD 28.1°)	62.2° (SD 24.5°)
MP initial contracture	38.0° (SD 24.0°)	27.3° (25.9°)
PIP initial contracture	26.2° (SD 25.0°)	35.0° (SD 24.7°)
Total contracture at 3 months	15.2° (SD 19.7°)	13.0° (SD 16.5°)
MP contracture at 3 months	7.1° (SD 11.4°)	4.1° (SD 8.6°)
PIP contracture at 3 months	14.3° (SD 14.9°)	13.3° (SD 17.0°)

improvement of the contracture in each finger and in each joint was also compared.

Statistical analysis

For the comparison of both techniques, regarding the qualitative variable 'obtaining or not complete correction', the chi-square statistic was calculated. For the quantitative 'percentage of correction', after checking for the normality of the series, Student's *T*-test was used. In both cases, values of $p \leq 0.05$ were considered as significant.

Results

The clinical data of the cases treated in both groups are shown in Table 1. The comparison of the means of the severity of pre-injection contracture showed no significant differences ($p = 0.939$) in both groups. Although treatment with CCH was repeated in the same finger in some of the patients in order to improve the initial result, in this study only the results after a single injection in one cord in both groups are presented to allow for comparison.

Complete correction was obtained in more fingers in the ultrasound-guided injection group than in the standard injection group, although this difference was not significant (Figure 3). The same was observed when comparing the complete correction of the MP and PIP joints (Figure 4). When the percentage of cases that obtained complete correction was compared, depending on whether one or two joints were implicated, the results were similar in both groups when only one joint was affected. However, when two joints were affected, the percentage was higher in the ultrasound-guided injection group, although without any statistical significance (Figure 5).

Regarding the percentage of correction of the overall contracture of each finger, 77.3% (SD 25.0) was obtained in the standard injection group, and 81.2% (SD 23.3) in the ultrasound-guided injection group ($p = 0.389$), (Figure 6). The percentage of correction of the contracture in each joint was also examined. In the MCP joint this was 84.0% (SD 25.0) in the standard injection group, and 92.5% (SD 15.1) in the ultrasound-guided injection group ($p = 0.086$). In the PIP joint it was 65.3% (SD 32.8) in the standard injection group, and 75.1% (SD 30.0) in the ultrasound-guided injection group ($p = 0.162$), (Figure 7).

Discussion

When CCH was approved as treatment of DC, the majority of hand surgeons were continuing to follow strictly the recommendations for use (dose of 0.58 mg in each treatment, injecting in one single cord of only one finger). This created problems for us

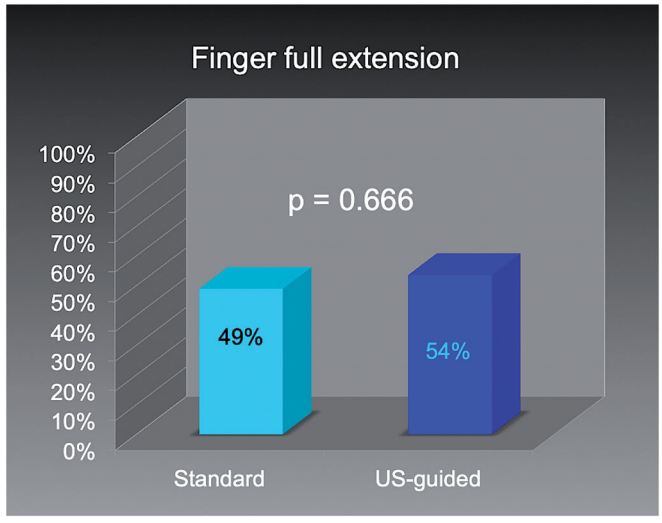


Figure 3. Comparison of percentage of cases with complete finger extension in each treatment group.

when treating one finger with two affected joints, and with two distinct palpable cords. Although the patients were warned that two injections might be necessary in order to obtain a complete extension, we were trying to solve the case with one single injection in order to justify the cost-effectiveness of the technique in our hospital, as had been done in other hospitals [9,10]. This led us to optimize the result of one single injection, trying to select the most suitable cord in terms of correction of the contracture using the hyperflexion manoeuvre, mentioned previously in Methods. This was also the reason which brought us to administer the CCH through ultrasound-guided injection. Even so, some patients did require a second injection in order to improve the extension of the finger. The result of the second injection has been excluded from the study with the objective of allowing for comparison of ultrasound-guided injection with standard injection after a single injection.

Subsequently, new studies have demonstrated the safety of using simultaneously two doses of CCH in distinct cords [11,12] and many hand surgeons no longer limit the dose to 0.58 mg, but use all of the medication available in the vial, injecting in more than one cord [13,14]. This study was carried out using always the same recommended dose of 0.58 mg, injecting in one single cord, although later on we have adopted the practice of using more dose and applying it in more than one cord if needed.

In order to perform the ultrasound-guided injection, the collaboration of the Radiology Department of our hospital was requested. In this way, learning curve errors were excluded since

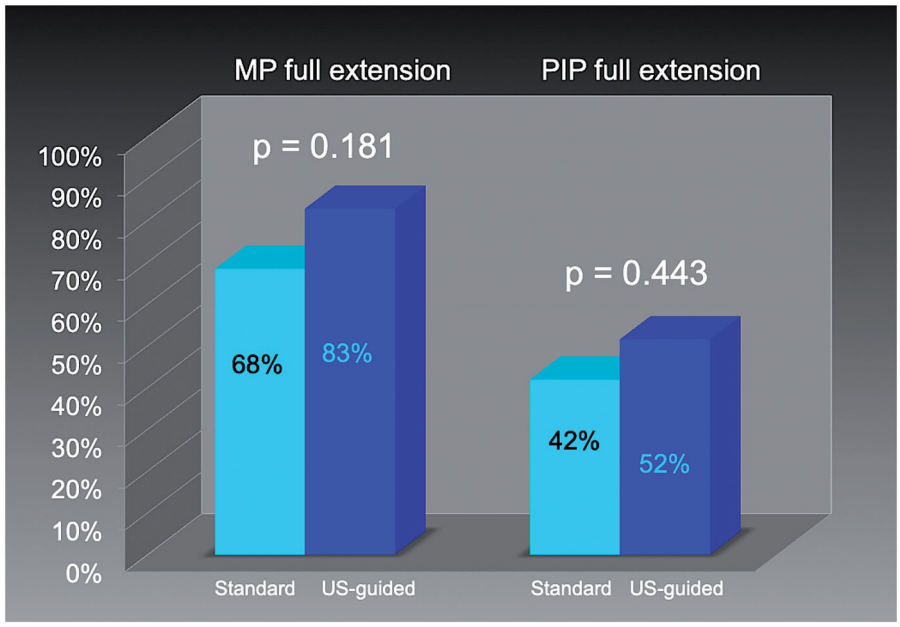


Figure 4. Comparison of percentage of joints obtaining complete extension in each treatment group.

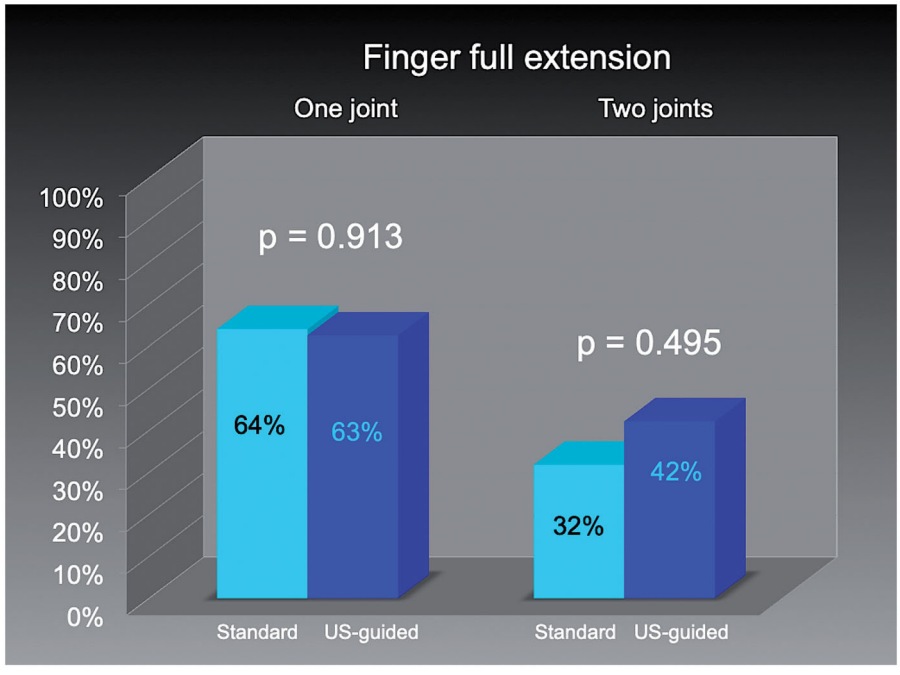


Figure 5. Comparison of percentage of cases with complete finger extension in each treatment group, depending on whether one joint or two joints of the same finger were affected.

the musculoskeletal radiologists of our hospital have expertise in this field. Even so, they treated some patients before initiating this study in order to gain experience. All of the ultrasound-guided injection cases were performed by the same radiologist (ELL). This collaboration with the Radiology Department provided us with confidence in the correct realisation of the technique, but it also limited the number of cases of the ultrasound-guided injection series, since it involved extra use of human and material resources.

The results obtained show a tendency toward the superiority of ultrasound-guided injection over standard injection, although it was not possible to demonstrate statistically. Both groups had a similar pre-injection finger contracture, but a slightly larger PIP contracture in group B may have influenced the results, since that joint is more difficult to treat.

Our results with standard injection are similar to other studies published with similar criteria for evaluation [15], both in the percentages of complete extension, as well as in the percentages of correction in each joint.

In regard to ultrasound-guided injection, we only have knowledge of one study which has used it [16], although not comparing with standard injection. These authors analysed the results of

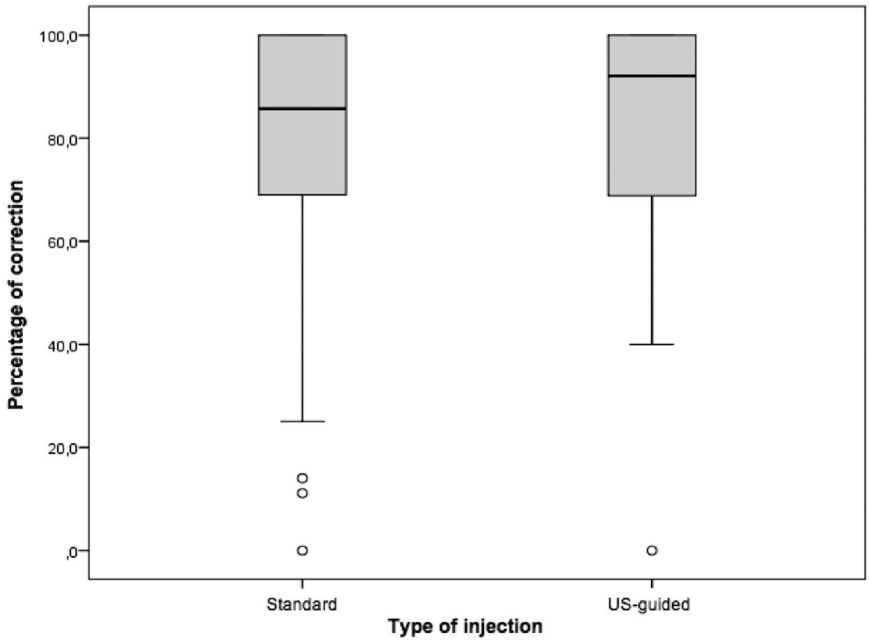
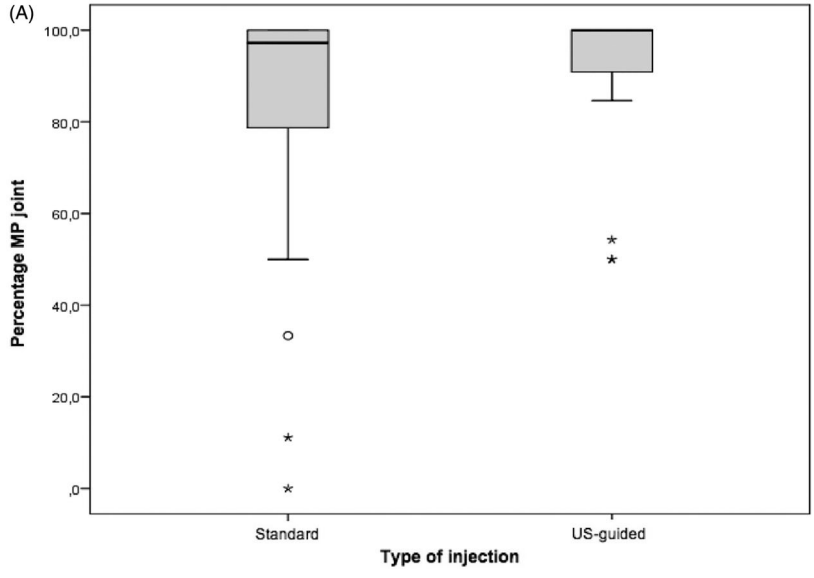


Figure 6. Comparison of percentage of correction of total finger contracture in each treatment group.



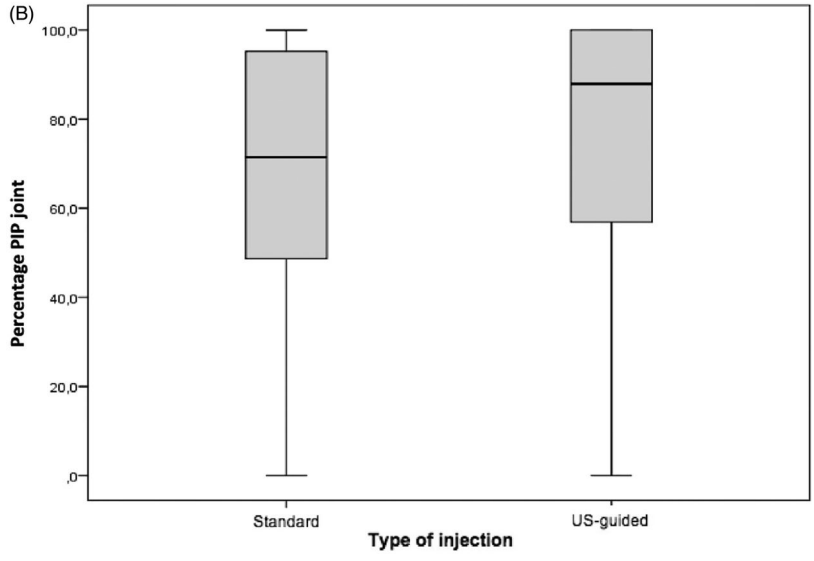


Figure 7. Comparison of percentage of correction of contracture in the MP joint (A) and in the PIP joint (B), in each treatment group.

ultrasound-guided injection after a minimum of 6 months, in both joints. The mean MP joint contracture was 37° and 8°, respectively, before and at the final control, and mean PIP joint contracture was 36° and 15°, respectively. These results do not differ from ours, although they used more than one injection in eight cases. Another study [17] has used ultrasonography to examine the cords before and after CCH treatment or needle fasciotomy, but not for injecting.

The effectiveness of the standard injection of CCH does not cease to surprise, even though there is no guarantee of being in the centre of the cord. It would appear that CCH is capable of extending itself and acting, with the sole requirement of being in the interior of the cord. Moreover, in some of the ultrasound-guided injection cases, we have been able to observe echo-graphically the extravasation outside of the cord of some amount of liquid injected exactly into its centre. This phenomenon brings us to question the importance that we had previously assigned to the precision of needle placement.

In respect to secondary effects, which have not been objective of this study, there was not much difference between standard injection and ultrasound-guided injection, especially regarding tears in the skin. Except for severe complications such as flexor tendon rupture, infection or CRPS, we have observed all kind of minor complications described with CCH [18] using both injection techniques.

The strong point of our study is that two consecutive groups of patients have been compared, with similar clinical characteristics, in which one or the other injection technique has been used, without making any prior selection of the patients. On the other hand, our study has some weaknesses. The first is that the cases were not randomly assigned to each treatment group; the second is that the number of cases is limited, and the third is that, although using the same criteria, different physicians treated each group.

The hypothesis that ultrasound-guided injection of CCH is more effective than standard injection was not demonstrated in our study. Even though ultrasound-guided injection shows improvement in the percentages of complete correction of the finger and of correction of the contracture, in comparison with standard injection, we have not seen any significant difference that would make worthwhile any change in our routine.

Once hand surgeons have incorporated echography into their standard practice, it is possible that ultrasound-guided injection could be used without any additional outlay in resources. A larger number of cases would make it possible to verify whether ultrasound-guided injection is sufficiently superior to conventional standard injection to merit its introduction into clinical practice.

Disclosure statement

No potential competing interest was reported by the author(s).

ORCID

Luis Aguilella http://orcid.org/0000-0001-7357-1654
Rosana Pérez-Giner http://orcid.org/0000-0003-4050-0379
Victoria Higueras-Guerrero http://orcid.org/0000-0003-3336-1841
Elena Belloch-Ramos http://orcid.org/0000-0002-2556-6284
María Cuenca-Torres http://orcid.org/0000-0001-7282-0639
Eva Llopis-San Juan http://orcid.org/0000-0003-0972-1616

References

[1] Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase *Clostridium histolyticum* for Dupuytren's contracture. N Engl J Med. 2009;361(10):968–979.
[2] Gilpin D, Coleman S, Hall S, et al. Injectable collagenase *Clostridium histolyticum*: a new nonsurgical treatment for Dupuytren's disease. J Hand Surg Am. 2010;35(12):2027–2038.
[3] Witthaut J, Jones G, Skrepnik N, et al. Efficacy and safety of collagenase *Clostridium histolyticum* injection for Dupuytren contracture: short-term results from 2 open-label studies. J Hand Surg Am. 2013;38(1):2–11.
[4] Warwick D, Arner M, Pajardi G, et al. Collagenase *Clostridium histolyticum* in patients with Dupuytren's contracture: results from POINT X, an open-label study of clinical and patient-reported outcomes. J Hand Surg Eur Vol. 2015;40(2):124–132.
[5] Peimer CA, Blazar P, Coleman S, et al. Dupuytren contracture recurrence following treatment with collagenase *Clostridium histolyticum* (CORDLESS study): 3-year data. J Hand Surg Am. 2013;38(1):12–22.
[6] Peimer C, Blazar P, Coleman S, et al. Dupuytren contracture recurrence following treatment with collagenase *Clostridium histolyticum* (CORDLESS [collagenase option for reduction of Dupuytren long-term evaluation of safety study]): 5-year data. J Hand Surg Am. 2015;40(8):1597–1605.
[7] Bainbridge C, Gerber RA, Szczypa PP, et al. Efficacy of collagenase in patients who did and did not have previous hand surgery for Dupuytren's contracture. J Plast Surg Hand Surg. 2012;46(3–4):177–183.
[8] Rodrigues JN, Zhang W, Scammell BE, et al. Dynamism in Dupuytren's contractures. J Hand Surg Eur Vol. 2015;40(2):166–170.
[9] De Salas-Cansado M, Cuadros M, Del Cerro M, et al. Budget impact analysis in Spanish patients with Dupuytren's contracture: fasciectomy vs. collagenase *Clostridium histolyticum*. Chir Main. 2013;32(2):68–73.
[10] Sanjuan-Cerveró R, Franco-Ferrando N, Poquet-Jornet J. Use of resources and costs associated with the treatment of Dupuytren's contracture at an orthopedics and traumatology surgery department in Denia (Spain): collagenase *Clostridium hystolyticum* versus subtotal fasciectomy. BMC Musculoskelet Disord. 2013;14:293.
[11] Coleman S, Gilpin D, Kaplan FT, et al. Efficacy and safety of concurrent collagenase clostridium histolyticum injections for multiple Dupuytren contractures. J Hand Surg Am. 2014;39(1):57–64.
[12] Gaston RG, Larsen SE, Pess GM, et al. The efficacy and safety of concurrent collagenase *Clostridium histolyticum* injections for 2 dupuytren contractures in the same hand: a prospective, multicenter study. J Hand Surg Am. 2015;40(10):1963–1971.
[13] Verheyden JR. Early outcomes of a sequential series of 144 patients with Dupuytren's contracture treated by collagenase injection using an increased dose, multi-cord technique. J Hand Surg Eur Vol. 2015;40(2):133–140.
[14] Warwick D. Dupuytren's disease: my personal view. J Hand Surg Eur Vol. 2017;42(7):665–672.
[15] Sanjuan-Cerveró R, Vazquez-Ferreiro P, Gomez-Herrero D, et al. Efficacy of collagenase *Clostridium histolyticum* for dupuytren disease: a systematic review. Rev Iberoam Cir Mano. 2017;45(02):070–088.

[16] Leclère FM, Mathys L, Vögelin E. Collagenase injection in Dupuytren's disease, evaluation of the ultrasound assisted technique. Chir Main. 2014;33(3):196–203.
[17] Strömberg J, Vanek P, Fridén J, et al. Ultrasonographic examination of the ruptured cord after collagenase treatment or needle fasciotomy for Dupuytren's contracture. J Hand Surg Eur Vol. 2017;42(7):683–688.
[18] Badalamente MA, Hurst LC. Development of collagenase treatment for Dupuytren disease. Hand Clin. 2018;34(3): 345–349.