Different collagenase delivery for Dupuytren’s disease in public hospitals

Jessica A Paynter, Vicky Tobin PhD, James CS Leong MBBS FRACS MS, Warren M Rozen MBBS PhD FRACS, David J Hunter-Smith MBBS MPH FRACS

1 Peninsula Health
Frankston Victoria
AUSTRALIA
2 The Alfred Centre
Melbourne Victoria
AUSTRALIA
3 Monash Health
Dandenong Victoria
AUSTRALIA
4 Monash Medical Centre
Clayton Victoria
AUSTRALIA

OPEN ACCESS

Correspondence
Name: David J Hunter-Smith
Address: Frankston Hospital
Peninsula Health
2 Hastings Road
Frankston Victoria 3199
AUSTRALIA
Email: david.hunter-smith@monash.edu
Phone: +61 (0)3 9784 8416

Citation: Paynter JA, Tobin V, Leong JCS, Rozen WM, Hunter-Smith DJ. Different collagenase delivery for Dupuytren’s disease in public hospitals. Australas J Plast Surg. 2020;3(2):22–31. DOI https://doi.org/10.34239/ajops.v3n2.163

Manuscript received: 30 August 2019
Manuscript revised: 20 December 2020
Manuscript accepted: 2 June 2020

Copyright © 2020. Authors retain their copyright in the article. This is an open access article distributed under the Creative Commons Attribution 4.0 Licence which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

Section: Hand

Abstract

Background: The delivery protocol of collagenase Clostridium histolyticum (collagenase) injection for Dupuytren’s disease is variable, due to limited evidence for any one approach and widespread ‘off-label’ delivery occurring in Australia. As such, this preliminary study aimed to assess whether different collagenase delivery protocols for treating Dupuytren’s disease have an impact on effectiveness and safety. It was hypothesised that different collagenase delivery would affect outcomes.

Methods: This preliminary, prospective study included a consecutive cohort of adult patients with Dupuytren’s disease being treated with collagenase within two Australian public hospitals to determine whether different collagenase delivery protocols impact on effectiveness and safety. The therapeutic effect was measured objectively using the total passive extension deficit (TPED), clinical success and clinical improvement. Three patient-reported outcome measures (PROMs) were used: Unité Rhumatologique des Affections de la Main (URAM), the Southampton Dupuytren’s Scoring Scheme and the Canadian Occupational Patient-Specific Functional Scale (PSFS).

Results: The delivery of collagenase was variable at both clinics. The number of patients treated with collagenase at Institute I and Institute II was 49 and 18, respectively. Clinical success was achieved in 42 per cent of the Institute I and 35 per cent of the Institute II cohort. A statistically significant reduction in all three PROMs was observed for both cohorts. No significant differences between effectiveness (clinical success, clinical improvement, TPED, PROMs) or safety was found when comparing the two cohorts.

Conclusion: The delivery of collagenase was variable at Institutes I and II, but these differences did not appear to impact the effectiveness or safety of collagenase delivery.
Introduction
Dupuytren's disease is a common, benign fibrotic disease resulting in finger flexion contractures.\(^1\) It can lead to significant functional hand impairment,\(^2\) with patients therefore seeking treatment.\(^3\) Treatment focuses on four characteristics identified by Tubiana in 1975: ‘to correct deformity, avoid complications, shorten postoperative recovery, and prophylactically prevent recurrences.’\(^4\)

Surgical correction of Dupuytren's disease via fasciotomy, fasciectomy and dermofasciectomy has been the mainstay of therapy over recent decades.\(^5,6\) Minimally invasive techniques include percutaneous needle aponeurotomy and collagenase injections. Percutaneous needle aponeurotomy is advantageous due to rapid recovery times and the ability for outpatient management.\(^7\) However, recurrence rates are higher compared with fasciectomy and dermofasciectomy.\(^8\) These two surgical options are associated with a lengthier recovery time and a lower recurrence rate but an increased complication profile.\(^3\)

In 2013, collagenase was licensed by the Therapeutic Goods Administration in Australia for the treatment of Dupuytren's disease. The drug is not Medicare indexed, limiting its accessibility for patients.

The aim of this study was to assess differences in effectiveness and safety that may arise due to different collagenase delivery protocols. It was hypothesised that different protocols would have an impact on the effectiveness and safety of collagenase delivery.

Methods
A preliminary, prospective study occurred from February to October 2018. It was undertaken at two tertiary hospitals in Australia. Institute II commenced collagenase treatment in 2014 and Institute I in 2015.
success (failure, partial success, complete success) and any complications on a manipulation form.

Data were then analysed using STATA version 15 (StataCorp, College Station, TX). For each clinic, and subsequent data set, continuous data were assessed using the Shapiro-Wilk normality test, and normally distributed and unpaired data were assessed using Student’s t-test. Categorical or interval data expressed as a percentage were compared between the two cohorts using Fisher’s exact test.

Data were assessed for each individual digit and as a percentage of all digits. Furthermore, when clinical success or clinical improvement was detected, the clinical improvement values were used to calculate the median and range of clinical success and clinical improvement. This was repeated for each individual joint injected with collagenase (metacarpophalangeal joint, proximal interphalangeal joint, distal interphalangeal joint). The percentage of digits that achieved clinical success and clinical improvement within the cohorts was compared using Fisher’s exact test.

A Shapiro-Wilk test was implemented to assess for normal distribution of the three PROMs and TPED (continuous, paired data). The data were found to be non-normally distributed. Continuous non-normal data within each clinic that was paired (TPED or PROMs—before versus after collagenase injection) were compared using the Wilcoxon signed rank test. Comparison between the two clinics for pre- and post-collagenase outcomes (TPED and PROMs) was undertaken after generating a new variable (eg, TPED difference=TPED pre-collagenase—TPED post-collagenase). This was performed to simplify the data structure and enable a non-parametric equivalent of a t-test (Mann–Whitney U-test) to be used.

Adverse effects

Adverse effects were recorded by asking or observing patients for any side effects that they had experienced. These were recorded as a percentage of the participant cohort that developed the side effects. Complications were analysed as a total sum across all digits and joints. Complications were classified as treatment-related and serious treatment-related adverse effects.

A p-value less than 0.05 was deemed statistically significant.

Analysis

Study population

At Institute I and Institute II, 49 and 18 participants, respectively, were recorded at initial visit, manipulation and first review (six weeks post-treatment).

Clinic design comparison

Table 1 shows the key constituents of each clinic design. This is a qualitative tabulation of how collagenase is delivered at each clinic.

Clinic quantitative results

Demographic data

Seven statistically significant demographic differences were recorded when comparing Institute I and Institute II. Average age (Institute I > Institute II: 68 years old:58 years old), body mass index (BMI) >30 (Institute I > Institute II: 51%:19%), diabetes history, smoking history, family history, current use of blood thinning medication and weekly alcohol consumption were significantly different between the two cohorts. The most common country of origin was Australia for both cohorts, although Institute II recorded a higher percentage of diversity in country of origin.

Dupuytren’s disease history

Two statistically significant disease history variables were recorded when comparing Institute I and Institute II—disease length and previous hand surgery or injury. The mean length of years with Dupuytren’s disease was 9.7±5.8 years at Institute I versus 7.2±6.8 years at Institute II. A statistically significant greater percentage of Institute II participants recorded a previous hand injury or surgery unrelated to Dupuytren’s disease (75%) compared with Institute I (35%).
### Table 1: Hospital comparison of key collagenase *Clostridium histolyticum* delivery design features: Institute I versus Institute II

| Collagenase criteria                      | Institute I                  | Institute II                  |
|------------------------------------------|------------------------------|------------------------------|
| Dupuytren’s disease severity             | High severity                | High severity                |
| Low severity                             |                              |                              |
| Number of cords                          | One                          | Multiple                     |
| Recurrent cords                          | Yes                          | Yes                          |
| Patient autonomy                         | Yes                          | Yes                          |
| Recent stroke                            | Yes                          | Yes                          |
| Pregnancy/breastfeeding                  | No                           | No                           |
| Bleeding disorder                        | Yes                          | Yes                          |
| Chronic neuromuscular condition          | Yes                          | Yes                          |
| Anticoagulant use                        | Yes                          | Yes                          |
| Tetracycline use                         | Yes                          | Yes                          |

| Injection protocol                       |                             |                             |
|------------------------------------------|------------------------------|------------------------------|
| Frequency                                | Weekly                       | Quarterly                    |
| No. of patients                          | 4                            | 20–30                       |
| Location                                 | Clinic                       | Clinic                       |
| Anaesthetic (Y or N)                     | Yes                          | No                           |
| Type of anaesthetic                      | Lidocaine (lignocaine) 1%–2%| Not applicable               |
| Anaesthetic volume                       | 5–20mL                       | Not applicable               |
| Anaesthetic location                     | Palm/ring block              | Not applicable               |
| Powdered drug amount                     | 0.9                          | 0.9                          |
| Diluent volume (mL)                      | 0.5                          | 0.39                         |
| Solution volume (mL)                     | 0.5                          | 0.25                         |
| Dose per injection                       | 0.9                          | 0.58                         |
| Number of injections                     | Single                       | Multiple                     |
| Bilateral injections                     | No                           | Yes                          |
| Injection direction (at skin)            | Oblique=45°                  | Perpendicular=90°           |
| Multiple mini injections                 | Yes                          | Yes                          |
| <30 days since last injection (re-injection) | Yes                      | No                           |
| Dressing                                 | Gauze                        | Gauze                        |
| Crepe bandage                            | Yes                          | No                           |
| Sling                                    | No                           | No                           |

| Observation                              |                             |                             |
|------------------------------------------|------------------------------|------------------------------|
| Vitals checked                           | Yes                          | No                           |
| Time observing                           | 10 minutes                   | Nil                          |

| Staff at injection                       |                             |                             |
|------------------------------------------|------------------------------|------------------------------|
| Consultants                              | 2                            | 1                            |
| Registrars                               | 1                            | 1                            |
| Resident                                 | 1                            | 1                            |
| Clinical coordinator                     | 1                            | 2                            |
| Nurse                                    | 0                            | 0                            |
| **Manipulation** |   |   |
|------------------|---|---|
| Time since collagenase (days) | 7 | 2 |

| **Location** |   |   |
|---------------|---|---|
| Clinic |   | Theatre |

| **Anaesthetic type** |   |   |
|----------------------|---|---|
| Local |   | Sedation |

| **Anaesthetic classification** |   |   |
|--------------------------------|---|---|
| Palm/ring block |   | Light sedation |

| **Lidocaine (lignocaine) 1–2%** |   |   |
|---------------------------------|---|---|
| Yes |   | No |

| **Propofol 1%** |   |   |
|-----------------|---|---|
| No |   | Yes |

| **Fentanyl** |   |   |
|---------------|---|---|
| No |   | Yes |

| **Oxygen mask** |   |   |
|-----------------|---|---|
| No |   | Yes |

| **Consultant surgeon** |   |   |
|-------------------------|---|---|
| 1 |   | 1 |

| **Surgical registrar** |   |   |
|------------------------|---|---|
| 1 |   | 2 |

| **Surgical resident** |   |   |
|-----------------------|---|---|
| 0 |   | 1 |

| **Anaesthetic consultant** |   |   |
|---------------------------|---|---|
| 0 |   | 1 |

| **Anaesthetic registrar** |   |   |
|---------------------------|---|---|
| 0 |   | 1 |

| **Anaesthetic nurse** |   |   |
|-----------------------|---|---|
| 0 |   | 1 |

| **Scrub/scout nurse** |   |   |
|-----------------------|---|---|
| 0 |   | 2 |

| **Preoperative/postoperative nurse** |   |   |
|--------------------------------------|---|---|
| 0 |   | 2 |

| **Outpatients nurse** |   |   |
|-----------------------|---|---|
| 1 |   | 0 |

| **Theatre technician** | 0 | 1 |

| **Porter** |   |   |
|-----------|---|---|
| 0 |   | 1 |

| **Clinic coordinator** | 0 | 2 |

| **Total staff** |   |   |
|-----------------|---|---|
| 3 |   | 15 |

| **Dressings** |   |   |
|---------------|---|---|
| Gauze |   | No |

| **Crepe bandage** |   | No |

| **Plaster cast/back slab** |   | No |

| **Skin split protocol** |   |   |
|-------------------------|---|---|
| Dressing |   | Jelonet, crepe, gauze |

| **Antibiotics** |   |   |
|-----------------|---|---|
| No |   | Yes—cefalexin |

| **Analgesia** |   |   |
|----------------|---|---|
| No |   | Yes |

| **Follow-up** |   |   |
|---------------|---|---|
| As per normal |   | Earlier |

| **Splint** |   |   |
|------------|---|---|
| As per normal—volar splint |   | Only for wound healing |

| **Frequency** |   |   |
|---------------|---|---|
| Worn nightly |   | All the time |

| **Length** |   |   |
|------------|---|---|
| 4 months |   | Until wound heals |

| **Restrictions** |   |   |
|------------------|---|---|
| No |   | Full-time until healed |

| **Hand therapy** |   |   |
|------------------|---|---|
| Yes |   | No |

| **Hand exercises provided by** |   |   |
|-------------------------------|---|---|
| Hand therapist |   | Information sheet provided by doctors |

| **Follow-up frequency** |   |   |
|-------------------------|---|---|
| 3 visits (average) |   | 0 visits (average) |

| **Clinic review** |   |   |
|-------------------|---|---|
| 1 week review |   | Yes |

| **First review** |   |   |
|------------------|---|---|
| 6 weeks |   | 1 month |
Effectiveness

Correction of contracture

There was no statistically significant difference in the effectiveness measures between the two clinics when analysing effectiveness.

There was nil significant difference in the proportion of each digit at each clinic that achieved clinical success or clinical improvement.

Overall, Institute I recorded greater clinical success (42%) compared with Institute II (35%). This was not statistically significant, as shown in Table 2. In comparison, CORD I and CORD II recorded a clinical success cohort percentage of 85 per cent and 78 per cent, respectively.2,14

Institute II achieved a greater clinical improvement (86%) compared with Institute I (78%), which was not statistically significant, as highlighted in Table 2. In comparison, CORD I and CORD II recorded a clinical success cohort percentage of 85 per cent and 78 per cent, respectively.2,14

The change in total passive extension deficit (TPED) at first review following collagenase was found to be statistically significant in both cohorts (Figure 1). As shown in tables 2 and 3, in both cohorts the fourth and fifth digit had a better response to treatment. To determine whether differences existed between the TPED at each clinic a Mann–Whitney U-test was used. Nil statistically significant difference in the median TPED values from the two clinics (p=0.09) (Figure 1) was recorded.

Patient-reported outcome measures

A statistically significant reduction in all three PROMs occurred within Institutes I and II at six weeks post-collagenase treatment (Table 3). The three most common patient-reported responses to the PSFS were difficulty, concerns or grievances with the following tasks:

- ‘catching on things’
- ‘getting gloves on’
- ‘progression’.

A Mann–Whitney U Test was employed to determine whether significant differences existed in the three PROMs when comparing the two clinics. There

Table 2: Effect of collagenase: clinical success and clinical improvement per digit at first review: Institute I versus Institute II

| Digit | Clinical success | Clinical improvement |
|-------|------------------|----------------------|
|       | Institute I | Institute II | Test: Ins I vs Ins II | Institute I | Institute II | Test: Inst I vs Ins II |
|       | Total no. of digits injected at 6 wks | (% of total no. of digits injected) at 6 wks | Total number of digits injected at 1 m | (% of total no. of digits injected) at 1 m | Fisher's exact test | Fisher's exact test |
| Thumb | 4/7 | 57% | 3/7 | 43% |
| Index | 3/4 | 75% | 2/4 | 50% |
| Middle | 8/10 | 80% | 1/5 | 20% | p=0.09 | 8/10 | 80% | 5/5 | 100% | p=0.52 |
| Ring | 22/31 | 71% | 9/12 | 75% | p=1.00 | 28/31 | 90% | 11/12 | 92% | p=1.00 |
| Little | 12/37 | 32% | 12/37 | 25% | p=0.731 | 33/37 | 89% | 10/12 | 83% | p=0.63 |
| Overall | 49/89 | 55% | 13/29 | 45% | p=0.395 | 74/89 | 83% | 26/29 | 90% | p=0.56 |

Ins I=Institute I; Ins II=Institute II
Table 3: Results of patient reported outcome measures pre- and first review post-collagenase injection

| Test                                      | Institute I | Institute II |
|-------------------------------------------|-------------|--------------|
|                                           | Number      | Median Range (min max) | Number      | Median Range (min max) |
| Test: Wilcoxon signed rank test           | 46          | Z=5.8 p=0.0000       | 17          | Z=2.9 p=0.003          |
| Southampton difference                     |             |                |             |                |
| Institute I vs Institute II               |             |                |             |                |
| Mann Whitney test                         |             |                |             |                |
| Test: Wilcoxon signed rank test           | 49          | Z=6.1 p=0.000    | 17          | -3.6 p<0.001         |
| URAMs difference                          |             |                |             |                |
| Institute I vs Institute II               | p=0.12      |                |             |                |
| Mann Whitney test                         |             |                |             |                |
| Test: Wilcoxon signed rank test           | 43          | Z=5.7 p=0.000    | 17          | 3.5 p=0.0004         |
| PSFS difference                           | p=0.53      |                |             |                |

First review—6 weeks for Institute I and 1 month for Institute II. Wilcoxon signed rank test: used to assess whether significant change was achieved in each PROM following collagenase treatment at first review at each clinic. Mann Whitney test: used to assess significant differences in PROM outcomes between the two hospitals.

Table 4: Adverse effects post-injection—Institute I vs Institute II versus CORD I vs CORD II results

| Adverse effect   | Institute I | Institute II | CORD I | CORD II |
|------------------|-------------|--------------|--------|---------|
| Treatment-related adverse effects         | 88%         | 95%          | 96.60% | 100%    |
| Serious adverse effects                     | 1%          | 0            | 1%     | 2.20%   |
| Skin tears                                  | 56%         | 48%          | 10.80% | Not documented |
| Pain                                         | 22%         | 76%          | 26.50% | Not documented |
| Bruising                                    | 40%         | 76%          | 51%    | 73.30%  |
| Oedema                                       | 71%         | 91%          | 72.50% | 77.80%  |
| Lymphadenopathy                              | 2%          | 10%          | 9.80%  | 24.40%  |
| Blisters                                    | 13%         | 24%          | Not documented | Not documented |
| Other                                        | 7%          | 0            | Not documented | Not documented |
| Self-manipulation                            | 14%         | 5%           | Not documented | Not documented |

was no statistically significance difference in each PROM (URAM, Southampton score and PSFS) reduction that occurred when comparing the two, as shown in Table 3.

Safety
Adverse effects following collagenase treatment at both clinics were comparable with results from the CORD I and II studies (Table 4). Of the Institute I and II cohorts, 88 per cent and 95 per cent, respectively, developed a treatment-related adverse effect. Nil serious adverse effects were recorded at Institute II, compared with one per cent of the Institute I cohort. These included two admissions for pain. Skin tears were more frequently observed, compared with the trial
cohorts. The most common adverse effect recorded was oedema, reported in 71 per cent and 91 per cent and of the Institute I and Institute II cohort, respectively.\textsuperscript{2,14}

**Discussion**

This study explored the application of collagenase as a therapeutic for people with Dupuytren's disease within two public hospital clinics using different delivery protocols. The preliminary data show that collagenase is a safe and effective treatment for people with Dupuytren's disease, irrespective of clinic design and delivery of collagenase. All outcomes of effectiveness (clinical success, clinical improvement, TPED and the three PROMs) showed a statistically significant improvement of contracture and hand function following collagenase treatment at six weeks post-injection in both clinics, and no significant difference was found when comparing between the two.

When collagenase was first introduced as a treatment option, the literature recommended its use for low-severity disease, with a maximum of only three doses per patient.\textsuperscript{2} However, since the drug's approval, and its increasing use within the surgical profession, clinicians have become increasingly familiar and professionally comfortable with providing collagenase. This is evident as Institutes I and II currently offer the treatment for any level of disease severity. Institute II offers treatment to bilateral hands at the same sitting if warranted, whereas Institute I only treats one hand per sitting. Both clinics treat recurrent cords (those that have previously been treated with collagenase or by another non-surgical/surgical method).

**Injection delivery**

Injection of collagenase was variable—the dose of collagenase, number of injections, injection direction and neo-adjunctive use of anaesthesia all differed between the two clinics. Institute I provided local anaesthesia with lidocaine (lignocaine), whereas Institute II solely injected the collagenase. Both clinics provided multiple small injections of the collagenase dose, which involved injecting a small amount of solution at a point along the cord, and continually injecting with the same solution along the cord.

The dosage delivered between the two clinics varied. Institute I provided an on-label solution dose of 0.25mg, in a diluent volume of 0.39mL, which equates to a dose of 0.58mg/mL. Institute I administered a dose of 0.9mg/mL across an average of 2.5 joints per ampoule. Institute II would frequently use 0.58mg over more than one joint. Institute II provided multiple doses of collagenase compared with Institute I. It is important to highlight that as this was a preliminary study, a conclusion cannot currently be made regarding different doses, their impact upon effectiveness and adverse effects.

**Manipulation**

**Timeframe**

The timeframe for manipulation was two days after the collagenase injection at Institute II, compared with seven days at Institute I. Institute I recorded a higher percentage of self-manipulation, potentially due to the increased timeframe, which may have enabled this to occur.

**Location**

Manipulation was performed in an operating theatre at Institute II and an inpatient clinic at Institute I. Manipulation in the operating theatre was primarily attributed to the ability to provide intravenous light sedation.

**Anaesthesia**

Institute I provided local anaesthetic for patients undergoing manipulation, whereas at Institute II patients received intravenous sedation (so the patients maintained their airway under anaesthetic supervision).

**Hand therapy**

Institute I provided individualised, thermal hand splints and an appointment with a hand therapist to learn exercises aimed at maintaining the contracture correction. Institute II provided all patients with a paper instruction sheet explaining and illustrating the hand exercises.
Collagenase effectiveness

Contracture degree
A statistically significant reduction in median contracture degree (clinical success, clinical improvement and TPED) for both cohorts was recorded post-collagenase treatment at the first review. Furthermore, the range and interquartile across outcomes also decreased. In both cohorts, an improvement in the degree of flexion contracture was recorded at first review.

Across both cohorts, no digit was more responsive to collagenase treatment than another. Although Dupuytren’s disease is more prevalent in the fourth and fifth digits, it does not appear that collagenase has a pertinent response to a particular digit (for all effectiveness outcome measures).

Patient-reported outcome measures
A statistically significant reduction in functional impairment in both cohorts was recorded for all three PROMS. Similarly, patients in both cohorts reported a significant decrease in their functional impairment for the URAM, Southampton score and PSFS.9–11

Collagenase safety
Adverse effects occur with treatment. Nil serious adverse effects were recorded at Institute II, while one per cent of the Institute I cohort experienced a serious adverse effect. This is comparative to the existing literature, whereby in CORD I Hurst and colleagues reported one per cent of the treatment cohort developing a serious treatment adverse effect.2 The most common treatment-related adverse effects recorded were oedema, bruising and pain, which are acute, self-limiting occurrences that indicate an inflammatory response to the collagenase treatment.

The Institute II cohort recorded a greater proportion of adverse effects, which may be attributed to timing manipulation two days after injection and manipulation occurring under intravenous sedation.

Most adverse effects relied upon patient recall or reporting. Consequently, the validity of adverse effects is lessened by the impact of recall or reporting bias. This could be further heightened by the memory and hearing impairments of the ageing cohort.

Conclusion
These preliminary data demonstrate that collagenase results in improved functional outcomes, both objectively and as perceived by the patient. Collagenase leads to reduced contracture degree, as reported by the outcomes of clinical success, clinical improvement and TPED scoring as measured by a goniometer. This small, preliminary study investigated two different collagenase clinics and found that collagenase clinic design did not impact upon effectiveness or safety outcomes, rejecting the hypothesis. Both clinics deliver collagenase off-label and unconventionally, with nil statistically significant difference in outcomes, and outcomes that were comparable with CORD II (which was undertaken in Australia).14

This preliminary study demonstrated that there is no best way to approach Dupuytren’s disease management. Different collagenase delivery protocols at public hospitals can effectively and safely treat the disease.

Ethics approval
This study was approved by both clinics’ human research ethics and governance committees with reference numbers LRR17PH7 and 13226, respectively. Informed consent was obtained for data and photographs collected for this study.

Disclosure
The authors received no financial support for the research, authorship and/or publication of this article.

David J Hunter-Smith and Warren M Rozen were consultants for Actelion (previous distributor of XIAFLEX® in Australia). The authors have no other conflicts of interest to declare.
References

1. Shih B, Bayat A. Scientific understanding and clinical management of dupuytren disease. *Nat Rev Rheumatol*. 2010;6(12):715–26. https://doi.org/10.1038/nrrheum.2010.180 PMid:21060335

2. Hurst LC, Badalamente MA, Hentz VR, Hotchkiss RN, Kaplan FT, Meals RA, Smith TM, Rodzvilla J. Injectable collagenase Clostridium histolyticum for Dupuytren's contracture. *N Engl J Med*. 2009;361(10):968–79 https://doi.org/10.1056/NEJMoA0810866 PMid:19726771

3. Ball C, Pratt AL, Nanchahal J. Optimal functional outcome measures for assessing treatment for Dupuytren's disease: a systematic review and recommendations for future practice. *BMC Musculoskelet Disord*. 2013;14(1):131 https://doi.org/10.1186/1471-2474-14-131 PMid:23575442 PMCid:P-MC3637830

4. Tubiana R. Planning of surgical treatment. *The Hand*. 1975;7(3):223–27. https://doi.org/10.1016/0072-968X(75)90057-1

5. Shaw RB, Chong AK, Zhang A, Hentz VR, Chang J. Dupuytren's disease: history, diagnosis, and treatment. *Plast Reconstr Surg*. 2007;120(3):44e–54e. https://doi.org/10.1097/01PRS.0000278455.63546.03 PMid:17700106

6. Eaton C. Evidence-based medicine: Dupuytren contracture. *Plast Reconstr Surg*. 2014;133(5):1241–251. https://doi.org/10.1097/PRS.0000000000000889 PMid:24776555

7. Lee Matthew VK, Hunter-Smith D. Needle fasciectomy for Dupuytren's disease: an Australian perspective. *ANZ J Surg*. 2009;79(11):776–78. https://doi.org/10.1111/j.1445-2197.2009.05101.x PMid:20078523

8. Eaton C. Percutaneous fasciectomy for Dupuytren's contracture. *J Hand Surg Am*. 2011;36(5):910–15. https://doi.org/10.1016/j.jhsa.2011.02.016 PMid:21527145

9. Beaudreuil J, Allard A, Zerkak D, Gerber RA, Cappelleri JC, Quintero N, Lasbleiz S, Bernabé B, Orcel P, Bardin T, URAM Study Group. Unité Rhumatologique des Affections de la Main (URAM) scale: development and validation of a tool to assess Dupuytren's disease-specific disability. *Arthritis Care Res*. 2011;63(10):1448–455. https://doi.org/10.1002/acr.20564 PMid:21786431

10. Mohan A, Vadher J, Ismail H, Warwick D. The Southampton Dupuytren’s Scoring Scheme. *J Plast Surg Hand Surg*. 2014;48(1):28–33. https://doi.org/10.3109/2000656X.2013.794349 PMid:24428161

11. Chatman AB, Hyams SP, Neel JM, Binkley JM, Stratford PW, Schomberg A, Stabler M. The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction. *Phys Ther*. 1997;77(8):820–29. https://doi.org/10.1093/ptj/77.8.820 PMid:9256870

12. Stratford P, Gill C, Westaway M, Binkley J. Assessing disability and change on individual patients: a report of a patient specific measure. *Physiother Can*. 1995;47(4):258–63. https://doi.org/10.3138/ptc.47.4.258

13. STATA Statistical Software. Release fifteen [web page]. StataCorp [2017]. Available from: https://www.stata.com.

14. Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N. Injectable collagenase Clostridium histolyticum: a new nonsurgical treatment for Dupuytren’s disease. *Hand Surg Am*. 2010;35(12): 2027–38. https://doi.org/10.1016/j.jhsa.2010.08.007 PMid:21134613