Hand function 5 years after treatment with collagenase *Clostridium histolyticum* injection for Dupuytren's disease

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Goransson, I., Brudin, L., Irbe, A., Turesson, C., (2021), Hand function 5 years after treatment with collagenase *Clostridium histolyticum* injection for Dupuytren's disease, *Journal of Hand Surgery, European Volume*, , 17531934211002383. <https://doi.org/10.1177/17531934211002383>

Original publication available at:

<https://doi.org/10.1177/17531934211002383>

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TITLE: Hand function five years after treatment with collagenase clostridium histolyticum injection for Dupuytren's disease.

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Keywords Dupuytren's disease, collagenase, long term follow-up, hand function, satisfaction, activities of daily living

Acknowledgements The authors would like thank to the Orthopaedic Clinic and Department of Occupational Therapy at Kalmar County Hospital and Department of Hand Surgery, Plastic Surgery and Burns, Linköping University Hospital for generous help and support during the study process.

Declaration of conflicting interests The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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

Ethical approval The study was approved by the Swedish Ethical Review Authority in Linköping, Sweden, Dnr 2017 / 389-31.

Informed consent Verbal informed consent was obtained from all patients before the study.

ABSTRACT

The aim of this study was to report hand function, disability and satisfaction, and patients' perception of functionally troublesome contractures five years after injection with collagenase clostridium histolyticum and hand therapy for Dupuytren's disease. Data from 79 patients were collected before and at three, 12 and 60 months after treatment. Hand function was significantly improved, and 70% achieved a functional range of motion in the treated hand. QuickDASH scores and range of motion were best at three months follow-up. At 60 months, mean total extension deficit was 48 degrees which was 57% of the deficit before treatment. Thirty-seven patients (47%) had developed recurrent contractures in treated finger(s) meeting the criteria for new treatment. The threshold for functionally troublesome contractures was found to be 30-60 degrees in the finger joints. Treatment was experienced as painful, but few hand function problems occurred. Most patients would choose this treatment method again.

Level of evidence: IV

Key words: Dupuytren's disease, collagenase, long-term follow-up, hand function, satisfaction, activities of daily living.

INTRODUCTION

Since injection with collagenase clostridium histolyticum (CCH) was approved for treatment of Dupuytren's disease in 2011, it has become an alternative to fasciectomy and needle aponeurotomy (Zhao et al., 2016). Recurrence can occur after all treatment methods (Layton and Nanchahal, 2019) and has been defined as loss of 20° of passive motion per treated joint (Kan et al. 2017). Recurrence and complication rates have been shown to be important in patients' preferences for treatment (Kan et al., 2016). Long-term outcomes (3-5 years) after CCH injection have shown the treatment to be more effective in metacarpophalangeal (MCP) joints, while risk of recurrence is higher in proximal interphalangeal (PIP) joints (Nordenskjöld et al., 2019; Peimer et al., 2015a). Outcomes on disability and satisfaction five years after CCH injection have shown improvements, especially among those treated for the MCP joints (Werlinrud et al., 2018). However, further knowledge is needed about long-term changes in hand function after CCH injection that may affect the ability to use the hand in daily activities. Thus, a combination of outcome measures has been proposed to best evaluate treatment results (Ball et al., 2013; Layton and Nanchahal, 2019).

The aim of this study was to report hand function, disability and satisfaction, and patients' perception of functionally troublesome contractures five years after injection with CCH and hand therapy for Dupuytren's disease.

METHODS

This was a retrospective, single centre cohort study including examination on four occasions: before treatment and at three, 12- and 60-months after CCH injection. A quantitative method was used with physical measurements and standardized questionnaires as well as interview-based study-specific questions. The study was approved by the Swedish Ethical Review Authority in Linköping, ref 2017 / 389-31.

Patients

The study group consisted of the first 102 patients treated with CCH injection at the Kalmar county hospital during 2012 – 2014. They had been followed in a structured way for one year for quality assurance purposes. Inclusion criteria for the present study were being willing to participate in the study and having had treatment with CCH. The cases included both primary and recurrent Dupuytren's disease. Criteria used at the clinic, when the method was introduced, were a palpable cord impairing daily activities and causing an extension deficit of at least 45 degrees in an isolated finger joint (MCP or PIP joint) or more than 60 degrees as the sum of the extension deficits in the whole finger.

Exclusion criteria were treatment for the thumb or having other health problems that affected the possibility of participation, e.g. dementia. Of the 102 patients, 96 had participated in a 12-month follow-up. When checking against the population register, eleven of those 96 had died, leaving 85 patients eligible for the present study. The patients were contacted by letter which was followed up by telephone with a request for participation in a five-year follow-up. As many patients were elderly, we offered to carry out the follow-up at home or at a convenient care facility. Three declined to participate, two had other health issues and one was living abroad. Seventy-nine patients accepted and gave verbal consent to participate. Of these, 56 were treated for one finger and 23 for two or three fingers. The first treatment for each patient was included in the study. Background data on the study sample is given in Table 1.

Treatment

All CCH injections and extension procedures were performed by the same experienced specialist physician (AI) (level 3, Tang and Giddins, 2016), who had also assessed that criteria for treatment were met at a preparatory visit. CCH was given in accordance with the pharmaceutical company's safety directives. For each patient, a vial of 0.9 mg of clostridium powder was diluted with 0.4 ml of sterile diluent and injected into the cord. A maximum of three cords in the hand were treated at the same time. Extension of the finger(s) was performed after a mean of four days (range 2-6). Local anaesthesia with 1% Carbocaine was used to prevent pain. Thirty-two patients experienced some degree of skin rupture after the extension procedure of which deep skin lesions ($n = 8$) were bandaged in a plaster splint for one week (Table 1). Oedema occurred after both the injection and the extension procedure which was severe in 6 cases. Ongoing treatment with anticoagulants was not paused, to avoid circulatory/blood clotting risks to the patients ($n=6$).

After extension of the finger(s) (or removal of the plaster), an occupational therapist (OT) fitted the patient with a palmar custom-made finger extension orthosis immobilizing the wrist and part of the hand to be used day and night for 3 - 5 days. Thereafter, the patients were instructed to use it at night for 3 months. Instructions were given for active finger flexion and extension at the same first visit. Hand function and fit of the orthosis was checked by the OT after one week. The participants used the orthosis for varying lengths of time (median 87, range 8 -198 days). Additional visits to the OT for follow-up were based on the patients' need (median 2, range 1 – 8 visits).

Data collection

Data from before treatment and at three- and 12-month follow-up was obtained from the patients' records. Information collected consisted of physical examination of hand function and self-reported questionnaires. The initial measurements at baseline had been performed by OTs just before treatment. The follow-up examinations and measurements at three and 12 months had been performed by OTs at the county hospital or, in some cases, by OTs at nearby hospitals. Data collection at the five-year follow-up was carried out by one of the OTs who participated in the introduction of the CCH treatment at the clinic.

Physical examination of hand function consisted of:

- Active range of movement of the MCP, PIP and distal interphalangeal (DIP) joints in treated fingers measured with a goniometer according to guidelines (HAKIR, 2010, 2019) at all follow-up assessments.
- Palpation and note of nodules and new cords in the hand.
- Touch sensibility in the worst finger measured at the fingertip with Semmes-Weinstein's monofilaments (SWM) (Bell Krotoski, 2011) at baseline and after three and 12 months.

The questionnaires filled in at all follow-up visits consisted of:

- Swedish translation of the Quick Disabilities of the Arm, Shoulder and Hand questionnaire (QuickDASH) (Atroshi et al., 2000; Rodrigues et al., 2016). Minimal clinically important difference for the QuickDASH is 16 - 20 points (Franchignoni et al., 2014).
- Problems with hand function questions taken from the survey HQ-8 in the Swedish National Quality register for Hand Surgery (HAKIR) (HAKIR, 2010, 2018) relating to pain on load, pain during motion without load, pain at rest, stiffness, weakness,

numbness/tingling and cold sensitivity. All questions were estimated on a visual analogue scale (VAS) where 0 = no problems and 100 = worst possible problems.

- Diagnostic and study-specific questionnaires that included the patient's experience of treatment and physical and mental satisfaction with the result of treatment.

Satisfaction with current hand function was estimated on a 7-degree scale from very satisfied to very dissatisfied. Overall satisfaction with outcome of treatment was collected from the HAKIR survey (HAKIR, 2010, 2018) and was estimated with VAS where 0 = very satisfied and 100 = very dissatisfied. Ability to use the hand in daily activities was estimated on a ten-point scale where 1=very poor and 10=very good.

- Experience of pressure/touch discomfort to the palmar surface was estimated at all follow-up assessments on a 4-degree scale from “not at all” to “severe problems”.
- Two open-ended questions were included at the five-year follow-up. The first question regarded difficulties in everyday life before treatment and the second about patients’ opinion when the contractures became troublesome for these activities. The patients were instructed to shape their fingers into the estimated interfering position. The MCP and PIP joints angles were then measured with a goniometer.

Analysis

We calculated the total active flexion (TAF) and total active extension deficit (TAE) by adding measurement of the isolated finger joints respectively, giving the total active range of motion (AROM). Hyperextension at any joint was converted to 0 degrees. To manage multiple observations, (Altman and Bland, 1997; Bryant et al., 2006) patients were divided into two subgroups: patients with one treated finger (n = 56) and patients with multiple treated fingers (n = 23). For the patients with multiple treated fingers, we calculated a mean ROM for the MCP, PIP and DIP joints as well as for total AROM (Matthews et al., 1990). Outcomes

were compared to a mean total arc of functional range of motion of 170 degrees (Bain et al., 2015), using the McNemar test.

Differences between subgroups were analysed using Fisher's exact test and Mann-Whitney U-test. Analyses of hand function and questionnaires were conducted on the entire group ($n = 79$). Repeated measures ANOVA with subgroups as categorical predictor was used to compare changes over time, followed by Tukey's post hoc test in case of significance. When analysing recurrence rates and satisfaction with current hand function, the results were also compared for two age groups, divided by median age (68) to 68 years or less ($n = 41$) and over 68 years ($n = 38$) at treatment. Patients who had further treatment for the same finger(s) ($n = 9$) were excluded from the calculation of recurrence.

RESULTS

Multiple treatments

During the five-year period after CCH injection, 17 of 79 patients had been treated with further CCH injection or fasciectomy, nine of them for recurrence in treated finger(s) and others for increasing contractures in another finger or in the other hand. Three had been treated for both hands. When participants were asked if they wanted to repeat treatment with CCH if a new contracture was to be developed, 63 (80%) said yes. Those who answered no cited advanced age, pain/discomfort during treatment, acceptance of their hand function or desire for a long-lasting treatment. Four participants would prefer fasciectomy.

Changes in range of motion

Changes in digital range of motion up to five years after treatment are presented for individual joints and whole fingers (Figure 1, Table S1 A-C). The changes in digital extension and total active range of motion were statistically significant ($p < 0.001$). Changes in finger flexion were not significant.

Among patients who did not have further treatment, 49 (70%) exceeded a total arc of functional ROM (170°) in the fingers (Table 2). Among the isolated finger joints the MCP joints ($n=99$) were especially improved and showed slightly less deterioration of extension than the PIP joints ($n=81$) (mean 12° , SD 21, and mean 14° , SD 18 respectively). There was significantly greater TAE ($p=0.031$) and lower AROM ($p=0.016$) in patients who had had previous fasciectomy in the same hand ($n=11$) compared to those with less extension deficits who had CCH injection as primary treatment ($n=53$) (Table S1 A and C).

There was a non-significant tendency for lower recurrence ($p=0.08$) in the older group (mean 22° , SD 31) compared to the younger one (mean 35° , SD 39). Overall, after five years, 47%

(37 of 79) in the study group had redeveloped contractures in the treated finger(s) that met the inclusion criteria for new treatment (palpable cord, 45° in a single joint or a total of 60° in the same finger, and the finger impeding in daily activities).

Hand function

Patients rating of hand function showed moderate problems with stiffness but also mild problems with weakness and cold sensitivity before treatment (Table 3). Stiffness was reduced during the first year after treatment but had increased at the five-year follow-up. The CCH injection was described as painful by 65% of the patients. Over time, perceived pain in the hand decreased as well as problems with pressure/touch to the palm.

At baseline, cold sensitivity was estimated with VAS >50/100 by 38% (n=30 of 79) participants. At the five-year follow-up, the number had decreased to 16% (n=13 of 79). However, four patients described new or increased problems with cold sensitivity in the treated finger after CCH treatment. About 70% of the participants perceived touch with 0.4 grams of pressure (reduced light touch) with SWM. Minor insignificant changes occurred between baseline and 12 months, in both a positive and negative direction.

Disability and satisfaction

Disability measured with Quick-DASH was significantly reduced ($p<0.001$) after treatment and was, for the entire group, best after three months (Table 3). The subgroup with multiple treated fingers consistently had higher scores than the group with one treated finger. The tasks in QuickDASH that were considered most difficult were opening jar lids, power-intensive leisure activities and coping with daily work or activities requiring dexterity. At five-year follow-up most were no longer employed, which reduced the demands of speed, dexterity, and ROM in the hand.

Participants were asked to estimate satisfaction with their current hand function and the ability to use the hand in their daily activities five years after treatment (Table 4). Those who had no other treatment before the CCH injection and did not undergo further treatment were most satisfied with both their hand function and with their ability to use the hand in daily activities, especially those treated for one finger.

Persons with $\leq 45^\circ$ TAE deficit in the treated finger(s) at five-year follow-up estimated themselves more satisfied with their hand function and were able to use their hand better in daily activities than those with larger extension deficits (Table S2). Both age groups had similar results for satisfaction. Overall satisfaction with CCH treatment results, assessed with VAS 0 – 100, was best after three months (mean 7, SD 13), decreased at 12 months (mean 14, SD 23), and decreased further to the five-year follow-up (mean 26, SD 35).

Functionally disturbing contractures

Divergent perceptions emerged regarding difficulties in everyday life; what degree of contracture and which joint had affected the participants' hand function the most. For the MCP joint, problems were considered to arise from extension deficits from 25 to 60 degrees, the most common estimate being 40 to 45 degrees. In the PIP joint 30 degrees was considered disturbing and 55 degrees very troublesome. Having both MCP and PIP joints affected, even less than 30 degrees, was more disturbing than having the equivalent contracture in only one joint. The ability to hyperextend the MCP joint made a PIP joint contracture more easily tolerated.

DISCUSSION

The present study showed significantly improved ROM after CCH treatment, although extension deficits gradually deteriorated over time. Five years after treatment, the total extension deficit averaged 48°, which is 57% of the deficit before treatment. Of the self-reported hand function aspects, stiffness caused most problems both before and five years after treatment, while pain, problems with pressure/touch to the palm and cold sensitivity decreased over time. QuickDASH scores and overall satisfaction with treatment were best at three months after treatment and then deteriorated slightly over time. However, disability was still significantly lower compared to before treatment and most patients were satisfied with their hand function and ability to use the hand in daily activities five years after treatment.

The clinical experience of the CCH treatment observed in the present study was that some oedema and pain decreased before the extension manipulation was performed, which differs from previous studies (Gaston et al., 2015; Hurst et al., 2009). In several cases, the cord had partially ruptured before the patients' return visit to the physician. A lower residual contracture before manipulation has been described previously (Mickelson et al., 2014).

Another choice regarding treatment in the present study was not to withhold anticoagulant medication before CCH treatment, which differs from recommendations by Hurst et al. (2009). The regimen was initially chosen for a patient who was at serious risk if the anticoagulant treatment was discontinued. The patient was able to complete the CCH treatment without any problems, and therefore this protocol was implemented.

Most studies about Dupuytren's disease report passive extension measures (Hurst et al., 2009; Kaplan and Crosby, 2018; van Rijssen et al., 2012; Strömberg et al., 2018), while it is unclear in others if active or passive extension is measured (Gaston et al., 2015; Peimer et al., 2015a), which may affect the result (Pratt and Ball, 2016; Rodrigues et al., 2015). In the present study active extension was measured as recommended in the Swedish national quality register of

hand surgery because it correlates better with hand function and patients experience of extension deficit (Rodrigues et al., 2015).

Patients often perceive CCH treatment as a simple procedure compared to fasciectomy due to the rapid healing process (Hurst et al., 2009; Leclère et al., 2018). In general, the participants reported few hand function problems in the present study. However, oedema and pain occurred from the CCH injection which has also been described previously (Nordenskjöld et al., 2017; Peimer et al., 2015b; Sanjuan-Cervero et al., 2017). CCH injection appears not to cause reduced touch sensation although some participants reported new or increased cold sensitivity in treated fingers at the final follow-up without having trauma or other explanation. Reasons for developing cold sensitivity after treatment for Dupuytren's disease are still unknown (King and Belcher, 2014; Mckirdy et al., 2007; Namazi and Majd, 2014). Overall, CCH treatment seems to be well suited also for older people resulting in improved hand function.

Although satisfaction with treatment declined after decreasing finger extension, the majority in the present study were still pleased, which is consistent with previous findings (Bradley and Warwick, 2016; Leclère et al., 2018). At five-year follow-up satisfaction with hand function and ability to use the hand was, in general, high which may reflect that most participants had an improved functional ROM. Participants in the present study had varying opinions about troublesome joint deficits with lower thresholds for reduced mobility in daily activities compared to a previous study by Raymond et al. (2015). However, the angles leading to dysfunctional contractures estimated by patients in the present study were similar to the inclusion criteria for treatment at our hospital.

There are limitations of the present study due to the retrospective study design and the small and heterogeneous sample. Extension deficit in a single PIP joint can affect hand function differently than an equivalent extension deficit distributed among all finger joints. Similarly,

treatment of contractures in MCP joints may have better results than contractures in PIP joints. The series did not have sufficient power for subgroup analysis of this. However, the sample is well represented for Dupuytren's disease patients in terms of gender, age, heredity, diabetes, bi-/ unilateral disease, etc. Another limitation of the present study is that we cannot compare our outcomes to previous definitions of recurrence, such as by Kan et al. (2017), due to not measuring passive movement. However, the focus of the present study was on hand function and not primarily on recurrence rates.

The same physician treated all the patients, which led to consistent routines in the implementation. Close cooperation existed with OTs responsible for rehabilitation after the CCH injection which enabled structured follow-up and documentation of data. The findings of this long-term follow-up may be of interest for clinicians treating patients with Dupuytren's disease.

It can be concluded that hand function was significantly improved although the contractures deteriorated over time. Most patients (70%) gained more than the functional ROM needed for performance of common daily activities. Treatment with CCH injection was a valued method that many patients would choose again.

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Figure legends

Figure 1. Extension deficit in individual joints and the entire finger, presented per subgroup, before CCH treatment and at three months, twelve months, and five year follow-up.

One finger = whole line, two or three fingers = hatched line.

x= significant difference from baseline, $p < 0.001$

⊠= significant difference both from baseline and from previous assessments, $p < 0.001$

Table S1. Change over time in: A. Total active extension deficit and for isolated joints; B. Finger flexion; and C. Total active range of motion (AROM).

		Baseline	3 months	12 months	5 years
	n				
A. Extension deficit					
Total active extension deficit	79	84 (27)	20 (16)	26 (19)	48 (39)
Treated in 1 finger	56	87 (27)	19 (15)	25 (18)	48 (39)
Treated in 2-3 fingers	23	76 (28)	21 (18)	28 (21)	50 (40)
CCH injection as primary treatment	53	84 (28)	17 /14)	22 (19)	44 (41)
Previous fasciectomy in same finger	11	93 (28)	31 (17)	35 (20)	66 (32)
MCP-joint extension deficit		46 (20)	6 (8)	7 (10)	17 (21)
Treated in 1 finger	56	48 (22)	5 (8)	6 (8)	16 (21)
Treated in 2-3 fingers	23	42 (16)	7 (9)	12 (12)	21 (21)
CCH injection as primary treatment	53	48 (19)	5 (8)	7 (9)	15 (21)
Previous fasciectomy in same finger	11	39 (23)	3 (4)	8 (10)	26 (25)
PIP-joint extension deficit		34 (24)	13 (14)	17 (16)	28 (24)
Treated in 1 finger	56	37 (26)	14 (14)	18 (17)	30 (25)
Treated in 2-3 fingers	23	29 (20)	12 (12)	14 (14)	23 (21)
CCH injection as primary treatment	53	33 (26)	11 (12)	14 (16)	26 (25)
Previous fasciectomy in same finger	11	42 (19)	24 (14)	23 (15)	35 (17)
DIP-joint extension deficit		3 (8)	1 (3)	2 (5)	3 (7)
Treated in 1 finger	56	3 (7)	1 (2)	2 (5)	3 (7)
Treated in 2-3 fingers	23	5 (8)	2 (5)	2 (5)	5 (7)
CCH injection as primary treatment	53	3 (6)	2 (15)	1 (4)	3 (7)
Previous fasciectomy in same finger	11	11 (14)	4 (7)	4 (7)	6 (8)
B. Flexion					
Total active flexion	79	237 (19)	242 (20)	242 (19)	241 (21)
Treated in 1 finger	56	234 (19)	239 (21)	240 (19)	239 (23)
Treated in 2-3 fingers	23	245 (16)	250 (18)	248 (17)	245 (16)
MCP-joint flexion		88 (7)	88 (7)	88 (7)	87 (9)
Treated in 1 finger	56	88 (8)	88 (7)	88 (7)	87 (9)
Treated in 2-3 fingers	23	87 (6)	87 (6)	87 (6)	87 (8)
PIP-joint flexion		94 (9)	95 (10)	95 (9)	96 (10)
Treated in 1 finger	56	93 (10)	93 (11)	94 (10)	96 (11)
Treated in 2-3 fingers	23	96 (7)	99 (5)	97 (5)	97 (7)
DIP-joint flexion		56 (15)	60 (16)	60 (16)	57 (17)
Treated in 1 finger	56	53 (16)	58 (17)	58 (17)	56 (19)
Treated in 2-3 fingers	23	62 (12)	65 (13)	64 (14)	61 (12)

C. Total active range of motion

Total AROM	79	154 (35)	223 (29)	217 (30)	193 (44)
Treated in 1 finger	56	147 (33)	220 (29)	216 (30)	192 (45)
Treated in 2-3 fingers	23	170 (36)	229 (28)	220 (30)	195 (44)
CCH injection as primary treatment	53	154 (34)	226 (27)	221 (28)	200 (44)
Previous fasciectomy in same finger	11	143 (35)	207 (41)	205 (35)	170 (35)
MCP-joint AROM		42 (20)	82 (11)	80 (13)	70 (23)
Treated in 1 finger	56	40 (21)	84 (11)	83 (12)	72 (23)
Treated in 2-3 fingers	23	46 (17)	79 (12)	75 (14)	66 (22)
CCH injection as primary treatment	53	39 (18)	82 (10)	81 (12)	73 (21)
Previous fasciectomy in same finger	11	53 (23)	88 (10)	84 (15)	67 (28)
PIP-joint AROM		59 (24)	82 (17)	78 (19)	69 (25)
Treated in 1 finger	56	56 (25)	79 (17)	77 (20)	67 (26)
Treated in 2-3 fingers	23	67 (21)	87 (13)	83 (15)	74 (23)
CCH injection as primary treatment	53	61 (25)	84 (15)	81 (17)	71 (26)
Previous fasciectomy in same finger	11	47 (21)	66 (22)	67 (21)	56 (20)
DIP-joint AROM		52 (16)	59 (16)	58 (17)	54 (17)
Treated in 1 finger	56	51 (16)	57 (17)	57 (18)	53 (18)
Treated in 2-3 fingers	23	57 (13)	63 (15)	62 (15)	56 (13)
CCH injection as primary treatment	53	54 (13)	60 (14)	59 (15)	57 (14)
Previous fasciectomy in same finger	11	43 (24)	50 (27)	54 (25)	47 (23)

Data presented as mean (SD) degrees for the whole group, subgroups, patients with CCH injection as primary treatment and patients previous treated in same finger. * The difference between total active flexion and total active extension in MCP, PIP and DIP joints.

Table S2. Satisfaction with hand function and ability to use hand in daily activities related to degree of total active extension (TAE) deficit in worst finger at the five-year follow-up and to age (n=79).

		Satisfaction with hand function	Ability to use the hand
	n	High or very high, Yes (%)	Fairly good, good, very good, Yes (%)
Degree of extension deficit			
TAE deficit $\leq 45^\circ$ in worst finger	45	37 (82)	42 (93)
TAE deficit $> 45^\circ$ in worst finger	34	9 (26)	21 (62)
<i>Treated in 1 finger</i>	56		
TAE deficit $\leq 45^\circ$	33	30 (91)	31 (94)
TAE deficit $> 45^\circ$	23	4 (17)	13 (57)
<i>Treated in 2 or 3 fingers</i>	23		
TAE deficit $\leq 45^\circ$	12	7 (58)	11 (92)
TAE deficit $> 45^\circ$	11	5 (45)	8 (73)
Age (at injection)			
<i>The whole group</i>	79		
≤ 68 years	41	21 (51)	31 (76)
> 68	38	25 (66)	32 (84)
<i>Treated in 1 finger</i>	56		
≤ 68 years	30	17 (57)	23 (77)
> 68	26	17 (65)	21 (81)
<i>Treated in 2 or 3 fingers</i>	23		
≤ 68 years	11	4 (36)	8 (73)
> 68	12	8 (67)	11 (92)

Data is presented as number of patients (%).

Table1. Patient reported background data and interventions for study sample at 5 years.

		All patients n=79	Patients treated in 1 finger n=56	Patients treated in 2 or 3 fingers n=23	Difference between Groups p-values
<i>Background data</i>					
Sex	Male (%)	68 (86)	49 (88)	19 (82)	0,722
Age at injection	Mean (SD)	68 (9)	67 (8)	70 (11)	0,321
Working		13 (16)	11 (20)	2 (9)	0,326
Smoking		7 (8)	5 (9)	2 (9)	1,000
Diabetes		13 (16)	9 (16)	4 (17)	1,000
DD in family	Yes	48 (61)	33 (59)	15 (65)	0,758
	Uncertain	14 (18)	10 (18)	4 (17)	
Disease duration	0-5y	9 (11)	8 (14)	1 (4)	0,245
	6-10y	26 (33)	18 (32)	8 (35)	
	11-15y	18 (23)	13 (23)	5 (22)	
	>15y	26 (33)	17 (30)	9 (39)	
Bilateral disease		60 (76)	40 (71)	20 (87)	
<i>Previous treatment with fasciectomy (before injection)</i>					
In the same hand as injection		11 (14)	6 (11)	5 (22)	0,282
Treated once		6 (8)	5 (9)	1 (4)	0,666
Treated twice		1 (0)	0 (0)	1 (4)	0,291
Treated > two times		5 (6)	1 (1)	4 (17)	0,024
None		53 (67)	41 (73)	12 (52)	0,112
Treated only in the other hand		15 (19)	9 (16)	6 (26)	0,350
Treated in both hands		9 (11)	4 (7)	5 (22)	0,112
<i>Intervention given at baseline</i>					
Patients treated in one finger			56 (70)		-
Patients treated in two fingers				20 (25)	-
Patients treated in three fingers				3 (4)	-
Patients treated in index finger		0 (0)	0 (0)	0 (0)	-
Patients treated in long finger		13 (16)	3 (5)	10 (43)	-
Patients treated in ring finger		38 (48)	16 (29)	22 (96)	-
Patients treated in little finger		54 (68)	37 (66)	17 (74)	-
Treated in dominant hand		45 (57)	33 (59)	12 (52)	-
<i>Complications</i>					
Skin rupture		n= 79 32 (41)	20 (36)	12 (52)	0,212
<i>Repeated interventions given to the same hand and fingers after the first Xiapex injection until 5 years followup*</i>					
No further intervention after baseline		n=73 62 (78)	n=52 47 (84)	n=21 15 (65)	0,078

Xiapex injection	7 (8)	4 (7)*	3 (13)	-
Fasciectomy	4 (5)	1 (2)	3 (13)*	-

Data presented as number (%); *Two patients underwent repeated interventions with CCH injection and fasciectomy respectively.

Table 2. Active range of motion (AROM) for the whole finger and for isolated joints compared to functional range of motion at baseline and at 5-years follow up. Patients who had further treatment excluded, n=70.

	Baseline AROM (degrees)	Functional ROM* (degrees)	Patients exceeding Functional ROM at baseline	5 years AROM (degrees)	Patients surpassing Functional ROM at 5 years	<i>p</i> -values of change from baseline to 5-year follow up
Whole finger	154 (35)	170	27 (39)	193(44)	49 (70)	0.001
MCP-joints	42 20)	52	17 (24)	70 (23)	53 (76)	<0.001
PIP-joints	59 (24)	64	35 (50)	69 (25)	43 (61)	0.153
DIP-joints	52 (16)	54	39 (56)	54 (17)	42 (60)	0.479

Data presented as mean (SD) or number of patients (%); * The range of motion needed to perform activities of daily living according to Bain et al. (2015).

Table 3. Patients rating of hand function problems, sensibility testing and Quick-DASH at the follow-up assessments (n=79).

	Pre treatment	3 months	12 months	5 years
Pain (Median (Q1-Q3))				
at rest*	4 (2 - 13)	3 (1 - 5)	3 (2 - 6)	0 (0 - 0)
on motion without load*	4 (2 - 10)	2 (1 - 5)	3 (2 - 7)	0 (0 - 0)
on load*	11 (2 - 30)	3 (1 - 9)	3 (2 - 13)	0 (0 - 10)
at injection/ pain in hand, yes (%)	51 (65)	11 (14)	12 (15)	7 (9)
Stiffness*, median (Q1-Q3)	65 (48 - 90)	9 (2 - 22)	5 (3 - 31)	20 (0 - 40)
Weakness*, median (Q1-Q3)	27 (5 - 48)	3 (2 - 12)	5 (2 - 16)	0 (0 - 20)
Numbness/tingling in fingers*, median (Q1-Q3)	6 (2 - 35)	3 (2 - 12)	4 (2 - 10)	0 (0 - 10)
Cold sensitivity*, median (Q1-Q3)	22 (3 - 70)	4 (2 - 41)	5 (2 - 36)	0 (0 - 40)
VAS >50/100, n (%)	30 (38)	11 (14)	13 (16)	13 (16)
Sensibility during the first year after treatment ^a				
Decreased or no protective sensibility in worst finger, n (%)	16 (20)	9 (11)	11 (14)	
Discomfort from touch and pressure to the palm after treatment, n (%)				
No discomfort		69 (88)	63 (80)	71 (90)
Light discomfort		8 (10)	5 (6)	3 (4)
Moderate discomfort		1 (1)	5 (6)	5 (6)
Missing		1	6	0
Quick-DASH, mean (SD)				
All patients	24 (15)	7 (11)	10 (13)	12 (12)
Treated in 1 finger	21 (15)	7 (10)	8 (11)	11 (13)
Treated in 2 or 3 fingers	31 (13)	9 (13)	15 (16)	14 (12)

Data presented as median (interquartile range (Q1-Q3)), mean (m) and standard deviation (SD), or number of patients (n) (%); * Modalities from HAKIR rated with VAS 0 = no problem - 100 = worst imaginable problems; ^a Sensibility during the first year after treatment measured with Semmes-Weinstein monofilament 4.31 representing decreased sensation and 6.65 representing no protective sensation.

Table 4. Patients self-reported satisfaction with hand function and ability to use hand in daily activities at 5-year follow up presented based on subgroups of number of treated fingers and treatment history (n=79).

	All patients, regardless of treatment history		No previous treatment ^a		Previous treatment ^{b*}		New treatment ^{c*}	
Satisfaction with hand function, rated as high or very high	n		n		n		n	
The whole group	79	46 (58)	42	30 (71)	26	10 (38)	17	7 (41)
Treated in 1 finger	56	34 (61)	34	25 (74)	15	5 (33)	10	4 (40)
Treated in 2-3 fingers	23	12 (52)	8	5 (63)	11	5 (45)	7	3 (43)
Ability to use the hand in daily activities, rated as fairly good, good or very good ^d	n		n		n		n	
The whole group	79	63 (80)	42	35 (83)	26	19 (73)	17	13 (76)
Treated in 1 finger	56	44 (79)	34	30 (88)	15	8 (53)	10	7 (70)
Treated in 2-3 fingers	23	19 (83)	8	5 (63)	11	11 (100)	7	6 (86)

Data is presented as number (percentage);

* Including patients treated both before and after the first CCH injection;

^a Patients never treated for Dupuytren's disease before or after the CCH injection;

^b Patients treated for Dupuytren's disease with other methods in either hand before the CCH injection;

^c Patients treated in either hand for recurrent Dupuytren's disease after the CCH injection;

^d Rating 8-10 on a ten-point scale ranging from 1=very poor, 10=very good.