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Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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ABSTRACT

Objectives: To assess 2-year durability of joint contracture correction following collagenase injections for Dupuytren's disease.

Design: Prospective cohort study.

Setting: Orthopedic Department in Sweden.

Participants: Patients with palpable Dupuytren's cord and active extension deficit (AED) ≥20º in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. A surgeon injected 0.80 mg collagenase into multiple cord parts and performed finger manipulation under local anesthesia after 24-48 hours. A hand therapist measured joint contracture before and 5 weeks after injection. Of 57 consecutive patients (59 hands), 48 patients (50 hands) were examined by a hand therapist and another 4 were telephone interviewed 24-35 (mean 26) months after injection. The first 29 patients completed the QuickDASH activity limitations scale.

Outcome measures: Proportion of treated joints with ≥20° worsening in AED from 5 weeks to 2 years (primary), passive extension deficit (PED), QuickDASH score, and treatment satisfaction.

Results: Mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years, and for the PIP joints 30°, 13° and 16°, respectively. Between 5 weeks and 2 years AED of MCP or PIP joint worsened by ≥20° in 14 hands (28%). For joints with ≥10° contracture at baseline, mean (95% CI) baseline-to-2 years AED improvement was for MCP 49º (41-54) and for PIP 25º (17-32). At 2 years, PED was 0°-5° in 83% of MCP and 48% of PIP joints. Median QuickDASH score (25th, 75th percentiles) improved from 11.4 (2.3, 21) at baseline to 2.5 (0, 9) at 5 weeks (p<0.001) and 2.3 (0, 18) at 2 years (p=0.034); 83% were satisfied.

Conclusion: Two years after collagenase injections for Dupuytren's disease, improvement was maintained in 3 of 4 patients. Complete contracture correction was seen in more than 80% of the MCP but in less than half of the PIP joints.

Strengths and limitations

- Indications for collagenase treatment similar to those conventionally used for surgery.
- Measurements of joint contracture outcomes at baseline and follow-up independent of the treating surgeon.
- Use of a validated measure of patient-reported activity limitations and evaluation of patient satisfaction.
- High participation rate with 2-year outcomes data available for 95% of the treated hands.
- Limitations include a single center and moderate sample size.

Introduction

Collagenase injection is a non-surgical treatment for patients with Dupuytren's disease causing finger joint contractures.[1] Treatment comprises injection of collagenase into the cord followed, after about 24 to 48 hours, by finger manipulation (extension). In the initial multicenter randomized trial by Hurst et al.,[1] surgeons performed finger manipulation without anesthesia. Finger manipulation is usually painful and lack of anesthesia may hamper contracture reduction. In addition, contractures of the metacarpophalangeal (MCP) joint and proximal interhlangeal (PIP) joint were treated separately with repeated injections given with at least 1-month interval. These procedures have been modified; use of anesthesia prior to finger manipulation is now standard and treating both joints in one session is common. We have used a modified method, injecting a higher collagenase dose (0.80 mg) into multiple parts of the cord and shown good short-term (5 weeks) contracture correction.[2;3] With this method, fingers with contracture of both MCP and PIP joints are treated in 1 stage. Injecting more collagenase along the cord may also imply that a larger part of the cord is disrupted or dissolved. It is not known whether this would result in a more durable correction. Although the initial multicenter study has reported outcomes at 3 and 5 years,[4;5] the study had substantial follow-up attrition (about one third) and the treating surgeons themselves were outcome assessors. No other prospective studies have reported outcomes at 2 years or longer.

Because patients mainly have activity limitations rather than symptoms, measuring patient-reported activity limitations is important in evaluating treatment outcomes. No studies have evaluated outcomes of collagenase treatment with regard to activity limitations up to 2 years after treatment. The purpose of this study was to determine the durability of collagenase efficacy with regard to joint contractures and activity limitations 2 years after injections.

Patients and methods

Study design and eligibility criteria

We conducted a prospective cohort study at one orthopedic department in Southern Sweden. The department is the only center that treats patients with Dupuytren's disease in a region with 300,000 inhabitants. The indication for treatment with collagenase injections was presence of a palpable cord and a total extension deficit of ≥20º in the MCP joint and/or PIP joint. All patients who had received at least one injection and reached 2 years after first injection from November 2013 through October 2014 were eligible.

Patients

From September 2011 through October 2012, we treated 57 consecutive patients (59 hands) with collagenase injections. In the 2 bilaterally treated patients the interval between treatments was 1 week and 6 months, respectively. All patients were asked to participate in a follow-up examination at a minimum of 2 years after first injection; 5 patients (5 hands) did not participate (2 deceased, 1 had dementia, and 2 did not respond) and 4 patients (4 hands) declined to attend examination but agreed to a telephone interview. Thus, 48 patients (50 hands; 85% of the treated hands) underwent physical examination at a mean of 26 (median 25, range 24 to 35) months after first injection (Table 1).

Intervention

A hand surgeon injected collagenase into the cord using a modification of the standard technique.[2] After reconstituting collagenase with 0.39 ml of diluent, the surgeon injected all reconstituted collagenase (0.80 mg) into in the cord, distributed in 3 or 4 spots along the palpable cord, from the PIP joint to the palmar crease. After injection, a nurse applied a soft

dressing and the hand therapist gave the patient verbal and written instructions regarding edema prophylaxis and avoidance of heavy use of the hand.

The surgeon performed finger manipulation 1 day or 2 days after collagenase injection, as schedule permitted. The surgeon injected local anesthetic (10 ml of 10 mg/ml mepivacaine buffered with sodium bicarbonate) proximal to the palmar crease (a few centimeters proximal to the collagenase injection sites) to block the nerves to the treated finger. After about a 20-minute interval the surgeon performed finger manipulation by applying pressure with the thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into maximum possible extension.

Immediately after finger manipulation, the patients went to the hand therapist and received a static splint with maximally extended fingers; the therapist gave instructions on range of motion exercises, to use the hand as tolerated during daytime, and to use the splint at night for 8 weeks. The patients returned to the hand therapist after 1 week for splint adjustment. In case contracture correction was incomplete and the patient was willing to receive further treatment, the surgeon scheduled the patient for a second injection.

Measurements

Before treatment, one of three hand therapists measured active extension deficit (AED) in the fingers with a goniometer and recorded the results in a standardized protocol. The first 29 patients in the study completed the 11-item disabilities of the arm, shoulder and hand (QuickDASH) scale.[6] At 5 weeks after injection, a hand therapist measured AED in the fingers and the first 29 patients completed the QuickDASH. At 2 years after injection, a hand therapist contacted the patients and asked them to attend the hospital for a physical

examination. During this visit, the therapist measured AED as well as passive extension deficit (PED) in the fingers and examined the hand for possible treatment-related complications. The therapist asked the patients to report any symptoms from the treated hand and about their satisfaction with the results of treatment (satisfied or dissatisfied). All patients completed the QuickDASH. The same hand therapist (AL) examined all patients who attended the 2-year follow-up evaluation and telephone-interviewed patients who did not attend examination. During the telephone interview, the therapist asked the patients whether they believed their treated finger had worsened since the 5-week follow-up visit and whether they were satisfied with the results. Two of the patients interviewed by telephone also completed the QuickDASH.

We reviewed the electronic records of all participants and non-participants to ascertain any subsequent surgery or other procedures on the study hand. We also recorded the number of any additional treatment visits to the hand therapist (outside the preplanned visit at 1 week).

Statistical analysis

The primary outcome was worsening of ≥20° in AED from 5 weeks to 2 years. We considered this cut-off as clinically important because it has been used in the previous collagenase multicenter study.[4] In that study, recurrence or nondurability (≥20°increase in PED in fully or partially corrected joints with presence of palpable cord, or subsequent treatment) among 924 joints was 24% at 2 years. We estimated that approximately 50 patients would be eligible and a 70% participation rate. With 80% power and 5% significance level, a sample of 30 patients can show treatment effect durability among 75% of the patients. We present the data as means with standard deviations or 95% confidence intervals and/or medians with 25th and 75th percentiles as appropriate. We calculated the extension deficit

values for MCP and PIP joints for all treated fingers and for joints that had at least 10° pretreatment AED. We considered hyperextension as 0° extension deficit. We also calculated total (MCP+PIP) extension deficit. Because previous studies defined complete correction as PED value 0° to 5°,[1;4] we also analyzed the data according to this definition. This was possible only for the 2-year values, because we measured only AED at baseline and 5 weeks. For one patient who had surgery on the treated finger 23 months after injection we used the extension deficit recorded immediately before surgery as the 2-year value in all analyses. The change in AED between evaluation times (baseline, 5 weeks and 2 years) was statistically tested with the paired t-test. We used the Mann-Whitney test to compare baseline and 5-week AED in joints that showed ≥20° AED worsening between 5 weeks and 2 years and joints that had not worsened after a single injection. We tested the change in QuickDASH scores with the Wilcoxon test (one score for both hands for the 2 bilaterally treated patient). We analyzed the correlation between the changes (baseline to 2 years) in total AED and QuickDASH scores with the Pearson correlation coefficient (r). We also analyzed change in total AED and the QuickDASH scores according to patient satisfaction using the independent t-test and analysis of covariance adjusting for sex and age. A 2-sided p-value of less than 0.05 indicated statistical significance.

Results

Joint contracture

Active extension deficit: The mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years and the corresponding values for the PIP joints were 30°, 13° and 16°, respectively (Table 2). Between 5 weeks to 2 years mean total AED had worsened by 6°, but this did not reach statistical significance. From the 5-week to the 2-year follow-up, AED had worsened by ≥20° in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a single injection). Comparison of the baseline and 5-week AED in joints that had worsened by ≥20° AED between 5 weeks and 2 years and those that had not worsened showed significant differences for the PIP but not for the MCP joints (Table 3). A larger proportion of PIP than MCP joints showed either persistent or increased AED (Figure 1). Total AED had worsened by ≥30° in 8 of the 50 hands (16%; all had received a single injection). Considering only joints with a pretreatment AED ≥10° (47 MCP joints [mean 57°, SD 19] and 31 PIP joints [mean 48°, SD 21]), mean improvement in AED from baseline was for the MCP joints 49º (95% CI 41-54, p<0.001) and for the PIP joints 25º (95% CI 17-32, p<0.001).

Passive extension deficit: Of the 47 MCP and 31 PIP joints with contracture before injection, PED of 0° to 5° at 2 years was recorded in 39 MCP joints (83%) and in 15 PIP joints (48%). A total PED ≥30° was present in 11 hands (22%). For all 50 treated fingers, mean PED for the MCP joints was 3.2° (SD 9; median 0; 25th and 75th percentiles 0, 0) and for the PIP joints was 11° (SD 19; median 0, percentiles 0, 20).

Telephone interview: None of the 4 patients telephone-interviewed at 2 years reported worsening of their treated finger since the 5 week follow-up.

Activity limitations

Of the first 29 patients (30 hands) to whom the QuickDASH was administered at baseline, 1 had subsequent surgery before and 1 did not participate in the 2-year follow-up. For the remaining 27 patients (28 hands) the median score (25^{th}, 75^{th} percentiles) at baseline was 11.4 (2.3, 21), at 5 weeks 2.5 (0, 9) and at 2 years 2.3 (0, 18). Changes from baseline to 5 weeks and to 2 years were statistically significant ($p<0.001$ and $p=0.034$, respectively) but not changes from 5 weeks to 2 years ($p=0.45$). The correlation between baseline to 2 years changes in total AED and QuickDASH score was moderate ($r=0.49$, $p=0.010$). For all 49 patients who completed the QuickDASH at 2 years, the median score was 2.5 (0, 18).

Patient satisfaction

The patients reported satisfaction with treatment results in 41 of the 50 hands examined and 4 hands evaluated with telephone interview (83% satisfied). Mean change (improvement) in total AED from baseline to 2 years among "satisfied" patients was 65 (SD 26) and among "dissatisfied" patients was 39 (SD 36); adjusted mean difference 24 (95% CI, 3-45, $p=0.027$). Mean change in QuickDASH score for the satisfied patients was -8 (SD 10) and for the dissatisfied patients 1 (SD 25); adjusted mean difference -9 (95%, CI -24-6, $p=0.25$). Mean 2-year QuickDASH score for "satisfied" patients was 9 (SD 15) and for "dissatisfied" patients 26 (SD 13); adjusted mean difference -16 (95% CI -27-5, $p=0.007$).

Subsequent surgery and adverse events

One patient had recurrent MCP contracture after 1 injection and chose to have limited fasciectomy, which was done 23 months after injection. No other patients had surgery or needle fasciotomy. At the 2-year follow-up evaluation, the examining therapist did not observe and the patients did not report any treatment-related adverse events.

Discussion

This prospective cohort study of patients with Dupuytren's disease treated with collagenase injection shows that contracture improvement was maintained 2 years after treatment in 3 of 4 patients. However, up to 20% of the patients were not satisfied (assuming that the 2 patients who did not respond also were dissatisfied), possibly because of incomplete initial correction or recurrent contracture in the treated finger. Considering its relative simplicity compared to fasciectomy the results of this the 2-year treatment effect durability assessment support the continued use of collagenase injection as an effective treatment option in patients with Dupuytren's disease. Assuming hypothetically that all patients with ≥30° total PED at 2 years would receive a new injection, implying almost a third of all patients require 2 injections, the treatment costs would still be lower compared to surgery.[2] The comparison involves only direct treatment costs; it does not take into consideration the costs of possible surgical complications.[2] Because patients who have good results may still experience worsening after 2 years, a new assessment is necessary with longer follow-up.

Most patients received a single injection but about 10% of the patients needed a second injection because the initial reduction was inadequate. Similar to previous studies of both collagenase and surgery, outcomes were better for MCP joints than PIP joints; more than 80% of MCP joints but less than half of PIP joints achieved complete correction. The PIP joints that had worsened after the 5-week follow-up had more severe contracture both before treatment and at 5 weeks (inadequate correction), but this was not the case for MCP joints. This may suggest that in case the first injection fails to achieve adequate correction for PIP joints the surgeon should consider a second injection early. This question needs further study.

Comparison with other collagenase studies

We measured AED before treatment and at 5 weeks and 2 years. We measured PED only at 2 years to facilitate comparison with previous studies. With regard to joint contracture, passive deficit would be equal or less than active deficit. Thus, our posttreatment AED values are conservative when compared to studies that reported posttreatment PED values.

In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS), 621 of 950 (65%) of the initial study participants could be followed.[4] The authors defined "recurrence" as contracture worsening by ≥20° *combined with* presence of palpable cord *or* further treatment including injection, in successfully treated joints (0° to 5° extension deficit; 70% of treated MCP and 40% of treated PIP), implying that joints in which treatment had failed initially were excluded. Same definition applied to partially corrected joints (improved by ≥20°) was classified as "nondurability". At 2 years, recurrence had occurred in 20% and nondurability in 33%. Contracture "worsening" (defined as ≥20° increase in contracture in fully or partially corrected joints with or without palpable cord *or* subsequent treatment) at 3 years was 28% for MCP and 58% for PIP; no 2-year data were reported. The study reported that for successfully treated MCP joints mean PED at baseline was 37 (SD 16) and at 2 years was 8 (SD 13), and for PIP joints 38 (SD 16) and 20 (SD 19), respectively,[4] and a substantial number of patients received multiple injections. In our study, mean PED for the MCP and PIP joints at 2 years was 3 (SD 9) and 11 (SD 19), respectively.

Because we measured PED only at 2 years, it is not possible to make a direct comparison with the CORDLESS study, but we can assume that PED is always equal or less than AED. Of 32 hands with baseline MCP joint AED of 25° or more and AED of 0° to 5° at 5 weeks (ie "successfully treated" according to CORDLESS definition), 2 had PED ≥20° at 2 years and 1

had undergone surgery, thus 9% would be defined as recurrence according to CORDLESS. This is an overestimate because the CORDLESS patients had to have *both* contracture worsening *and* palpable cord to be considered as recurrence and a large number of different surgeons recorded presence of palpable cord (validity uncertain). Although it is difficult to compare results because of differences in definitions, our results appear to be more favorable.

Comparison with limited fasciectomy and percutaneous needle fasciotomy

Although many studies have reported fasciectomy results,[7] we believe only prospective studies with high follow-up participation can provide good-quality outcomes data. A recent prospective study of 90 patients treated with limited fasceictomy at a university hand surgery center in Sweden, reported that at 1 year the mean AED for the MCP joints was 5 (SD 9) and for the PIP joints 22 (SD 18).[8] It is unclear whether the authors used 0° for hyperextension (as in our study) or used the actual values, which would underestimate the reported extension deficit. They reported that 81% were satisfied at 1 year. Thus, our 2-year collagenase results compare favorably with the 1-year results after limited fasciectomy. Surgery-related complications reported in the study included nerve injury (4 patients) and complex regional pain syndrome (4 patients) and many patients required extensive therapy.[8] Collagenase treatment does not require extensive hand therapy. Almost all patients required only two hand therapist visits (immediately after finger manipulation and at 1 week for splint adjustment).

In a randomized study that defined recurrence after needle fasciotomy as ≥30° worsening in the treated finger's total PED from 6 weeks to 2 years, 29 of 52 patients (56%) had recurrence.[9] Applying the same definition to our study but using total AED, 8 of 50 hands (16%) would be defined as having recurrence.

The Swedish National Quality Register for Hand Surgery have reported outcome data for patients treated for Dupuytren's contracture at the Swedish Hand Surgery departments between 2010 and 2014.[10] The mean DASH score in patients treated with collagenase had improved from 23 before (n=399) to 11 at 1 year (n=250); the corresponding values for limited fasciectomy were 24 (n=273) and 11 (n=252) and for needle fasciotomy 25 (n=52) and 17 (n=54), respectively. The average patient satisfaction (visual analog scale from 0 to 100) after collagenase treatment (n=260) was 78%, after limited fasciectomy (n=262) was 79%, and after closed fasciotomy (n=73) was 69%.[10]

We do not use the outcome "recurrence" because of lack of consensus about the definition of recurrence. Treatment with collagenase inherently implies that part of the cord is left intact and therefore it would be impossible to know with acceptable certainty whether a presence of a cord is indicative of recurrence. We believe the degree of joint contracture before and after treatment is a more valid measure of outcome irrespective of whether the cause of the contracture is incomplete correction, disease recurrence/progression, or other cause.

Activity limitations

We used the QuickDASH as patient-reported measure of activity limitations and the results show that the scores improved significantly after treatment. The magnitude of improvement differed according to changes in joint contracture and with patient satisfaction. These findings support the use of the QuickDASH in DC. Because the median pretreatment QuickDASH score was relatively low, it may not be appropriate in studies comparing different treatments because it would be difficult to detect important between-group differences. However, in patients with DC, no thresholds have been established for within-group and between-group differences in QuickDASH score to be considered as clinically important. Besides, it is not

obvious that the same threshold should apply to complex treatments that include surgery and extensive rehabilitation as to less invasive treatments that are associated with substantially lower risks and burden on patients.

The limitations of our study include a single center and a moderate sample size, implying uncertain generalizability. We did not measure passive but only active extension deficit at baseline and at 5 weeks after injection and only the first 29 patients completed the QuickDASH. Further, patients stated whether they were satisfied or not satisfied with the results; a scale with more response options may have yielded different results. Our study has several strengths. First, hand therapists measured joint contractures at baseline, 5 weeks and 2 years, independent of the treating surgeon, and a validated scale used to measure patient-reported activity limitations. The high participation rate is a major strength with 2-year outcomes data available for 95% of the treated hands of patients still living.

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Contributors

AL: contributed to study design, collected the data, assisted in the analysis and interpretation of the data, contributed to drafting of the manuscript, and approved the final version submitted for publication.

IA: led the project, designed the study, conducted data analysis and interpretation, contributed to drafting of the manuscript, and approved the final version submitted for publication.

Ethics approval

This research was approved by the Regional Ethical Review Board in Lund (Dnr 2013/656) and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000.

Competing interests

IA was a member of an Expert Group on Dupuytren's disease for Pfizer in 2012 and participated in meetings organized by Sobi in 2014 and 2015.

Funding

No external funding.

Data sharing statement

No additional data available.

Figure legend

Figure 1. Active extension deficit (AED) for the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints 5 weeks and 2 years after collagenase injection for Dupuytren's contracture in 50 treated fingers. The joints shown in this diagram are those with AED of at least 10° at 5 weeks or in which AED had changed between 5 weeks and 2 years; AED measured with 5° intervals and joints with identical values juxtaposed for visual clarity. In 4 joints a second injection after the 5-week measurement was given. Joints without contracture (AED 0° to 5°) at both evaluation times (27 MCP and 23 PIP joints) are not shown in the diagram.

Table 1. Characteristics of the participants and non-participants in the 2-year follow-up physical examination

	Participants	Non-participants
Number of hands / patients	50 / 48	9 / 9
Sex, men : women	38 : 12	8 : 1
Age, median (range)	68 (51-83)	66 (55-84)
Hand treated, right : left	34 : 16	8 : 1
Finger treated: small : ring : middle : index	25: 24 : 1 : 1	5 : 3 : 1 : 0
Previous fasciectomy on treated finger, n (%)	6 (12)	1 (11)
Additional treatment visits to therapist, n (%)	3 (6)	0 (0)
Repeat injection, n (%)	5 (10)*	1 (11)
Total extension deficit†		
before injection	80 (54, 108)	68 (49, 119)
5 weeks after injection	15 (0, 29)	20 (9, 63)

*Interval: 4 weeks (1 patient), 2 months (1 patient), 6 months (3 patients), all 5 had MCP and PIP contracture at baseline (3 had reinjection because of inadequate PIP correction and 2 because of inadequate MCP and PIP correction).

†Median (25^{th}, 75^{th} percentiles) active extension deficit of the metacarpophalangeal and proximal interphalangeal joints of the treated finger.

Table 2. Active extension deficit before and after collagenase injection for Dupuytren's disease

	Baseline	5 wk	2 yr	Mean difference (95% CI), p-value			
	n = 50	n = 50	n = 50	Baseline to 2 yr		5 wk to 2 yr	
MCP	54 (23)	6 (12)	9 (16)	45 (38 to 52)	<0.001	-3.1 (-7.8 to 1.6)	0.20
PIP	30 (28)	13 (17)	16 (21)	14 (9 to 20)	<0.001	-3.3 (-6.7 to 0.1)	0.056
MCP+PIP	84 (37)	18 (22)	25 (25)	59 (51 to 68)	<0.001	-6.4 (-12 to -0.06)	0.031

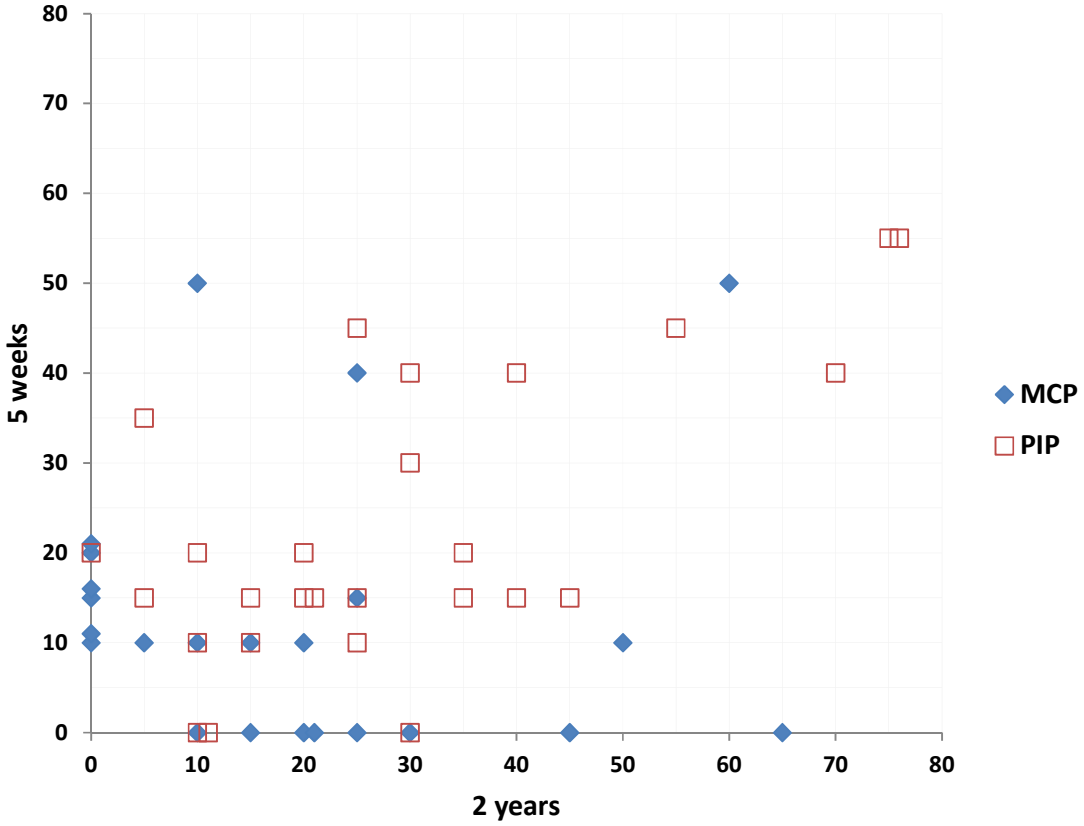
MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

Table 3. Baseline and 5-week active extension deficit for the joints that had worsened by ≥20° and the joints that had not worsened between 5 weeks and 2 years after a single collagenase injection

	Worsened	Not worsened	p-value
MCP, n	7	38	
Baseline	60 (40, 65)	55 (40, 70)	0.87
5 weeks	0 (0, 0)	0 (0, 10)	0.57
PIP, n	7	38	
Baseline	60 (30, 75)	10 (0, 40)	0.017
5 weeks	15 (15, 55)	0 (0, 15)	0.004

Values are median (25^{th}, 75^{th} percentile)

MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint



423

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P1,2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	P2,3	
Introduction		
Background/rationale	2 P4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P5	Present key elements of study design early in the paper
Setting	5 P5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
	P5,6	(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
	P6,7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
	P6,7	
Bias	9 P7,8	Describe any efforts to address potential sources of bias
Study size	10 P7	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
	P7,8	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
	P7,8	(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* P5 & T1	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* T1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	P5, T1	(b) Indicate number of participants with missing data for each variable of interest
	P5	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P9-11, T2, Fig	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 P9-11, T2	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 P9,10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 P11	Summarise key results with reference to study objectives
Limitations	19 P14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P11-14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 P17	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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ABSTRACT

Objectives: To assess 2-year durability of joint contracture correction following collagenase injections for Dupuytren's disease.

Design: Prospective cohort study.

Setting: Orthopedic Department in Sweden.

Participants: Patients with palpable Dupuytren's cord and active extension deficit (AED) ≥30º in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. A surgeon injected 0.80 mg collagenase into multiple cord parts and performed finger manipulation under local anesthesia after 24-48 hours. A hand therapist measured joint contracture before and 5 weeks after injection in all treated patients. Of 57 consecutive patients (59 hands), 48 patients (50 hands) were examined by a hand therapist 24-35 (mean 26) months after injection. Five of the patients had received a second injection in the same finger within 6 months of the first injection.

Outcome measures: Primary outcome was proportion of treated joints with ≥20° worsening in AED from 5 weeks to 2 years.

Results: Mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years, and for the PIP joints 30°, 13° and 16°, respectively. Between the 5-week and 2-year measurements AED of MCP or PIP joint worsened by ≥20° in 14 hands (28%). For joints with ≥10° contracture at baseline, mean (95% CI) baseline-to-2 years AED improvement was for MCP 49º (41-54) and for PIP 25º (17-32). No treatment-related adverse events were observed at the 2-year follow-up evaluation.

Conclusion: Two years after collagenase injections for Dupuytren's disease, improvement was maintained in 72% of the treated hands. Complete contracture correction was seen in more than 80% of the MCP but in less than half of the PIP joints.

Strengths and limitations

- Indications for collagenase treatment similar to those conventionally used for surgery.
- Measurements of joint contracture outcomes at baseline and follow-up independent of the treating surgeon.
- Use of an upper-extremity specific measure of patient-reported activity limitations (QuickDASH) and evaluation of patient satisfaction.
- High participation rate with 2-year outcomes data available for 95% of the treated hands.
- Limitations include a single center, moderate sample size, lack of 12-month follow-up, QuickDASH administered to only a subgroup of patients at baseline, QuickDASH not validated specifically in patients with Dupuytren's disease, and use of binary patient satisfaction item.

INTRODUCTION

Collagenase injection is a non-surgical treatment for patients with Dupuytren's disease causing finger joint contractures.[1,2] Treatment comprises injection of collagenase into the cord followed, after about 24 to 48 hours, by finger manipulation (extension). In the initial multicenter randomized trial by Hurst et al.[1] surgeons performed finger manipulation without anesthesia. Finger manipulation is usually painful and lack of anesthesia may hamper contracture reduction. In addition, contractures of the metacarpophalangeal (MCP) joint and proximal interhlangeal (PIP) joint were treated separately with repeated injections given with at least 1-month interval. These procedures have been modified; use of anesthesia prior to finger manipulation is now standard and treating both joints in one session is common.[3] We have used a modified method, injecting a higher collagenase dose (0.80 mg) into multiple parts of the cord and shown good short-term (5 weeks) contracture correction.[4,5] With this method, fingers with contracture of both MCP and PIP joints are treated in 1 stage. Injecting more collagenase along the cord may also imply that a larger part of the cord is disrupted or dissolved. It is not known whether this would result in a more durable correction. Although the initial multicenter study has reported outcomes at 3 years and 5 years,[6,7] the study had substantial follow-up attrition (about one third) and the treating surgeons themselves were outcome assessors. No other prospective studies have reported outcomes at 2 years or longer.

Because patients mainly have activity limitations rather than symptoms, measuring patient-reported activity limitations is important in evaluating treatment outcomes. Little is known about outcomes of collagenase treatment with regard to activity limitations up to 2 years after treatment. The purpose of this study was to determine the durability of collagenase efficacy with regard to joint contractures and activity limitations 2 years after injections.

PATIENTS AND METHODS

Study design and eligibility criteria

We conducted a prospective cohort study at one orthopedic department in Southern Sweden. The department is the only center that treats patients with Dupuytren's disease in a region with 300,000 inhabitants. The indication for treatment with collagenase injections was presence of a palpable cord and a total extension deficit of ≥20º in the MCP joint and/or PIP joint. All patients who had received at least one injection and reached 2 years after first injection from November 2013 through October 2014 were eligible.

Patients

From September 2011 through October 2012, we treated 57 consecutive patients (59 hands) with collagenase injections. In the 2 bilaterally treated patients the interval between treatments was 1 week and 6 months, respectively. All patients were asked to participate in a follow-up examination at a minimum of 2 years after first injection; 5 patients (5 hands) did not participate (2 deceased, 1 had dementia, and 2 did not respond) and 4 patients (4 hands) declined to attend examination but agreed to a telephone interview. Thus, 48 patients (50 hands; 85% of the treated hands) underwent physical examination at a mean of 26 (median 25, range 24 to 35) months after first injection (Table 1).

Intervention

A hand surgeon injected collagenase into the cord using a modification of the standard technique.[4] After reconstituting collagenase with 0.39 ml of diluent, the surgeon injected all reconstituted collagenase that could be withdrawn (approximately 0.80 mg) in the cord, distributed in 3 or 4 spots along the palpable cord, from the PIP joint to the palmar crease.

After injection, a nurse applied a soft dressing and the hand therapist gave the patient verbal and written instructions regarding edema prophylaxis and avoidance of heavy use of the hand.

The surgeon performed finger manipulation 1 day or 2 days after collagenase injection, as schedule permitted. The surgeon injected local anesthetic (10 ml of 10 mg/ml mepivacaine buffered with sodium bicarbonate) proximal to the palmar crease (a few centimeters proximal to the collagenase injection sites) to block the nerves to the treated finger. After about a 20-minute interval the surgeon performed finger manipulation by applying pressure with the thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into maximum possible extension.

Immediately after finger manipulation, the patients went to the hand therapist and received a static splint with fingers in maximal possible extension; the therapist gave instructions on edema management, range of motion exercises, to use the hand as tolerated during daytime, and to use the splint at night for 8 weeks. The patients returned to the hand therapist after 1 week for splint adjustment. In case contracture correction was incomplete and the patient was willing to receive further treatment, the surgeon scheduled the patient for a second injection.

Measurements

Before treatment, one of three hand therapists measured active extension deficit (AED) in the fingers with a goniometer and recorded the results in a standardized protocol. The first 29 patients in the study completed the 11-item disabilities of the arm, shoulder and hand (QuickDASH) scale.[8] At 5 weeks after injection, a hand therapist measured AED in the fingers and the first 29 patients completed the QuickDASH. At 2 years after injection, a hand therapist contacted the patients and asked them to attend the hospital for a physical

examination. During this visit, the therapist measured AED as well as passive extension deficit (PED) in the fingers and examined the hand for possible treatment-related complications. The therapist asked the patients to report any symptoms from the treated hand and about their satisfaction with the results of treatment (satisfied or dissatisfied). All patients completed the QuickDASH. The same hand therapist (AL) examined all patients who attended the 2-year follow-up evaluation and telephone-interviewed patients who did not attend examination. During the telephone interview, the therapist asked the patients whether they believed their treated finger had worsened since the 5-week follow-up visit and whether they were satisfied with the results. Two of the patients interviewed by telephone also completed the QuickDASH.

We reviewed the electronic records of all participants and non-participants to ascertain any subsequent surgery or other procedures on the study hand. We also recorded the number of any additional treatment visits to the hand therapist (outside the preplanned visit at 1 week).

Statistical analysis

Sample size: The primary outcome was worsening of ≥20° in AED between the 5-week and the 2-year measurements. We considered this cut-off as clinically important because it has been used in the previous collagenase multicenter study.[6] In that study, recurrence or nondurability (≥20°increase in PED in fully or partially corrected joints with presence of palpable cord, or subsequent treatment) among 924 joints was 24% at 2 years. We estimated that approximately 50 patients would be eligible and a 70% participation rate. With 80% power and 5% significance level, a sample of 30 patients can show treatment effect durability among 75% of the patients.

Primary analysis: We recorded AED values for MCP and PIP joints for all treated fingers at 3 measurement times (baseline, 5 weeks and 2 years) and calculated the proportion of fingers that showed worsening of ≥20° in AED from the 5-week to the 2-year measurements. *Secondary analyses*: In addition to AED values for all MCP and PIP joints and total (MCP+PIP) extension deficit in the treated fingers we analyzed AED values for joints that had at least 10° pretreatment AED. We considered hyperextension as 0° extension deficit. Because previous studies defined complete correction as PED value 0° to 5°,[1,6] we also analyzed the data according to this definition. This was possible only for the 2-year values, because we measured only AED at baseline and 5 weeks. The change in AED between evaluation times (baseline, 5 weeks and 2 years) was statistically tested with the paired t-test. We used the Mann-Whitney test to compare baseline and 5-week AED in joints that showed ≥20° AED worsening between the 5-week and 2-year measurements and joints that had not worsened after a single injection. We tested the change in QuickDASH scores with the Wilcoxon test (one score for both hands for the 2 bilaterally treated patients). We analyzed the correlation between the changes (baseline to 2 years) in total AED and QuickDASH scores with the Pearson correlation coefficient (r). We also analyzed treatment satisfaction according to changes in total AED and QuickDASH scores using analysis of covariance adjusting for sex, age and baseline total AED or QuickDASH score, respectively. We did a similar analysis for the 2-year QuickDASH scores adjusting for sex and age.

We present the data as proportions, means with standard deviations or 95% confidence intervals, and/or medians with 25th and 75th percentiles as appropriate. For one patient who had surgery on the treated finger 23 months after injection we used the extension deficit recorded immediately before surgery as the 2-year value in all analyses. A 2-sided p-value of less than 0.05 indicated statistical significance.

RESULTS

Joint contracture

Active extension deficit: Between the 5-week and the 2-year measurements, AED had worsened by ≥20° in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a single injection). For all treated fingers, the mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years and the corresponding values for the PIP joints were 30°, 13° and 16°, respectively (Table 2). Between the 5-week and 2-year measurement mean total AED had worsened by 6°, but this did not reach statistical significance.

Comparison of the baseline and 5-week AED in joints that had worsened by ≥20° AED between the 5-week and the 2-year measurements and those that had not worsened showed significant differences for the PIP but not for the MCP joints (Table 3). The difference was large for the baseline AED but smaller for the 5-week AED. Thus, PIP joints with a large pretreatment AED and incomplete initial correction were more likely to worsen between the 5-week and 2-year measurements than joints with less severe contracture and good initial correction, but this was not the case for MCP joints.

A larger proportion of PIP than MCP joints showed either persistent or increased AED (figure 1). Total AED had worsened by ≥30° in 8 of the 50 hands (16%; all had received a single injection). Considering only joints with a pretreatment AED ≥10° (47 MCP joints [mean 57°, SD 19] and 31 PIP joints [mean 48°, SD 21]), mean improvement in AED from baseline was for the MCP joints 49º (95% CI 41 to 54, p<0.001) and for the PIP joints 25º (95% CI 17 to 32, p<0.001).

Passive extension deficit: Of the 47 MCP and 31 PIP joints with contracture before injection, PED of 0° to 5° at 2 years was recorded in 39 MCP joints (83%) and in 15 PIP joints (48%). A total PED ≥30° was present in 11 hands (22%). For all 50 treated fingers, mean PED for the MCP joints was 3.2° (SD 9; median 0; 25th and 75th percentiles 0, 0) and for the PIP joints was 11° (SD 19; median 0, percentiles 0, 20).

Telephone interview: None of the 4 patients telephone-interviewed at 2 years reported worsening of their treated finger since the 5 week follow-up.

Activity limitations

Of the first 29 patients (30 hands) to whom the QuickDASH was administered at baseline, 1 had subsequent surgery before and 1 did not participate in the 2-year follow-up. For the remaining 27 patients (28 hands) the median score (25th, 75th percentiles) at baseline was 11 (2, 21), at 5 weeks 3 (0, 9) and at 2 years 2 (0, 18). Changes from baseline to 5 weeks and to 2 years were statistically significant ($p<0.001$ and $p=0.034$, respectively) but not changes from 5 weeks to 2 years ($p=0.45$). The correlation between baseline to 2 years changes in total AED and QuickDASH score was moderate ($r=0.49$, $p=0.010$). For all 49 patients who completed the QuickDASH at 2 years, the median score was 3 (0, 18).

Patient satisfaction

The patients reported satisfaction with treatment results in 41 of the 50 hands examined and 4 hands evaluated with telephone interview (83% satisfied). Mean change (improvement) in total AED from baseline to 2 years among "satisfied" patients was 65 (SD 26) and among "dissatisfied" patients was 39 (SD 36); adjusted mean difference 37 (95% CI 26 to 49, $p<0.001$). Mean change in QuickDASH score for the satisfied patients was -8 (SD 10) and for

the dissatisfied patients 1 (SD 25); adjusted mean difference -12 (95% CI -23 to -2, p=0.047). Mean 2-year QuickDASH score for "satisfied" patients was 9 (SD 15) and for "dissatisfied" patients 26 (SD 13); adjusted mean difference -16 (95% CI -27 to -5, p=0.007).

Subsequent surgery and adverse events

One patient had recurrent MCP contracture after 1 injection and chose to have limited fasciectomy, which was done 23 months after injection. No other patients had surgery or needle fasciotomy. At the 2-year follow-up evaluation, the examining therapist did not observe and the patients did not report any treatment-related adverse events.

DISCUSSION

This prospective cohort study of patients with Dupuytren's disease treated with collagenase injection shows that contracture improvement was maintained 2 years after treatment in 3 of 4 patients. However, up to 20% of the patients were not satisfied (assuming that the 2 patients who did not respond also were dissatisfied), possibly because of incomplete initial correction or recurrent contracture in the treated finger. Considering its relative simplicity compared to fasciectomy the results of this the 2-year treatment effect durability assessment support the continued use of collagenase injection as an effective treatment option in patients with Dupuytren's disease. Assuming hypothetically that all patients with ≥30° total PED at 2 years would receive a new injection, implying almost a third of all patients require 2 injections, the treatment costs would still be lower compared to surgery.[2] The comparison involves only direct treatment costs; it does not take into consideration the costs of possible surgical complications.[2] Because patients who have good results may still experience worsening after 2 years, a new assessment is necessary with longer follow-up.

Most patients received a single injection but about 10% of the patients needed a second injection because the initial reduction was inadequate. Similar to previous studies of both collagenase and surgery, outcomes were better for MCP joints than PIP joints; more than 80% of MCP joints but less than half of PIP joints achieved complete correction. The PIP joints that had worsened after the 5-week follow-up had more severe contracture both before treatment and at 5 weeks (inadequate correction), but this was not the case for MCP joints. This may suggest that in case the first injection fails to achieve adequate correction for PIP joints the surgeon should consider a second injection early. This question needs further study.

Comparison with other collagenase studies

We measured AED before treatment and at 5 weeks and 2 years. We measured PED only at 2 years to facilitate comparison with previous studies. With regard to joint contracture, passive deficit would be equal or less than active deficit. Thus, our posttreatment AED values are conservative when compared to studies that reported posttreatment PED values.

In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS), 621 of 950 (65%) of the initial study participants could be followed.[6] The authors defined "recurrence" as contracture worsening by ≥20° *combined with* presence of palpable cord *or* further treatment including injection, in successfully treated joints (0° to 5° extension deficit; 70% of treated MCP and 40% of treated PIP), implying that joints in which treatment had failed initially were excluded. Same definition applied to partially corrected joints (improved by ≥20°) was classified as "nondurability". At 2 years, recurrence had occurred in 20% and nondurability in 33%. Contracture "worsening" (defined as ≥20° increase in contracture in fully or partially corrected joints with or without palpable cord *or* subsequent treatment) at 3 years was 28% for MCP and 58% for PIP; no 2-year data were reported. The study reported that for successfully treated MCP joints mean PED at baseline was 37 (SD 16) and at 2 years was 8 (SD 13), and for PIP joints 38 (SD 16) and 20 (SD 19), respectively,[6] and a substantial number of patients received multiple injections. In our study, mean PED for the MCP and PIP joints at 2 years was 3 (SD 9) and 11 (SD 19), respectively.

Because we measured PED only at 2 years, it is not possible to make a direct comparison with the CORDLESS study, but we can assume that PED is always equal or less than AED. Of 32 hands with baseline MCP joint AED of 25° or more and AED of 0° to 5° at 5 weeks (ie "successfully treated" according to CORDLESS definition), 2 had PED ≥20° at 2 years and 1

had undergone surgery, thus 9% would be defined as recurrence according to CORDLESS. This is an overestimate because the CORDLESS patients had to have *both* contracture worsening *and* palpable cord to be considered as recurrence and a large number of different surgeons recorded presence of palpable cord (validity uncertain). Although it is difficult to compare results because of differences in definitions, our results appear to be more favorable. A study of 47 patients with 1 MCP contracture (30°-60°) and no PIP contracture, treated with a single 0.58-mg collagenase injection, reported a 25% 2-year recurrence (>20° contracture).[9]

Comparison with limited fasciectomy and percutaneous needle fasciotomy

Although many studies have reported fasciectomy results,[10] we believe only prospective studies with high follow-up participation can provide good-quality outcomes data. A recent prospective study of 90 patients treated with limited fasciectomy at a university hand surgery center in Sweden, reported that at 1 year the mean AED for the MCP joints was 5 (SD 9) and for the PIP joints 22 (SD 18).[11] It is unclear whether the authors used 0° for hyperextension (as in our study) or used the actual values, which would underestimate the reported extension deficit. They reported that 81% were satisfied at 1 year. Thus, our 2-year collagenase results compare favorably with the 1-year results after limited fasciectomy. Surgery-related complications reported in the study included nerve injury (4 patients) and complex regional pain syndrome (4 patients) and many patients required extensive therapy.[11] Collagenase treatment does not require extensive hand therapy. Almost all patients required only two hand therapist visits (immediately after finger manipulation and at 1 week for splint adjustment).

In a randomized study that defined recurrence after needle fasciotomy as ≥30° worsening in the treated finger's total PED from 6 weeks to 2 years, 29 of 52 patients (56%) had

recurrence.[12] Applying the same definition to our study but using total AED, 8 of 50 hands (16%) would be defined as having recurrence.

The Swedish National Quality Register for Hand Surgery have reported outcome data for patients treated for Dupuytren's contracture at the Swedish Hand Surgery departments between 2010 and 2014.[13] The mean DASH score in patients treated with collagenase had improved from 23 before (n=399) to 11 at 1 year (n=250); the corresponding values for limited fasciectomy were 24 (n=273) and 11 (n=252) and for needle fasciotomy 25 (n=52) and 17 (n=54), respectively. The average patient satisfaction (visual analog scale from 0 to 100) after collagenase treatment (n=260) was 78%, after limited fasciectomy (n=262) was 79%, and after closed fasciotomy (n=73) was 69%.[13] A Swedish 2-center randomized study of collagenase versus needle fasciotomy found no differences at 1 year, but it included mainly patients with only MCP contractures and the treating surgeons measured the outcomes.[14]

We do not use the outcome "recurrence" because of lack of consensus about the definition of recurrence. Treatment with collagenase inherently implies that part of the cord is left intact and therefore it would be impossible to know with acceptable certainty whether a presence of a cord is indicative of recurrence. We believe the degree of joint contracture before and after treatment is a more valid measure of outcome irrespective of whether the cause of the contracture is incomplete correction, disease recurrence/progression, or other cause.

Activity limitations

We used the QuickDASH as patient-reported measure of activity limitations and the results show that the scores improved significantly after treatment. The magnitude of improvement differed according to changes in joint contracture and with patient satisfaction. Because the

median pretreatment QuickDASH score was relatively low, it may not be appropriate in studies comparing different treatments because it would be difficult to detect important between-group differences. However, in patients with DC, no thresholds have been established for within-group and between-group differences in QuickDASH score to be considered as clinically important. Besides, it is not obvious that the same threshold should apply to complex treatments that include surgery and extensive rehabilitation as to less invasive treatments that are associated with substantially lower risks and burden on patients.

The limitations of our study include a single center and a moderate sample size, implying uncertain generalizability. We did not measure passive but only active extension deficit at baseline and at 5 weeks after injection and only the first 29 patients completed the QuickDASH at these follow-up times. Another limitation is lack of 12-month follow-up. Further, patients stated whether they were satisfied or not satisfied with the results at 2 years; a scale with more response options may have yielded different results. Our study has several strengths. First, hand therapists measured joint contractures at baseline, 5 weeks and 2 years, independent of the treating surgeon, and a validated scale used to measure patient-reported activity limitations. The high participation rate is a major strength with 2-year outcomes data available for 95% of the treated hands of patients still living.

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Contributors

AL: contributed to study design, collected the data, assisted in the analysis and interpretation of the data, contributed to drafting of the manuscript, and approved the final version submitted for publication.

IA: led the project, designed the study, conducted data analysis and interpretation, contributed to drafting of the manuscript, and approved the final version submitted for publication.

Ethics approval

This research was approved by the Regional Ethical Review Board in Lund (Dnr 2013/656) and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000.

Competing interests

IA was a member of an Expert Group on Dupuytren's disease for Pfizer in 2012 and has participated in meetings organized by Sobi.

Funding

No external funding.

Data sharing statement

No additional data available.

Figure legend

Figure 1. Active extension deficit (AED) for the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints 5 weeks and 2 years after collagenase injection for Dupuytren's contracture in 50 treated fingers. The joints shown in this diagram are those with AED of at least 10° at 5 weeks or in which AED had changed between the 5-week and the 2-year measurements; AED measured with 5° intervals and joints with identical values juxtaposed for visual clarity. For example, the ♦ farthest to the right on the X-axis represents a treated finger in which MCP AED was 0° at 5 weeks and 65° at 2 years, and the □ in the upper right corner of the graph represent a treated finger in which PIP AED was 55° at 5 weeks and 75° at 2 years. In 4 joints a second injection after the 5-week measurement was given. Joints without contracture (AED 0° to 5°) at both the 5-week and the 2-year measurement (27 MCP and 23 PIP joints) are not shown in the diagram.

Table 1 Characteristics of the participants and non-participants in the 2-year follow-up physical examination

	Participants	Non-participants
Number of hands / patients	50 / 48	9 / 9
Sex, men : women	38 : 12	8 : 1
Age, median (range)	68 (51-83)	66 (55-84)
Hand treated, right : left	34 : 16	8 : 1
Finger treated: small : ring : middle : index	25: 24 : 1 : 1	5 : 3 : 1 : 0
Previous fasciectomy on treated finger, n (%)	6 (12)	1 (11)
Additional treatment visits to therapist, n (%)	3 (6)	0 (0)
Repeat injection, n (%)	5 (10)*	1 (11)
Total extension deficit†		
before injection	80 (54, 108)	68 (49, 119)
5 weeks after injection	15 (0, 29)	20 (9, 63)

*Interval: 4 weeks (1 patient), 2 months (1 patient), 6 months (3 patients), all 5 had MCP and PIP contracture at baseline (3 had reinjection because of inadequate PIP correction and 2 because of inadequate MCP and PIP correction).

†Median (25^{th}, 75^{th} percentiles) active extension deficit (degrees) of the metacarpophalangeal and proximal interphalangeal joints of the treated finger. For all treated fingers, the minimum total extension deficit was 30 degrees.

Table 2 Active extension deficit in the treated fingers immediately before collagenase injection (baseline) and at 5 weeks and 2 years after injection.

	Baseline	5 wk	2 yr	Mean difference (95% CI), p-value			
	n = 50	n = 50	n = 50	Baseline - 2 yr		5 wk - 2 yr	
MCP	54 (23)	6 (12)	9 (16)	45 (38 to 52)	<0.001	-3.1 (-7.8 to 1.6)	0.20
PIP	30 (28)	13 (17)	16 (21)	14 (9 to 20)	<0.001	-3.3 (-6.7 to 0.1)	0.056
MCP+PIP	84 (37)	18 (22)	25 (25)	59 (51 to 68)	<0.001	-6.4 (-12 to -0.06)	0.031

MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

Table 3 Baseline and 5-week active extension deficit for the joints that had worsened by ≥20° at the 2-year measurement (compared to the 5-week measurement) and the joints that had not worsened between these two measurement times; hands treated with a single collagenase injection.

	Worsened ≥20° after the 5-week postinjection measurement	Not worsened after the 5-week postinjection measurement	p-value
MCP, n	7	38	
Baseline	60 (40, 65)	55 (40, 70)	0.87
5 wk	0 (0, 0)	0 (0, 10)	0.57
PIP, n	7	38	
Baseline	60 (30, 75)	10 (0, 40)	0.017
5 wk	15 (15, 55)	0 (0, 15)	0.004

Values are median (25^{th}, 75^{th} percentile) active extension deficit

MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

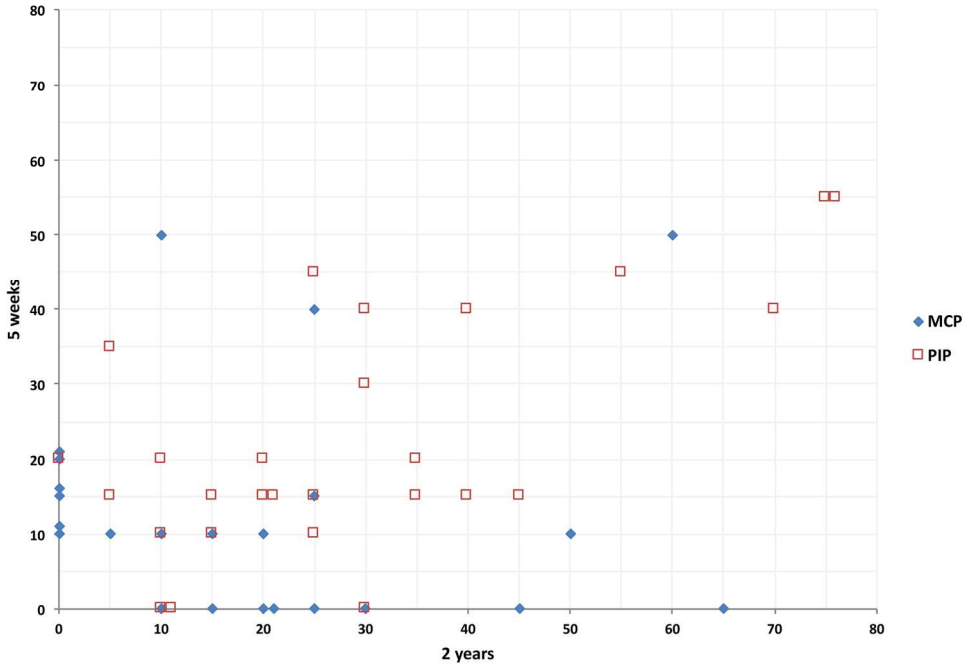

figure 1
173x117mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 P1,2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P2,3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 P4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P5	Present key elements of study design early in the paper
Setting	5 P5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 P5,6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 P6,7,9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* P6,7	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 P7,8	Describe any efforts to address potential sources of bias
Study size	10 P7	Explain how the study size was arrived at
Quantitative variables	11 P7,8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 P7,8,9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* P5 & T1	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* T1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	P5, T1	(b) Indicate number of participants with missing data for each variable of interest
	P5	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P9-11, T2, Fig	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 P9-11, T2	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 P9,10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 P11	Summarise key results with reference to study objectives
Limitations	19 P14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P11-14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 P17	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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Collagenase injections for Dupuytren's disease: prospective cohort study assessing 2-year treatment effect durability

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ABSTRACT

Objectives: To assess 2-year durability of joint contracture correction following collagenase injections for Dupuytren's disease.

Design: Prospective cohort study.

Setting: Orthopedic Department in Sweden.

Participants: Patients with palpable Dupuytren's cord and active extension deficit (AED) ≥30º in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. A surgeon injected 0.80 mg collagenase into multiple cord parts and performed finger manipulation under local anesthesia after 24-48 hours. A hand therapist measured joint contracture before and 5 weeks after injection in all treated patients. Of 57 consecutive patients (59 hands), 48 patients (50 hands) were examined by a hand therapist 24-35 (mean 26) months after injection. Five of the patients had received a second injection in the same finger within 6 months of the first injection.

Outcome measures: Primary outcome was proportion of treated joints with ≥20° worsening in AED from 5 weeks to 2 years.

Results: Between the 5-week and the 2-year measurements, AED had worsened by ≥20° in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a single injection). Mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years, and for the PIP joints 30°, 13° and 16°, respectively.. For joints with ≥10° contracture at baseline, mean (95% CI) baseline-to-2 years AED improvement was for MCP 49º (41-54) and for PIP 25º (17-32). No treatment-related adverse events were observed at the 2-year follow-up evaluation.

Conclusion: Two years after collagenase injections for Dupuytren's disease, improvement was maintained in 72% of the treated hands. Complete contracture correction was seen in more than 80% of the MCP but in less than half of the PIP joints.

Strengths and limitations

- Indications for collagenase treatment similar to those conventionally used for surgery.
- Measurements of joint contracture outcomes at baseline and follow-up independent of the treating surgeon.
- Use of an upper-extremity specific measure of patient-reported activity limitations (QuickDASH) and evaluation of patient satisfaction.
- High participation rate with 2-year outcomes data available for 95% of the treated hands.
- Limitations include a single center, moderate sample size, lack of 12-month follow-up, QuickDASH administered to only a subgroup of patients at baseline, QuickDASH not validated specifically in patients with Dupuytren's disease, and use of binary patient satisfaction item.

INTRODUCTION

Collagenase injection is a non-surgical treatment for patients with Dupuytren's disease causing finger joint contractures.[1,2] Treatment comprises injection of collagenase into the cord followed, after about 24 to 48 hours, by finger manipulation (extension). In the initial multicenter randomized trial by Hurst et al.[1] surgeons performed finger manipulation without anesthesia. Finger manipulation is usually painful and lack of anesthesia may hamper contracture reduction. In addition, contractures of the metacarpophalangeal (MCP) joint and proximal interhlangeal (PIP) joint were treated separately with repeated injections given with at least 1-month interval. These procedures have been modified; use of anesthesia prior to finger manipulation is now standard and treating both joints in one session is common.[3] We have used a modified method, injecting a higher collagenase dose (0.80 mg) into multiple parts of the cord and shown good short-term (5 weeks) contracture correction.[4,5] With this method, fingers with contracture of both MCP and PIP joints are treated in 1 stage. Injecting more collagenase along the cord may also imply that a larger part of the cord is disrupted or dissolved. It is not known whether this would result in a more durable correction. Although the initial multicenter study has reported outcomes at 3 years and 5 years,[6,7] the study had substantial follow-up attrition (about one third) and the treating surgeons themselves were outcome assessors. No other prospective studies have reported outcomes at 2 years or longer.

Because patients mainly have activity limitations rather than symptoms, measuring patient-reported activity limitations is important in evaluating treatment outcomes. Little is known about outcomes of collagenase treatment with regard to activity limitations up to 2 years after treatment. The purpose of this study was to determine the durability of collagenase efficacy with regard to joint contractures and activity limitations 2 years after injections.

PATIENTS AND METHODS

Study design and eligibility criteria

We conducted a prospective cohort study at one orthopedic department in Southern Sweden. The department is the only center that treats patients with Dupuytren's disease in a region with 300,000 inhabitants. The indication for treatment with collagenase injections was presence of a palpable cord and a total extension deficit of ≥20º in the MCP joint and/or PIP joint. All patients who had received at least one injection and reached 2 years after first injection from November 2013 through October 2014 were eligible.

Patients

From September 2011 through October 2012, we treated 57 consecutive patients (59 hands) with collagenase injections. In the 2 bilaterally treated patients the interval between treatments was 1 week and 6 months, respectively. All patients were asked to participate in a follow-up examination at a minimum of 2 years after first injection; 5 patients (5 hands) did not participate (2 deceased, 1 had dementia, and 2 did not respond) and 4 patients (4 hands) declined to attend examination but agreed to a telephone interview. Thus, 48 patients (50 hands; 85% of the treated hands) underwent physical examination at a mean of 26 (median 25, range 24 to 35) months after first injection (Table 1).

Intervention

A hand surgeon injected collagenase into the cord using a modification of the standard technique.[4] After reconstituting collagenase with 0.39 ml of diluent, the surgeon injected all reconstituted collagenase that could be withdrawn (approximately 0.80 mg) in the cord, distributed in 3 or 4 spots along the palpable cord, from the PIP joint to the palmar crease.

After injection, a nurse applied a soft dressing and the hand therapist gave the patient verbal and written instructions regarding edema prophylaxis and avoidance of heavy use of the hand.

The surgeon performed finger manipulation 1 day or 2 days after collagenase injection, as schedule permitted. The surgeon injected local anesthetic (10 ml of 10 mg/ml mepivacaine buffered with sodium bicarbonate) proximal to the palmar crease (a few centimeters proximal to the collagenase injection sites) to block the nerves to the treated finger. After about a 20-minute interval the surgeon performed finger manipulation by applying pressure with the thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into maximum possible extension.

Immediately after finger manipulation, the patients went to the hand therapist and received a static splint with fingers in maximal possible extension; the therapist gave instructions on edema management, range of motion exercises, to use the hand as tolerated during daytime, and to use the splint at night for 8 weeks. The patients returned to the hand therapist after 1 week for splint adjustment. In case contracture correction was incomplete and the patient was willing to receive further treatment, the surgeon scheduled the patient for a second injection.

Measurements

Before treatment, one of three hand therapists measured active extension deficit (AED) in the fingers with a goniometer and recorded the results in a standardized protocol. The first 29 patients in the study completed the 11-item disabilities of the arm, shoulder and hand (QuickDASH) scale.[8] At 5 weeks after injection, a hand therapist measured AED in the fingers and the first 29 patients completed the QuickDASH. At 2 years after injection, a hand therapist contacted the patients and asked them to attend the hospital for a physical

examination. During this visit, the therapist measured AED as well as passive extension deficit (PED) in the fingers and examined the hand for possible treatment-related complications. The therapist asked the patients to report any symptoms from the treated hand and about their satisfaction with the results of treatment (satisfied or dissatisfied). All patients completed the QuickDASH. The same hand therapist (AL) examined all patients who attended the 2-year follow-up evaluation and telephone-interviewed patients who did not attend examination. During the telephone interview, the therapist asked the patients whether they believed their treated finger had worsened since the 5-week follow-up visit and whether they were satisfied with the results. Two of the patients interviewed by telephone also completed the QuickDASH.

We reviewed the electronic records of all participants and non-participants to ascertain any subsequent surgery or other procedures on the study hand. We also recorded the number of any additional treatment visits to the hand therapist (outside the preplanned visit at 1 week).

Statistical analysis

Sample size: The primary outcome was treatment effect durability defined as the proportion of patients that do not worsen by ≥20° in AED, in a treated joint, between the 5-week and the 2-year measurements. We considered this cut-off as clinically important because it has been used in the previous collagenase multicenter study.[6] In that study, recurrence or nondurability (≥20°increase in PED in fully or partially corrected joints with presence of palpable cord, or subsequent treatment) among 924 joints was 24% at 2 years. We estimated that approximately 50 patients would be eligible and a 70% participation rate. With 80% power and 5% significance level, a sample of 30 patients can show treatment effect durability among 75% of the patients.

Primary analysis: We recorded AED values for MCP and PIP joints for all treated fingers at 3 measurement times (baseline, 5 weeks and 2 years) and calculated the proportion of fingers that showed worsening of ≥20° in AED from the 5-week to the 2-year measurements.

Secondary analyses: In addition to AED values for all MCP and PIP joints and total (MCP+PIP) extension deficit in the treated fingers we analyzed AED values for joints that had at least 10° pretreatment AED. We considered hyperextension as 0° extension deficit. Because previous studies defined complete correction as PED value 0° to 5°,[1,6] we also analyzed the data according to this definition. This was possible only for the 2-year values, because we measured only AED at baseline and 5 weeks. The change in AED between evaluation times (baseline, 5 weeks and 2 years) was statistically tested with the paired t-test. We used the Mann-Whitney test to compare baseline and 5-week AED in joints that showed ≥20° AED worsening between the 5-week and 2-year measurements and joints that had not worsened (only hands that received a single injection were included in this analysis). We tested the change in QuickDASH scores with the Wilcoxon test (one score for both hands for the 2 bilaterally treated patients). We analyzed the correlation between the changes (baseline to 2 years) in total AED and QuickDASH scores with the Pearson correlation coefficient (r). We also analyzed treatment satisfaction according to changes in total AED and QuickDASH scores using analysis of covariance adjusting for sex, age and baseline total AED or QuickDASH score, respectively. We did a similar analysis for the 2-year QuickDASH scores adjusting for sex and age.

We present the data as proportions, means with standard deviations or 95% confidence intervals, and/or medians with 25th and 75th percentiles as appropriate. For one patient who had surgery on the treated finger 23 months after injection we used the extension deficit recorded immediately before surgery as the 2-year value in all analyses.

A 2-sided p-value of less than 0.05 indicated statistical significance. We used Stata version 14.0 (Stata Corporation, College Station, TX, USA) for the sample size estimation and IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA) for the statistical analyses.

RESULTS

Joint contracture

Active extension deficit: Between the 5-week and the 2-year measurements, AED had worsened by ≥20° in 7 MCP and 7 PIP joints (28% of the treated hands; all had received a single injection). For all treated fingers, the mean AED for the MCP joints was 54° before injection, 6° at 5 weeks and 9° at 2 years and the corresponding values for the PIP joints were 30°, 13° and 16°, respectively (Table 2). Between the 5-week and 2-year measurement mean total AED had worsened by 6° (p=0.031).

Comparison of the baseline and 5-week AED in joints that had worsened by ≥20° AED between the 5-week and the 2-year measurements and those that had not worsened showed significant differences for the PIP but not for the MCP joints (Table 3). Thus, PIP joints with a large pretreatment AED and incomplete initial correction were more likely to worsen between the 5-week and 2-year measurements than PIP joints with less severe contracture and good initial correction, but this was not the case for MCP joints. Analyses including only joints with baseline contracture of at least 10° showed similar results.

A larger proportion of PIP than MCP joints showed either persistent or increased AED (figure 1). Total AED had worsened by ≥30° in 8 of the 50 hands (16%; all had received a single injection). Considering only joints with a pretreatment AED ≥10° (47 MCP joints [mean 57°, SD 19] and 31 PIP joints [mean 48°, SD 21]), mean improvement in AED from baseline was 49º (95% CI 41 to 54, p<0.001) for the MCP joints and 25º (95% CI 17 to 32, p<0.001) for the PIP joints.

Passive extension deficit: Of the 47 MCP and 31 PIP joints with contracture before injection, PED of 0° to 5° at 2 years was recorded in 39 MCP joints (83%) and in 15 PIP joints (48%). A total PED ≥30° was present in 11 hands (22%). For all 50 treated fingers, mean PED for the MCP joints was 3.2° (SD 9; median 0; 25th and 75th percentiles 0, 0) and for the PIP joints was 11° (SD 19; median 0; percentiles 0, 20).

Telephone interview: None of the 4 patients telephone-interviewed at 2 years reported worsening of their treated finger after the 5-week follow-up.

Activity limitations

Of the first 29 patients (30 hands) to whom the QuickDASH was administered at baseline, 1 had subsequent surgery before and 1 did not participate in the 2-year follow-up. For the remaining 27 patients (28 hands) the median score (25th, 75th percentiles) at baseline was 11 (2, 21), at 5 weeks was 3 (0, 9) and at 2 years was 2 (0, 18). Changes from baseline to 5 weeks and to 2 years were statistically significant ($p<0.001$ and $p=0.034$, respectively) but not changes from 5 weeks to 2 years ($p=0.45$). The correlation between baseline to 2 years changes in total AED and QuickDASH score was moderate ($r=0.49$, $p=0.010$). For all 49 patients who completed the QuickDASH at 2 years, the median score was 3 (0, 18).

Patient satisfaction

The patients reported satisfaction with treatment results in 41 of the 50 hands examined and 4 hands evaluated with telephone interview (83% satisfied). Mean change (improvement) in total AED from baseline to 2 years among "satisfied" patients was 65 (SD 26) and among "dissatisfied" patients was 39 (SD 36); adjusted mean difference 37 (95% CI 26 to 49, $p<0.001$). Mean change in QuickDASH score for the satisfied patients was -8 (SD 10) and for

the dissatisfied patients 1 (SD 25); adjusted mean difference -12 (95% CI -23 to -2, p=0.047). Mean 2-year QuickDASH score for "satisfied" patients was 9 (SD 15) and for "dissatisfied" patients 26 (SD 13); adjusted mean difference -16 (95% CI -27 to -5, p=0.007).

Subsequent surgery and adverse events

One patient had recurrent MCP contracture after 1 injection and chose to have limited fasciectomy, which was done 23 months after injection. No other patients had surgery or needle fasciotomy. At the 2-year follow-up evaluation, the examining therapist did not observe and the patients did not report any treatment-related adverse events.

DISCUSSION

This prospective cohort study of patients with Dupuytren's disease treated with collagenase injection shows that contracture improvement was maintained 2 years after treatment in 3 of 4 patients. However, up to 20% of the patients were not satisfied (assuming that the 2 patients who did not respond also were dissatisfied), possibly because of incomplete initial correction or recurrent contracture in the treated finger. Considering its relative simplicity compared to fasciectomy the results of this the 2-year treatment effect durability assessment support the continued use of collagenase injection as an effective treatment option in patients with Dupuytren's disease.

Assuming, hypothetically, that all patients with total PED of ≥30° at 2 years receive a new injection (implying almost a third of all patients would need two injections), treatment costs as estimated in a previous study,[2] would still be lower than costs of surgery. The comparison involves only direct treatment costs and does not take into consideration costs of possible surgical complications.[2] Since patients with good results may still experience worsening after 2 years, a new assessment with longer follow-up is necessary.

Most patients received a single injection but about 10% of the patients needed a second injection because the initial reduction was inadequate. Similar to previous studies of both collagenase and surgery, outcomes were better for MCP joints than PIP joints; more than 80% of MCP joints but less than half of PIP joints achieved complete correction. The PIP joints that had worsened after the 5-week follow-up had more severe contracture both before treatment and at 5 weeks (inadequate correction), but this was not the case for MCP joints.

This may suggest that in case the first injection fails to achieve adequate correction for PIP joints the surgeon should consider a second injection early. This question needs further study.

Comparison with other collagenase studies

We measured AED before treatment and at 5 weeks and 2 years. We measured PED only at 2 years to facilitate comparison with previous studies. With regard to joint contracture, passive deficit would be equal or less than active deficit. Thus, our posttreatment AED values are conservative when compared to studies that reported posttreatment PED values.

In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS), 621 of 950 (65%) of the initial study participants could be followed.[6] The authors defined "recurrence" as contracture worsening by ≥20° *combined with* presence of palpable cord *or* further treatment including injection, in successfully treated joints (0° to 5° extension deficit; 70% of treated MCP and 40% of treated PIP), implying that joints in which treatment had initially failed were excluded. Same definition applied to partially corrected joints (improved by ≥20°) was termed "nondurability". At 2 years, recurrence had occurred in 20% and nondurability in 33%. At 3 years, contracture "worsening" (defined as ≥20° increase in contracture in fully or partially corrected joints with or without palpable cord, *or* subsequent treatment) was 28% for MCP and 58% for PIP; no 2-year data for "worsening" are available. The study reported that for successfully treated MCP joints mean PED at baseline was 37 (SD 16) and at 2 years was 8 (SD 13), and for PIP joints 38 (SD 16) and 20 (SD 19), respectively,[6] and a substantial number of patients received multiple injections. In our study, mean PED for the MCP and PIP joints at 2 years was 3 (SD 9) and 11 (SD 19), respectively.

Because we measured PED only at 2 years, it is not possible to make a direct comparison with the CORDLESS study, but we can assume that PED is always equal or less than AED. Of 32 hands with baseline MCP joint AED of 25° or more and AED of 0° to 5° at 5 weeks (ie "successfully treated" according to CORDLESS definition), 2 had PED ≥20° at 2 years and 1 had undergone surgery, thus 9% would be defined as recurrence according to CORDLESS. This is an overestimate because in the CORDLESS study the definition of recurrence required that patients had *both* contracture worsening *and* palpable cord, and a large number of different surgeons recorded presence of palpable cord (validity uncertain). Although it is difficult to compare results because of differences in definitions, our results appear to be more favorable. A study of 47 patients with 1 MCP contracture (30°-60°) and no PIP contracture, treated with a single 0.58-mg collagenase injection, reported a 25% 2-year recurrence (>20° contracture).[9]

Comparison with limited fasciectomy and percutaneous needle fasciotomy

Although many studies have reported fasciectomy results,[10] we believe only prospective studies with high follow-up participation can provide good-quality outcomes data. A recent prospective study of 90 patients treated with limited fasciectomy at a university hand surgery center in Sweden, reported that at 1 year the mean AED for the MCP joints was 5 (SD 9) and for the PIP joints 22 (SD 18).[11] It is unclear whether the authors used 0° for hyperextension (as in our study) or used the actual values, which would underestimate the reported extension deficit. They reported that 81% were satisfied at 1 year. Thus, our 2-year collagenase results compare favorably with the 1-year results after limited fasciectomy. Surgery-related complications reported in the study included nerve injury (4 patients) and complex regional pain syndrome (4 patients) and many patients required extensive therapy.[11] Collagenase

treatment does not require extensive hand therapy. Almost all patients required only two hand therapist visits (immediately after finger manipulation and at 1 week for splint adjustment).

In a randomized study that defined recurrence after needle fasciotomy as ≥30° worsening in the treated finger's total PED from 6 weeks to 2 years, 29 of 52 patients (56%) had recurrence.[12] Applying the same definition to our study but using total AED, 8 of 50 hands (16%) would be defined as having recurrence.

The Swedish National Quality Register for Hand Surgery have reported outcome data for patients treated for Dupuytren's contracture at the Swedish Hand Surgery departments between 2010 and 2014.[13] The mean DASH score in patients treated with collagenase had improved from 23 before (n=399) to 11 at 1 year (n=250); the corresponding values for limited fasciectomy were 24 (n=273) and 11 (n=252) and for needle fasciotomy 25 (n=52) and 17 (n=54), respectively. The average patient satisfaction (visual analog scale from 0 to 100) after collagenase treatment (n=260) was 78%, after limited fasciectomy (n=262) was 79%, and after closed fasciotomy (n=73) was 69%.[13] A Swedish 2-center randomized study of collagenase versus needle fasciotomy found no differences at 1 year, but it included mainly patients with only MCP contractures and the treating surgeons measured the outcomes.[14]

We do not use the outcome "recurrence" because of lack of consensus about the definition of recurrence. Treatment with collagenase inherently implies that part of the cord is left intact and therefore it would be impossible to know with acceptable certainty whether a presence of a cord is indicative of recurrence. We believe the degree of joint contracture before and after treatment is a more valid measure of outcome irrespective of whether the cause of the contracture is incomplete correction, disease recurrence/progression, or other cause.

Activity limitations

We used the QuickDASH as patient-reported measure of activity limitations and the results show that the scores improved significantly after treatment. The magnitude of improvement differed according to changes in joint contracture and with patient satisfaction. Because the median pretreatment QuickDASH score was relatively low, it may not be appropriate in studies comparing different treatments because it would be difficult to detect important between-group differences. However, in patients with Dupuytren's disease, there are no established thresholds for within-group and between-group differences in QuickDASH score, considered as clinically important. Besides, it is not obvious that the same threshold should apply to complex treatments that include surgery and extensive rehabilitation as to less invasive treatments that are associated with substantially lower risks and burden on patients.

The limitations of our study include a single center and a moderate sample size, implying uncertain generalizability. We did not measure passive but only active extension deficit at baseline and at 5 weeks after injection and only the first 29 patients completed the QuickDASH at these follow-up times. Another limitation is lack of 12-month follow-up. Further, patients stated whether they were satisfied or not satisfied with the results at 2 years; a scale with more response options might have yielded different results. Our study has several strengths. First, hand therapists measured joint contractures at baseline, 5 weeks and 2 years, independent of the treating surgeon, and a validated scale used to measure patient-reported activity limitations. The high participation rate is a major strength with 2-year outcomes data available for 95% of the treated hands of patients still living.

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Contributors

AL: contributed to study design, collected the data, assisted in the analysis and interpretation of the data, contributed to drafting of the manuscript, and approved the final version submitted for publication.

IA: led the project, designed the study, conducted data analysis and interpretation, contributed to drafting of the manuscript, and approved the final version submitted for publication.

Ethics approval

This research was approved by the Regional Ethical Review Board in Lund (2013/656) and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000.

All patients received full verbal and written information about the study and gave informed consent.

Competing interests

IA was a member of an Expert Group on Dupuytren's disease for Pfizer in 2012 and has participated in meetings organized by Sobi.

Funding

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Data sharing statement

No additional data available.

Figure legend

Figure 1. Active extension deficit (AED) for the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints 5 weeks and 2 years after collagenase injection for Dupuytren's contracture in 50 treated fingers. The joints shown in this diagram are those with AED of at least 10° at 5 weeks or in which AED had changed between the 5-week and the 2-year measurements; AED measured with 5° intervals and joints with identical values juxtaposed for visual clarity. For example, the ♦ farthest to the right on the X-axis represents a treated finger in which MCP AED was 0° at 5 weeks and 65° at 2 years, and the □ in the upper right corner of the graph represent a treated finger in which PIP AED was 55° at 5 weeks and 75° at 2 years. In 4 joints a second injection after the 5-week measurement was given. Joints without contracture (AED 0° to 5°) at both the 5-week and the 2-year measurement (27 MCP and 23 PIP joints) are not shown in the diagram.

Table 1 Characteristics of the participants and non-participants in the 2-year follow-up physical examination

	Participants	Non-participants
Number of hands / patients	50 / 48	9 / 9
Sex, men : women	38 : 12	8 : 1
Age, median (range)	68 (51-83)	66 (55-84)
Hand treated, right : left	34 : 16	8 : 1
Finger treated: small : ring : middle : index	25: 24 : 1 : 1	5 : 3 : 1 : 0
Previous fasciectomy on treated finger, n (%)	6 (12)	1 (11)
Additional treatment visits to therapist, n (%)	3 (6)	0 (0)
Repeat injection, n (%)	5 (10)*	1 (11)
Total extension deficit†		
before injection	80 (54, 108)	68 (49, 119)
5 weeks after injection	15 (0, 29)	20 (9, 63)

*Interval: 4 weeks (1 patient), 2 months (1 patient), 6 months (3 patients), all 5 had MCP and PIP contracture at baseline (3 had reinjection because of inadequate PIP correction and 2 because of inadequate MCP and PIP correction).

†Median (25^{th}, 75^{th} percentiles) active extension deficit (degrees) of the metacarpophalangeal and proximal interphalangeal joints of the treated finger. For all treated fingers, the minimum total extension deficit was 30°.

Table 2 Active extension deficit in the treated fingers immediately before collagenase injection (baseline) and at 5 weeks and 2 years after injection.

	Baseline	5 wk	2 yr	Mean difference (95% CI), p-value			
	n = 50	n = 50	n = 50	Baseline - 2 yr		5 wk - 2 yr	
MCP	54 (23)	6 (12)	9 (16)	45 (38 to 52)	<0.001	-3.1 (-7.8 to 1.6)	0.20
PIP	30 (28)	13 (17)	16 (21)	14 (9 to 20)	<0.001	-3.3 (-6.7 to 0.1)	0.056
MCP+PIP	84 (37)	18 (22)	25 (25)	59 (51 to 68)	<0.001	-6.4 (-12 to -0.06)	0.031

Values are mean (SD) unless specified otherwise.

MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.

Table 3 Baseline and 5-week active extension deficit for the joints that had worsened by ≥20° at the 2-year measurement (compared to the 5-week measurement) and the joints that had not worsened between these two measurement times; hands treated with a single collagenase injection.

	Worsened ≥20° after the 5-week postinjection measurement	Not worsened after the 5-week postinjection measurement	p-value
MCP, n	7	38	
Baseline	60 (40, 65)	55 (40, 70)	0.87
5 wk	0 (0, 0)	0 (0, 10)	0.57
PIP, n	7	38	
Baseline	60 (30, 75)	10 (0, 40)	0.017
5 wk	15 (15, 55)	0 (0, 15)	0.004

Values are median (25^{th}, 75^{th} percentiles) active extension deficit.

MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.

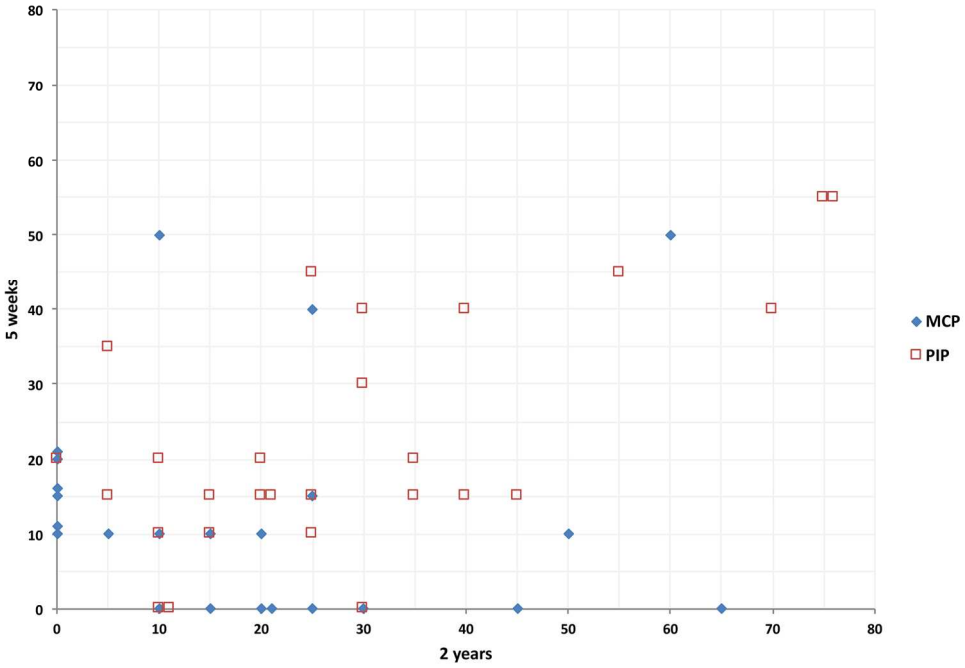

figure 1
173x117mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 P1,2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	P2,3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 P4	Explain the scientific background and rationale for the investigation being reported
Objectives	3 P4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 P5	Present key elements of study design early in the paper
Setting	5 P5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 P5,6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 P6,7,9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* P6,7	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 P7,8	Describe any efforts to address potential sources of bias
Study size	10 P7	Explain how the study size was arrived at
Quantitative variables	11 P7,8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 P7,8,9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* P5 & T1	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* T1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	P5, T1	(b) Indicate number of participants with missing data for each variable of interest
	P5	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* P9-11, T2, Fig	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 P9-11, T2	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 P9,10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 P11	Summarise key results with reference to study objectives
Limitations	19 P14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 P11-14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 P14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 P17	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.