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Surgical fasciectomy versus collagenase injection in treating recurrent Dupuytren disease: study protocol of a randomised controlled trial

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ABSTRACT

Introduction There is no definitive cure for Dupuytren disease (DD), and recurrence of finger contractures after treatment is common. Surgical fasciectomy is considered the standard treatment method for recurrence, although associated with a high incidence of complications. Collagenase injection, a non-surgical treatment option, has been shown to be a safe and effective method; however, most studies regarding collagenase have involved first-time treatment. Collagenase efficacy in patients with recurrent DD beyond the immediate effect has not yet been determined. The aim of our study is to compare surgical fasciectomy and collagenase injection in treating recurrent DD.

Methods and analysis The study is a single-centre randomised controlled trial. Inclusion criteria are recurrence of DD in one or more fingers after previous treatment with fasciectomy or collagenase injection, a passive extension deficit ≥30° in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint, and a palpable cord causing the recurrent contracture. A total of 56 patients will be randomised to either surgical fasciectomy or collagenase injection. A hand therapist blinded to patients' group allocation will measure range of motion at baseline, 3 months, 12 months, 24 months and 60 months. The primary outcomes are the total active extension deficit (MCP plus PIP) at 3 months and the proportion of patients with contracture worsening ≥20° in the treated finger joint at 2 years compared with 3 months. The secondary outcomes include changes in total active motion, active and passive extension deficit from baseline up to 5 years, scores on patient-reported outcome measures, adverse events and costs of treatment.

Ethics and dissemination Ethical approval has been obtained from the Regional Ethical Review Board, Lund University, Sweden(2017/623). The trial will be conducted according to the Helsinki Declaration of 1975, revised in 2000. The results of the trial will be disseminated as published articles in peer-reviewed journals.

Trial registration NCT03406338; Pre-results.

Strengths and limitations of this study

- Randomised controlled design comparing established treatment methods with long-term follow-up.
- Blinded outcome assessor, independent of the treating surgeons.
- Single-centre orthopaedic department, to which the vast majority of patients in the region are referred, enhances generalisability.
- Use of several patient-reported outcome measures, although responsiveness in patients treated for Dupuytren disease may be modest.
- Cost-effectiveness analysis may not be generalisable to other countries.

INTRODUCTION

Dupuytren disease (DD) is a common disorder of the hand.[1–5] A recent systematic review and meta-analysis concerning the prevalence of DD in the adult general population of Western countries suggested a prevalence of up to 30%.[6] Although DD most often has a benign clinical presentation with minor, usually asymptomatic, soft-tissue changes in the palm, a large number of patients seek healthcare for the disease and many undergo treatment for finger contractures.[7] According to a recent Cochrane review,[8] there is insufficient evidence to support the relative superiority of different surgical treatment methods for DD. Surgical fasciectomy has traditionally been the most common treatment method.[9–12] Surgical fasciectomy is a documented effective treatment method, but it can be technically challenging and complications such as digital neurovascular injury and wound-related problems are common.[13–15]

Treatments with minimally invasive procedures such as percutaneous needle fasciotomy[16 17] and collagenase injection[18] have been introduced in recent years and are being increasingly used as first-line treatments. Treatment with collagenase injections became available in 2011[18] and has proven to be an effective treatment method, although the long-term recurrence rate

needs to be further investigated.[19 20] Collagenase injection is considered a safe treatment method that is associated with few serious adverse events.[14 15] The method does not usually require specific hand therapy following intervention, in contrast to surgery, and has been shown to be a cost-effective alternative in comparison with surgery.[21]

There is no cure for DD as all established treatment methods today are associated with recurrence.[16 19 22 23] Treatment of recurrence is usually surgical, but it is even more technically difficult than the index surgery with a considerably higher rate of complications. Collagenase has recently also been used to treat recurrence of DD with good short-term results.[24] To our knowledge, there are yet no published studies or registered ongoing trials comparing different treatment methods for recurrent DD.

We will conduct a randomised controlled trial (RCT) to compare surgical fasciectomy and collagenase injection in the treatment of recurrent DD after previous fasciectomy or collagenase injections. The hypothesis of this RCT is that surgical fasciectomy is more effective in reducing recurrent contractures and has a lower re-recurrence rate, whereas collagenase injection is associated with fewer adverse events and is more cost-effective than surgery.

METHODS AND ANALYSIS

Study design

The study design is a parallel-group RCT that complies with the CONSORT guidelines.[25] The trial will be conducted at a single centre in southern Sweden, the Department of Orthopaedics, Hässleholm-Kristianstad Hospitals in Skåne County, the only centre that treats patients with DD in a region with 300 000 inhabitants.

Patient recruitment

Patients who are referred to the orthopaedic department by primary care physicians or who directly seek care at the department for recurrent DD are routinely appointed to and examined by specialists in hand surgery or orthopaedics and screened for eligibility.

Inclusion criteria

1. Patient (age ≥18 years) with DD seeking treatment for recurrence of contracture in at least one finger (small, ring or middle finger).
2. Passive extension deficit ≥30° in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint in a finger previously treated with surgical fasciectomy or collagenase injections.
3. Palpable cord in the palm and/or affected finger deemed to be the cause of the recurrent contracture.
4. No surgery or collagenase injections in the study hand in the past 12 months.

Exclusion criteria

1. Medical comorbidities constituting absolute contraindication for fasciectomy or collagenase.
2. Signs of nerve or vascular injury in the affected finger.
3. Complications after the previous treatment (infection, neurovascular injury, complex regional pain syndrome).
4. Previous trauma or other surgery involving the affected finger.
5. Severe osteoarthritis involving MCP or PIP joint in the affected finger.
6. More than two previous surgical fasciectomy procedures or collagenase treatments involving the affected finger.
7. Previous treatment with both fasciectomy and collagenase in the affected finger.
8. The examining surgeon deems further fasciectomy to be inappropriate or to be potentially associated with very high complication risk, for example in severe contracture and/or severe scarring after previous surgeries, and consider salvage procedures (such as amputation) as the more appropriate surgical treatment.

Randomisation

Patients are randomised to either surgical fasciectomy or collagenase injections according to a computer-generated randomisation list (in blocks of four or six). The randomisation ratio is 1:1 and stratified according to previous treatment (surgical fasciectomy or collagenase injection) and affected digit (small finger affected or small finger not affected). Patients randomised to surgical fasciectomy or collagenase injection are put on the department's waiting list according to standard routine, and will undergo surgery or injection treatment within 2 months.

Trial treatments

Surgical fasciectomy will be performed according to standard practice by a single hand surgeon with extensive experience in surgery for DD. The surgeon is allowed to choose the type of anaesthesia (general or axillary block) in consultation with the anaesthetist, type of incision, whether to perform supplemental procedures (such as capsulotomy and skin graft), and postoperative care (such as type and duration of any splinting, frequency of dressing change, etc). The patients will return to the outpatient department for suture removal approximately 2 weeks postoperatively. The treating hand occupational therapist (not involved in the trial) will decide the frequency of treatment visits, depending on the status of the treated hand (consulting the treating surgeon when necessary).

Collagenase injection will be performed, according to the modified method previously described,[21] by a single hand surgeon with extensive experience in treating patients with DD with collagenase injections. Approximately 0.8 mg of collagenase is injected into multiple sites along the cord after injecting local anaesthesia.[26] The treating surgeon is allowed to use two injections (two vials) when

treating patients with two or three affected fingers and to give additional injections when necessary. Finger manipulation is done under local anaesthesia 24 to 48 hours after collagenase injection.[27] A hand therapist not involved in the trial will provide the patient with a static splint, immediately after finger manipulation, for use at night for 3 months. The patient is then examined by the therapist 1 week after treatment for possible splint adjustment. The treating hand therapist will decide whether further treatment visits are needed depending on the status of the treated hand.

The two surgeons performing fasciectomy and collagenase injections, respectively, will not be involved in the care of patients randomised to receive the other treatment.

Outcome measures

Physical examination

All patients included in the trial will be examined by one of two trial hand therapists (not involved in the post-treatment care of the participants) according to a standardised protocol. The trial therapists will measure the extension deficit (both active and passive) in the MCP and PIP joints and the total active motion in the treated finger using a hand-held goniometer. Active and passive extension deficit of the PIP joints will be measured with the MCP joints actively extended, to standardise the phenomenon of dynamism.[28] Hyperextension will be recorded as 0° extension deficit. Measurements of sensation with Semmes-Weinstein monofilaments and of grip strength with the JAMAR dynamometer will also be done. Before follow-up examinations, the patients will wear thin gloves in the treated hands exposing only the finger pulps to conceal possible surgical scars so the examiner is blinded to the patients' group allocation.

Patient-reported outcomes (PROMs)

Patients will be asked to fill in a questionnaire package consisting of:

1. Demographic data and questions about factors that have previously been reported to have possible association with DD (family history, smoking, alcohol consumption, bilateral disease, type of work, diabetes).[3 29–33]
2. The 11-item Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire, a measure of activity limitations related to upper extremity disorders, with a total score range from 0 (best) to 100 (worst).[34]
3. The EuroQol 5-dimensions (EQ-5D), a five-item measure of health status and quality of life, with a score range from −0.594 (worst) to 1.0 (perfect health).[35]
4. The Cold Intolerance Symptom Severity Scale (CISSS), a six-item scale inquiring about symptoms of cold sensitivity involving the treated hand, with a score range from 4 (best) to 100 (worst).[36]
5. The Palmar Pain Scale, a two-item scale inquiring about pain in the palm and related activity limitations, with a score range from 0 (best) to 100 (worst).[37]
6. Pain Visual Analogue Scale (VAS), with a score range from 0 (best) to 100 (worst).
7. Treatment satisfaction VAS, with a score range from 0 (best) to 100 (worst).
8. Medication use for pain in the treated hand (response options; no, sometimes, daily).

All outcome measures will be completed by the patients during visits to the trial therapist or trial nurse, or sent by mail, independently of the treating surgeons.

Adverse events

All adverse events (AEs) and serious adverse events (SAEs) related to the interventions will be recorded. All patients will have scheduled appointments during which an orthopaedic surgeon or hand surgeon not involved in the treatment will examine the patients and record any observed complications using a standardised protocol. In addition, complications reported by the patients or healthcare personnel at any time will be evaluated and recorded on a standard form. The SAE include nerve injury (irreversible), vascular injury, tendon rupture, complex regional pain syndrome, deep infection, severe loss of flexion in the treated finger, or any complication requiring surgical intervention or hospital admission.

Costs of treatment

Treatment-related costs (interventions, medications, visits, materials, etc) and costs of sick-leave (for employed patients) will be documented.

Follow-up procedures

Measurements of range of motion in the study hand will be performed at baseline and at 3 months, 12 months, 24 months and 60 months after intervention (table 1). All reported or observed AEs and SAEs will be documented intraoperatively (by the surgeon) and in the follow-up examinations by orthopaedic surgeons, independently of the treating surgeon, at scheduled appointments at 1 week, 3 months, 24 months and 60 months after treatment and whenever reported.

The patient-reported outcome measures will be completed at baseline and at 3 weeks, 6 weeks, 3 months, 12 months, 24 months and 60 months after intervention. For employed patients, sick-leave periods will be recorded. All visits to healthcare personnel will be recorded, including type of visit and treatments given.

Primary outcomes

1. Change in total active extension deficit (MCP plus PIP) in the treated finger from baseline to 3 months (used for the sample size calculation).
2. Proportion of patients with contracture worsening ≥20° in total active extension deficit in the treated finger at 2 years compared with 3 months.

Secondary outcomes

1. Total active motion (sum of active range of motion in the MCP, PIP and distal interphalangeal joints in the

Table 1 Patients' visits during the trial, data collection and outcome measures during 5 years

	Baseline	Treatment day 0	1 week ±3 days	3 weeks ±3 days	6 weeks ±7 days	12 weeks ±7 days	52 weeks ±14 days	2 years ±21 days	5 years ±21 days
Diagnosis, eligibility	X								
Randomisation	X								
Surgery or injection		X							
Physical examination	X					X	X	X	X
Questionnaires	X			X	X	X	X	X	X
Sick-leave		X				X	X		
Adverse events		X	X			X	X		

treated finger): change from baseline to 3 months, 1 year, 2 years and 5 years.
2. Total active extension deficit (MCP plus PIP) in the treated finger: change from baseline to 1 year, 2 years and 5 years.
3. Total passive extension deficit (MCP plus PIP) in the treated finger: change from baseline to 3 months, 1 year, 2 years and 5 years.
4. Contracture worsening ≥20° in total active extension deficit in the treated finger: proportion of patients at 5 years compared with 3 months.
5. QuickDASH score: change over time, from baseline to 3 weeks, 6 weeks, 3 months, 1 year, 2 years and 5 years.
6. EQ-5D index: change over time, from baseline to 3 weeks, 6 weeks, 3 months, 1 year, 2 years and 5 years.
7. Palmar pain score: change over time, from baseline to 3 weeks, 6 weeks, 3 months, 1 year, 2 years and 5 years.
8. Pain VAS score: change over time, from baseline to 3 weeks, 6 weeks, 3 months, 1 year, 2 years and 5 years.
9. Satisfaction VAS score: 3 weeks, 6 weeks, 3 months, 1 year, 2 years and 5 years.
10. CISSS score: change over time, from baseline to 3 weeks, 6 weeks, 3 months, 1 year, 2 years and 5 years.
11. AEs and SAEs: 1 week, 3 months and 24 months.
12. Total treatment costs.

Sample size

There is no universal definition of recurrence of DD in the literature, although an expert group recently reached a consensus that recurrence should be defined as more than 20° of contracture recurrence in any treated joint at 1 year (or later) post-treatment compared with 6 weeks post-treatment.[38] In this study, we assume that surgical fasciectomy is more effective in reducing recurrent contractures and that a difference of 20° in total extension is considered clinically relevant.[18] A previous study has shown that patients treated with collagenase injection for recurrence after surgical fasciectomy had a mean improvement of 43° (SD 28) in total extension deficit.[39] To be able to show a difference of at least 20° in total extension deficit between the groups at 3 months with a SD of 25, alpha level of 0.05 and statistical power of 80%, a sample size of 50 patients (25 per group) will be needed. We aim to recruit 56 patients to account for any potential loss to follow-up. If we encounter a higher drop-out rate during the course of the trial, we will enrol more patients to achieve at least the pre-estimated sample size.

Statistical analysis

In the primary analysis, we will calculate the mean between-group difference in improvement in total active extension deficit (MCP plus PIP) at 3 months (figure 1). For the co-primary outcome, we will calculate the proportion of joints (MCP and PIP separately) with worsening of at least 20° in total active extension deficit at 24 months

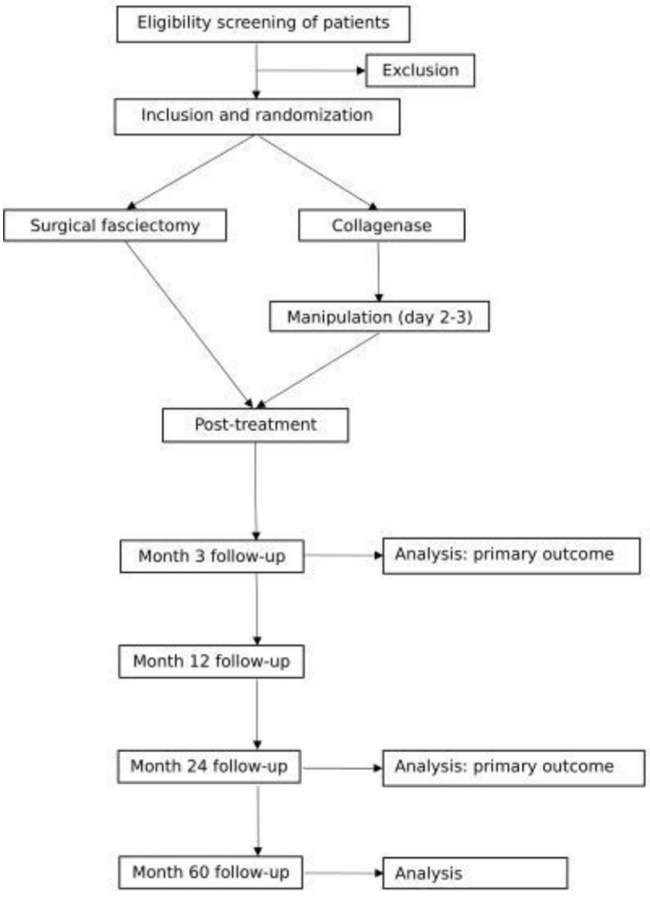

Figure 1 Flowchart of the study.

compared with 3 months. When comparing patients rather than joints, we will consider recurrence in any treated finger as an end-point. In the secondary analyses, we compare the groups regarding change over time in QuickDASH score, EQ-5D index, palmar pain score, CISSS score, pain VAS score and satisfaction VAS score. We will compare changes in total active motion, passive extension deficit and total active extension deficit from baseline to 3 months, 12 months, 24 months and 60 months. We will calculate the proportion of joints with worsening of at least 20° in extension measured at 5 years compared with 3 months.

All treated fingers are included in the primary analysis. For the primary outcome (changes in active extension deficit from baseline), a mixed-model analysis will be used, which accounts for the fact that some patients provide data from multiple fingers, with and without adjusting for baseline factors. We will conduct two subgroup analyses; severity of baseline PIP contracture (<40° vs ≥40°) and number of previous collagenase injections (1 vs 2). A two-sided p value of <0.05 will be used to indicate statistical significance.

Adherence and withdrawals

A trial research nurse will monitor patients' adherence to the follow-up protocol and assist when necessary. Patients can withdraw from the trial at any time without need to give reasons. Patients who do not wish to attend physical examination will be asked whether they would be willing to complete the questionnaire.

Data management

The trial will be monitored by an independent two-member monitoring committee; a senior orthopaedic surgeon with experience in clinical research and a research nurse. The collected data will be stored at the study centre research unit. The data will be entered coded into a password-protected database. A separate paper log will be kept at the research unit, available only to the researchers involved in the study. No interim analysis will be performed. If a higher drop-out rate than estimated is encountered during the course of the trial, more participants will be enrolled to achieve at least the pre-estimated sample size. Only the monitors and the principal researchers will have access to the final dataset. Data will be stored after the trial for 15 years.

Patient and public involvement

The development of the research question of this study is based on increasing request from patients with Dupuytren disease for minimally invasive treatment methods and lack of evidence regarding the comparative effectiveness of the treatment methods used in recurrent disease. At the trial conception stage, we asked a number of patients being treated for recurrent Dupuytren disease whether they would have considered participating in a study in which they would be randomly assigned to open surgery or collagenase injections. The patients or public were not involved in the design, recruitment to or conduct of the trial. The participants will receive a summary of the main findings at the end of the study.

Ethics and dissemination

Both treatments are established methods for the treatment of DD, and are considered to be safe. Patients eligible for inclusion are given full verbal and written information about the trial including potential risks and benefits. Patients who accept to participate in the trial provide written consent before inclusion and randomisation. Participants in whom an adverse event occurs will be given appropriate medical care and will be entitled to apply for compensation from the Swedish Patient Claims Panel.

DISCUSSION

This RCT will compare surgical fasciectomy with collagenase injection in the treatment of recurrent DD, a common cause of medical consultation and treatment.[7] The objective of the study is important since all available treatment methods are associated with recurrence.[16 19 22] Although surgical fasciectomy is a well-established method for treating recurrence, it is technically difficult with a high complication rate. The literature lacks studies comparing methods for treatment of disease recurrence. The minimally invasive method of injecting collagenase has been shown to be effective in the treatment of DD[19 20] and also to have the advantage of a low complication rate[15] and a quick recovery of hand function. It is unknown whether these advantages also apply for patients treated for recurrence.

The strength of this study is the randomised controlled design. Furthermore, the study setting, an orthopaedic department to which the vast majority of patients with DD in the region are referred, will enhance generalisability. The department have extensive experience in both surgical fasciectomy and collagenase injections. A single blinded experienced hand therapist will perform follow-up measurements using a standardised protocol with all patients, independently of the treating surgeons, which decreases the risk of examiners' influence on the measurements. Furthermore, the outcome assessor (trial hand therapist) is not involved in the clinical management of the participants and therefore blinded to group allocation. Besides, during examination, the patients will be wearing thin gloves that will conceal possible surgical scars and only expose the finger pulps. However, these measures may not guarantee successful blinding in all cases.

The study setting, a single-centre trial, may also be considered a limitation. A multicentre setting, involving several surgeons (who may use different surgical techniques), would probably increase generalisability. We have chosen to involve only one experienced hand surgeon to perform the open surgical procedures in this trial in order to provide optimal conditions for achieving

the best possible results that will be compared with the results of collagenase injections. A detailed description of surgical techniques used in the trial (ie, proportion of participants treated with limited fasciectomy only, fasciectomy combined with PIP release, skin graft or other procedures) will be presented.

The number of patients planned to be enrolled in this superiority trial is based on the pretrial estimation of the sample size needed to compare the treatment methods with regard to the primary outcome. However, a larger sample would yield greater precision of the estimates in the primary and secondary analyses and the subgroup analyses. We will consider increasing the study size if deemed appropriate and practical.

The randomisation procedure in this study is stratified according to affected digit (small finger affected or small finger not affected) because in our experience the small finger (especially the PIP joint) is the most difficult to treat and has a high tendency for recurrence. In the RTC by Skov *et al*,[40] comparing collagenase injections and needle fasciotomy for PIP joint contractures, 97% of patients in the collagenase group were treated in the small finger in comparison with 71% of patients in the needle fasciotomy group. We stratified according to small finger to avoid this situation that may introduce bias. We have chosen not to include patients presenting with contracture involving the index finger because it is uncommon; in a prospective cohort study, the index finger constituted less than 2% of collagenase-treated fingers.[20] Another possible limitation of the study is the length of follow-up for the primary outcome. Recurrence of contracture in DD is often a slow process that might not occur by 24 months after treatment. Furthermore, the literature lacks a clear universal definition of disease recurrence and what constitutes a clinically relevant difference in total extension deficit, although an expert group recently reached a consensus that recurrence should be defined as more than 20° of contracture recurrence in any treated joint at 1 year post-treatment (or later) compared with 6 weeks post-treatment.[38] This in turn may affect the sample size calculation. We base our calculation on a clinically relevant difference of 20° since it has been used most frequently in recent studies of collagenase treatment[18 19] and is supported by the expert group.[38] Another limitation is the use of PROMs in research on DD. Although the QuickDASH score, a measure of activity limitations related to upper-extremity disorders, is commonly used in hand surgery research, it may not be sensitive to changes in DD-related contractures.[41 42] Patient-reported measures developed specifically for patients with DD, such as the Unite Rhumatologique des Affections de la Main[43 44] and the Southampton Dupuytren's scoring scheme,[45] need further independent validation. Furthermore, the study is performed in Sweden and cost analysis may not be generalisable to other countries.

The goal of this study is to compare two well-established methods in the treatment of recurrent finger joint contracture in DD. The results will be useful to provide evidence regarding the most effective treatment method for patients with disease recurrence. As DD most commonly affects the elderly, and considering the ageing population is increasing with higher functional demands, it is highly important to compare treatment methods in terms of efficacy and also related to adverse events, patient satisfaction and treatment costs.

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