Collagenase injection versus limited fasciectomy surgery to treat Dupuytren's contracture in adult patients in the UK: DISC, a non-inferiority RCT and economic evaluation

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Scientific summary

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Scientific summary

Background

Dupuytren's disease affects over 2 million UK adults. Cords pull the fingers down towards the palm. This interferes with hand function and dexterity, impacting on quality of life.

Current treatments to remove, dissolve or break the cords include surgical correction [limited fasciectomy (LF)], collagenase injection (an enzyme injected into the cord), and percutaneous needle fasciotomy (a needle is used to puncture, weaken and cut the cord). None of these treatments cure the tendency to develop Dupuytren's contracture (DC) and so the cords and contracture can recur over time.

Collagenase has some benefits over LF surgery including shorter recovery and no dependence on operating theatre availability for delivery of the intervention. There is, however, limited robust evidence comparing surgical correction and collagenase injection in terms of clinical effectiveness, cost-effectiveness, and in terms of patient's experiences and preferences.

Objectives

The primary objective was to compare whether collagenase injection is not inferior to LF in the treatment of DC. Secondary objectives included investigation of recurrence at 1 and 2 years after treatment and cost-effectiveness. A qualitative substudy explored patients' views of collagenase and LF, and a photography substudy investigated whether measurements of extension and flexion made on photographs taken by patients reflect goniometric measurements to assess recurrence.

Methods

Design

The Dupytren's interventions surgery vs collagenase (DISC) trial was a multicentre, pragmatic, parallel two-arm randomised controlled non-inferiority trial with a cost-effectiveness evaluation, and nested qualitative and photography substudies.

Participants were randomised on an equal basis to receive either of the two treatment options via a remote randomisation service. Randomisation was blocked, with randomly varying block sizes, and stratified by reference (worst-affected) joint [metacarpophalangeal (MCP) joint or proximal interphalangeal (PIP) joint].

Participants were followed up at 3 months, 6 months, 1 year and 2 years after treatment. Data collection included joint measurements and photography at baseline, and all follow-up time points.

Setting

Trial recruitment was undertaken in 31 NHS hand units across England and Scotland between June 2017 and September 2021.

Participants

Patients aged 18 years and over with a discrete, palpable Dupuytren's cord causing contracture of ≥ 30 degrees and who were appropriate for both study treatments, were eligible for inclusion. Patients were excluded if they had severe contractures (> 135 degrees); had received treatment to the study digit; had other pre-existing disorders affecting hand function; had contraindications to collagenase; had

a coagulation disorder; were female and pregnant or breastfeeding; had participated in a study involving another investigational medicinal product within 12 weeks or had another disease or disorder which would put them at risk if participating.

Interventions

The intervention was collagenase *Clostridium histolyticum* injection, supplied through routine NHS stocks. Collagenase was injected as three aliquots at set anatomical points in line with the current approved summary of product characteristics. After an interval of 1–7 days, participants returned to the clinic, where under local anaesthetic the cord was snapped to correct the contracture. The control group received LF surgery to remove the diseased nodules and cord to correct the contracture. Participants were followed up at routine wound check appointments following intervention.

Outcomes

The primary outcome was the Patient Evaluation Measure (PEM) score (0–100 with higher scores indicating worse outcome) at 1 year after treatment. The PEM was also completed at 3 months, 6 months and 2 years after treatment.

Secondary outcomes included the Unité Rhumatologique des Affections de la Main (URAM) scale, Michigan Hand Outcomes Questionnaire (MHQ), recurrence, extension deficit and total active movement, complications, further treatments (including further care and/or re-intervention), health-related quality of life [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)], resource use, time to recovery of function (using a single assessment numeric evaluation measure) and overall hand assessment.

All outcomes were collected at 3 months, 6 months, 1 year and 2 years. The PEM was also recollected immediately prior to treatment delivery, and the time to recover function and quality of life were also collected at 2 and 6 weeks after treatment. Outcomes were collected primarily in hospital clinics, with some participants being followed up for postal, telephone, or video data collection during the COVID-19 pandemic.

The qualitative substudy explored participants experiences of DC and treatments. The photography substudy explored the agreement between measurements obtained using a goniometer and photographs taken by participants at home, to determine whether the two methods of measurement might feasibly be used interchangeably.

Results

Clinical effectiveness

In total 672 participants (64.6%) were recruited and randomised; 336 to receive collagenase injection and 336 to receive LF. Baseline characteristics were similar across groups.

Of the 672 randomised participants, 621 (92.4%) received treatment as part of the trial. Cross-over was limited: one participant (0.3%) allocated to collagenase received LF; seven participants allocated to LF received collagenase (2.1%). On average participants received collagenase by 12.1 weeks [standard deviation (SD) 13.7] and LF in 17.7 weeks (SD 16.5) after randomisation. Most participants (n = 315, 95.2%) had just one digit treated. No participants required an unplanned inpatient admission following treatment and 62.0% (n = 201) collagenase participants and 78.3% (n = 224) LF participants had full correction following treatment.

At 1 year (primary time-point) the difference in PEM scores showed that collagenase was inferior to LF; difference 5.95 [95% confidence interval (CI) 3.12 to 8.77; p = 0.49]. The benefit of LF over collagenase continued to increase to 2 years (7.18, 95% CI 4.18 to 10.88; p = 0.82). There were no material changes in these results for any of the sensitivity or additional analyses undertaken.

The primary analysis therefore shows that there is little evidence to support rejection of the hypothesis that collagenase is inferior to LF at 1 and 2 years post treatment. Indeed, the observed data are highly compatible with LF being superior to collagenase with regard to the primary outcome measure at both these time points.

Patient Evaluation Measure overall assessment scores corresponded with the primary outcome analyses and participants in both groups reported positive experiences of treatment.

The estimated difference in URAM scores followed those of PEM, increasing in favour of LF over time from 3 months (0.82, 95% CI −0.21 to 1.84; $p = 0.12$) to 5.37 (95% CI 3.85 to 6.88; $p \leq 0.00005$) at 2 years. At 1 year MHQ scores were higher (better) in the LF group (1 year: −4.69, 95% CI −7.27 to −2.12; $p = 0.0004$) and this continued at 2 years (2 years: −6.71, 95% CI −9.60 to −3.82; $p \leq 0.00005$).

Return to function was better in the short term for the collagenase group (week 2: 14.93, 95% CI 11.66 to 18.19; $p \leq 0.00005$; 6 weeks: 5.00, 95% CI 2.29 to 7.70; $p = 0.003$) but by 1 year function was superior after LF (−4.93, 95% CI −7.63 to −2.22; $p = 0.0004$). At 1 year participants who received LF were more likely to respond as being 'cured' or 'much better' than participants who received collagenase [odds ratio (OR) 3.01, 95% 2.15 to 4.23; $p \leq 0.00005$].

Passive extension deficit was similar between the groups at baseline (mean: 45.8°; SD 17.0). Following collagenase treatment, extension deficit seemed to be worse at all time points ranging from a difference of 5.73° (95% CI 2.88 to 8.59; $p = 0.0001$) at 3 months to 10.10° (95% CI 6.46 to 13.73; $p \leq 0.00005$) at 1 year and increasing again up to 2 years. Results when imputed data were included were similar. Increases in reference joint passive range of movement (RoM) were similar between the two groups following treatment. However, from 6 months there was strong evidence that collagenase resulted in poorer passive RoM (−7.42°, 95% CI −11.54 to −3.29; $p = 0.0004$) and this difference increased further over time.

Measurements of active extension deficit were similar between the two groups at baseline (mean: 51.9°, SD 16.1). Like passive extension deficit, active extension deficit was worse following collagenase treatment at all time points, ranging from a difference at 3 months of 5.57° (95% CI 3.02 to 8.12; $p \leq 0.00005$) to 11.52° (95% CI 8.13 to 14.91; $p < 0.00005$) at 1 year and increasing again up to 2 years. Results when imputed data were included were similar. Increases in active RoM of the reference joint were similar between the two groups following treatment. However, from 6 months there was strong evidence that collagenase resulted in poorer active RoM (−8.37°, 95% CI −11.99 to −4.75; $p \leq 0.00005$). Again, this difference increased further over time.

In total 54 participants (15.7%) experienced recurrence of DC. There was weak evidence to suggest that following collagenase treatment participants were more likely to experience recurrence compared to participants who received LF (OR 1.39, 95% CI 0.74 to 2.63; $p = 0.31$).

There were 267 complications (0.82 per participant) reported for the collagenase group, compared to 177 complications (0.60 per participant) reported for the LF group. Participants in the LF group experienced a higher proportion of 'moderate' or 'severe' complications (5% vs. 2%).

In the first year following intervention, most participants did not require re-intervention ($n = 399$, 64.3%), which dropped to 47.7% by 2 years. By 2 years, 10% of collagenase participants had re-intervention compared to 2.5% of LF participants.

Cost-effectiveness

The mean cost of surgery was estimated to be £2510 (SD £818) per participant compared to £1008 (SD £94) for the collagenase group. The overall mean healthcare cost was slightly lower in the collagenase group compared to the LF group at 2 years (mean difference: −£28, 95% CI −£87 to £30). Baseline

utility scores (EQ-5D-5L) were slightly higher in the LF group (mean 0.794, SD 0.170) compared to the collagenase group (mean 0.791, SD 0.174), but this was not statistically significant (95% CI −0.029 to 0.024).

For both groups, utility scores decreased immediately following treatment but by 3 months had reverted to baseline levels. The mean difference between groups at 2 years was −0.044 (95% CI −0.077 to −0.010).

After adjustment for baseline costs and utilities, participants who received collagenase showed a statistically insignificant decrease in quality-adjusted life-year (QALY) gains at 1 year (−0.003, 95% CI −0.006 to 0.0004) and a reduced cost (−£1090, 95% CI −£1139 to −£1042) compared to LF participants. The probability of collagenase being cost-effective was over 99% for both willingness-to-pay thresholds of £20,000 and £30,000 per QALY at 1 year and this finding was robust for the sensitivity analyses conducted. At 2 years collagenase continued to be both significantly less costly (−£1212, 95% CI −£1276 to −£1147) and less effective (−0.048, 95% CI −0.055 to −0.040). The probability of collagenase being cost-effective was 72% at the £20,000 threshold and 37% at the £30,000 threshold. The longer-term Markov model indicated that collagenase became less cost-effective than LF at the lifetime horizon, the probability of collagenase being cost-effective ranged from 22% to 16%.

Qualitative

Semistructured qualitative interviews were conducted with 45 patients, resulting in four core topics: Lived experience; knowledge; experience; and looking to the future. Participants reported living for extended periods with DC and seeking medical advice only when impacted by the difficulty in doing tasks or appearance of the hand. Most participants reported improvement in their contracture and function; some treated with collagenase noted that while the outcome was not perfect, it was acceptable. More participants treated with collagenase reported preferring this in the future compared to LF participants preferring the same intervention again.

Photography substudy

The difference between goniometric measurements and participant-taken photographs for active extension deficit was −9.7° (SD 16.2) for MCP, 8.0° (SD 15.1) for PIP and 5° (SD 9.5) for distal interphalangeal (DIP) joints. The limits of agreement were approximately ± 30° for MCP from ± 12° to ± 30° for PIP and ± 18° for DIP joints. For flexion, differences were −0.8° (SD 19.3) for MCP, −1.6° (SD 14.5) for PIP and −2.7° (SD 13.5) for DIP joints. Limits of agreement were approximately ± 36° for MCP, ± 20° for PIP, and a range of ± 33° to ± 24° for DIP joints.

Conclusions

In adults with moderate DC, collagenase, when delivered in an outpatient setting, proves to be significantly cost-saving compared to LF throughout the trial. While collagenase demonstrates comparable QALY gains to LF at 1 year, its effectiveness is significantly lower at 2 years. This leads to a changing cost-effectiveness profile over time, with collagenase being highly likely cost-effective at 1 year. However, the probability of its cost-effectiveness declines at 2 years. The Markov model results indicate that the likelihood of collagenase being considered cost-effective compared to LF at the lifetime horizon falls below 22% at thresholds of £20,000/QALY and above. The DISC trial followed participants for up to 2 years after treatment and therefore further research is required to better understand the longer-term trajectories for patients following initial contracture correction.

Implications for health care

The results from the DISC trial provide strong indicators for the planning of care of DC patients in the UK.

The comprehensive nature of the clinical and cost-effectiveness data provides the opportunity for the UK National Institute for Health and Care Excellence to update its recommendation on the treatment options for DC. Of relevance will be how to situate the use of collagenase if it is reintroduced for use in the NHS.

The role of primary care services in ensuring timely first diagnosis and referral of patients with DC needs to be strengthened. The results of the DISC trial provide a basis to engage further with primary care providers in relation to this.

The DISC photography substudy provides an indication of how patient-taken photographs can complement clinic measurements if processes are streamlined further. Further investigation will be key in establishing remote assessment and follow-up for DC patients but noting that clinic measurements remain necessary for final decisions on required care.

Recommendations for future research

Follow-up to 5 years or more would establish the evolution of differences observed at 2 years, particularly in relation to recurrence and re-intervention, which usually occurs after 1 year.

Also, the data collection in the DISC trial has been used as the basis for planning the data collection for the ongoing HAND-2 trial [NIHR: 127393; ISRCTN: 18254597], which will allow for a network meta-analysis of all key interventions for DC.

The results from the qualitative substudy provide direction on planning further research to understand behavioural trends that influence a patient's decision to seek care and return to care after initial intervention.

Study registration

Current Controlled Trials ISRCTN18254597.

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