



Lower costs for collagenase injections than fasciectomy in the treatment of Dupuytren's contracture: A single-centre controlled cohort study

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6 2 **Dupuytren's contracture: A single-centre controlled cohort study**

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3 18 **Abstract**
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20 **Objectives:** The aim of this controlled cohort study of Dupuytren's contracture (DC) was to
21 compare collagenase injections with surgery (fasciectomy) with regard to the actual total
22 direct treatment costs and short-term outcomes.

23 **Setting:** Orthopaedic department of a regional hospital in Sweden.

24 **Participants:** Patients aged 65 years or older with previously untreated DC of 30 degrees or
25 greater in the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints of the
26 small, ring or middle finger. The collagenase group comprised 16 consecutive patients treated
27 during the first 6 months following the introduction of collagenase as treatment for DC at the
28 study centre. The controls were 16 patients randomly selected among those operated on with
29 fasciectomy at the same centre during the preceding 3 years.

30 **Interventions:** Treatment with collagenase was given during two standard outpatient clinic
31 visits (injection and next-day finger extension under local anaesthesia) followed by night-time
32 splinting. Fasciectomy was done in the operating room (day surgery) under general or
33 regional anaesthesia using standard technique, followed by therapy and splinting.

34 **Primary and secondary outcome measures:** Actual total direct costs (salaries of all medical
35 personnel involved in care, medications, materials and other relevant costs), and total MCP
36 and PIP extension deficit (degrees) measured by hand therapists at 6-12 weeks after treatment.

37 **Results:** Collagenase injection required fewer hospital outpatient visits to a therapist and
38 nurse than fasciectomy. Total treatment cost for collagenase injection was 1418.04 USD and
39 for fasciectomy 2102.56 USD. The post-treatment median (interquartile range) total extension
40 deficit was 10 (0-30) for the collagenase group and 10 (0-34) for the fasciectomy group.

41 **Conclusions:** Treatment of Dupuytren's contracture with collagenase injection costs 33% less
42 than fasciectomy with equivalent short-term efficacy regarding reduction in contracture.
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3 43 **Strengths and limitations of this study**
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7 45 • This study presents previously unknown estimates of the actual costs of treating
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9 Dupuytren's contracture with Collagenase injections or fasciectomy
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11 47 • Comparison of the actual costs of the two treatments are based on detailed definition and
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13 measurement of all relevant costs
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15 49 • Outcomes of injections were prospectively measured but outcomes of surgery were based
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17 on medical records
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19 50
20 51 • Costs may vary across countries
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22 52 • Only short-term outcomes were compared
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53 INTRODUCTION

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55 Dupuytren's contracture (DC) is a common hand disorder causing finger contractures that
56 may compromise hand function. Surgery in the form of limited fasciectomy has been the main
57 treatment option for reducing the contracture.¹ In Sweden (population 9.5 millions), more
58 than 3000 fasciectomy procedures are performed annually;² the actual number is probably
59 higher because procedures performed by surgeons in private practice, although constituting a
60 small proportion,³ may not always be reported to the national database. Surgery is usually
61 done in the main operating room under general or regional anaesthesia and the operating time
62 is on average about 1 hour,⁴ but can be substantially longer when severe contractures are
63 present in multiple fingers. After surgery many patients require therapy and splints. Although
64 surgery is often effective in reducing the contracture, postoperative complications such as
65 nerve injury and wound healing problems are common and patients may develop contracture
66 recurrence.^{5,6}

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68 Recently, injection with collagenase clostridium histolyticum (CCH) has been introduced as
69 the first pharmacological treatment for DC after it was shown in a randomized controlled trial
70 to be more effective than placebo injections in reducing contractures.⁷ The treatment is a
71 relatively simple procedure given in the outpatient clinic and rarely requires prolonged
72 therapy. The current price of a CCH injection (in Sweden) is almost one thousand US dollars
73 (USD) and one injection is used for each finger involved (unless contractures in 2 fingers are
74 caused by a common cord). Because of economic pressure to control health care expenditures,
75 the cost-effectiveness of surgical procedures has gained increased significance in hospital
76 decision making. The cost analysis of different treatment procedures such as fasciectomy and

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3 77 injection is therefore essential and the differences in short-term costs associated with these
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5 78 two techniques are important to consider.
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9 80 To our knowledge no previous study has compared the actual costs of CCH injections with
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11 81 those of fasciectomy. One study based on a cost-utility analysis model concluded that open
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13 82 partial fasciectomy did not meet the cost-effectiveness threshold and that CCH injections
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15 83 would be cost-effective when priced below 945 USD.⁸ Studies concerning costs of surgery
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17 84 have usually used reimbursement as a measure of costs,⁹ but reimbursement does not
18
19 85 necessarily reflect the actual cost of a procedure. Reimbursement levels for a certain
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21 86 procedure may vary substantially across and even within countries. For cost comparison of
22
23 87 CCH injections and fasciectomy in DC the actual cost of each procedure is therefore a more
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25 88 relevant measure. When comparing the costs of two treatment methods, the outcome of the
26
27 89 treatments must also be taken into consideration. However, we could not find studies that
28
29 90 have compared the outcomes of CCH and fasciectomy.
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36 92 The main aim of this controlled cohort study was to compare CCH injections with
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38 93 fasciectomy regarding the actual total direct treatment costs. The secondary aim was to
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40 94 compare the short-term outcomes of these two treatment methods.
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3 96 **PATIENTS AND METHODS**
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8 98 **Study participants**

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10 99 We conducted a controlled cohort study at one orthopaedic department (Hässleholm,
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12 100 Kristianstad and Ystad Hospitals) in southern Sweden. The department is the only centre that
13
14 101 treats patients with DC in a region with approximately 300,000 inhabitants.
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19 103 Data on CCH injections were collected prospectively within a clinical study that started
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21 104 September 2011 when CCH was introduced as the main treatment option for DC at the
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23 105 department. The indication for treatment with CCH injections was identical to that previously
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25 106 used for surgery at the study centre, namely a palpable cord and contracture of 30 degrees or
26
27 107 greater in the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints. For this
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29 108 study we included the first 16 consecutive patients, aged 65 years or older, treated with CCH
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31 109 injections during the first 6 months (September 2011 through February 2012). We restricted
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33 110 the study to patients of non-working age because we aimed to compare only direct costs.
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39 112 Data on fasciectomy were extracted from the medical records of patients treated at the
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41 113 department before the introduction of CCH injections. The patients were chosen among those
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43 114 aged 65 years or older, operated on with fasciectomy January 2009 through June 2011.

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45 115 Patients with surgery on more than 2 fingers, previous surgery for DC in the same hand, and
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47 116 additional procedures performed (e.g. skin graft or amputation) were excluded. A total of 113
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49 117 patients were potentially eligible. Of these, a random sample of 15% was chosen by computer
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51 118 (statistical software), yielding 18 patients; 2 were excluded (1 had surgery for DC in the
52
53 119 thumb and 1 chose to have postoperative therapy at another location). Thus, the fasciectomy
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55 120 group included 16 patients.
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3 121 **Treatment and follow-up procedures**
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5 122 Both treatments required an initial standard outpatient consultation visit to a hand surgeon or
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7 123 an orthopaedic surgeon, usually as a referral from the patient's general practitioner. Each
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9 124 surgeon was assisted by a nurse at the outpatient clinic. During the visit the treatment decision
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11 125 was made and the patient was scheduled for treatment (Fig 1).
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16 127 **Collagenase injection:** Treatment with CCH required two standard outpatient visits to a hand
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18 128 surgeon: injection and next-day finger extension under local anaesthesia.⁷ During these visits
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20 129 the surgeon was assisted by a nurse (all treatments were given by the same hand surgeon).
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22 130 Immediately after finger extension the patient went to the therapist and received a splint for
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24 131 use at night for 8 weeks. A second visit to the therapist was done 1 week post-injection for
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26 132 splint adjustment and therapy instructions. Patients who during finger extension developed a
27
28 133 skin tear that was judged to require dressing change were asked to visit a nurse within 2 to 3
29
30 134 days. Further visits to the nurse were done when necessary, depending on wound status. No
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32 135 routine post-treatment visits were scheduled to the treating surgeon and the final follow-up
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34 136 (usually at 5-6 weeks) was done by the therapist who arranged a consultation to the treating
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36 137 surgeon if necessary (consideration for further treatment).
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43 139 **Fasciectomy:** Fasciectomy was done as a day-surgery procedure in the main operating room
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45 140 (OR). The surgery was done by one of six different surgeons (three experienced hand
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47 141 surgeons and three orthopaedic surgeons with experience in hand surgery) using standard
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49 142 technique for limited open fasciectomy.¹⁰ General anaesthesia or axillary block was used.
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51 143 According to routine procedures at the hospital general anaesthesia was administered by a
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53 144 nurse anaesthetist and axillary block was administered by an anaesthesiologist, after which
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55 145 the nurse anaesthetist was in charge of the patient's care with anaesthesiologist help obtained
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3 146 when needed. The surgery was done by a surgeon (no assistant) with a team consisting of an
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5 147 OR nurse, a nurse anaesthetist and 2 nurse assistants (1 participated only in the initial
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7 148 preparations). The electronic records for each surgical procedure include the exact start and
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9 149 finish times for the preparations before surgery, anaesthesia, the actual surgery (i.e. operating
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11 150 time from incision to dressing), and the work done after the surgeon has completed the
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13 151 operation and until the patient is taken back to the recovery room. After returning from the
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15 152 OR the patient stayed in the recovery room until discharge from the day-surgery unit. The
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17 153 time of discharge is documented in the electronic records. Thus, for each patient 3 times were
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19 154 recorded; the operating time, the total OR time (from start of preparations until room ready
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21 155 for next procedure), and the time at the recovery room until discharge.
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27 157 After fasciectomy all patients visited a nurse for dressing change after 5 to 7 days, followed
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29 158 immediately by a visit to a therapist for a splint and therapy instructions. A second visit to the
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31 159 nurse for wound inspection and suture removal was done at approximately 2 weeks. Further
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33 160 visits to the nurse were done when necessary, depending on wound status. Patients also had
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35 161 further visits to the therapist for scar management, splint adjustments and therapy instructions
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37 162 as required. The treating therapist decided on the frequency and duration of therapy. Patients
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39 163 had 1 postoperative follow-up visit to the surgeon timed according to surgeon preference.
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45 165 **Cost measurement**

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47 166 A detailed analysis of the salaries of physicians and non-physician medical personnel
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49 167 involved in the treatment of patients with DC was performed for CCH injection and
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51 168 fasciectomy. We identified the average salaries of individuals and used the average time units
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53 169 to calculate the cost of manpower. The costs of all materials, premises and other costs were
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55 170 calculated. We included fixed assets such as the costs of the premises and its expenses and the
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3 171 costs of surgical equipment. All costs were measured based on 2011 salaries/prices. These
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5 172 costs include; salaries of all medical personnel involved in the direct care of the patients
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7 173 including social security contributions, vacation pay and sick pay (averaged for each category:
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9 174 specialist orthopaedic surgeon, anaesthesiologist, nurse, nurse assistant and therapist),
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11 175 hospital overhead costs, the degree of capacity utilization, medications, surgical and other
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13 176 material, premises and other costs. The average salaries were based on all respective medical
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15 177 personnel group in the public health care sector in the region. We did not include costs of
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17 178 non-medical personnel involved in the care (such as receptionists, secretaries, cleaners, etc).
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23 180 A standard outpatient visit to a doctor was 20 minutes. For the 2 CCH visits (injection and
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25 181 finger extension) we used the standard time for the surgeon and 25 minutes for the assisting
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27 182 nurse (to account for the time needed for preparations and work after the session had ended).
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29 183 For fasciectomy we used the mean operating time, total OR time and recovery time, according
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31 184 to the personnel involved and adjusted as required. For the operating surgeon we used the
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33 185 mean operating time plus 25 minutes needed for additional work (assessing the patient and
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35 186 marking the surgical site before surgery, scrubbing, writing the surgical notes and discharging
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37 187 the patient after surgery). For the non-physician personnel we used the mean total operating
38
39 188 room time and for the anaesthesiologist we used half that time (one anaesthesiologist is
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41 189 usually assigned to 2 operating rooms simultaneously and the care of these patients after
42
43 190 surgery). For recovery room personnel (a nurse and a nurse assistant are in charge of up to 5
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45 191 patients simultaneously), we used a fifth of the recovery time plus 5 minutes (preoperative
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47 192 preparations). A standard outpatient visit to a nurse (for wound care after CCH injection or
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49 193 fasciectomy) was 45 minutes. A standard visit to therapist after CCH injection was 30
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51 194 minutes and after fasciectomy 45 minutes. For each patient the exact number of hospital
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3 195 outpatient visits to a doctor, nurse or therapist, related to the treatments, was retrieved from
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5 196 the Patient Administrative System.
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9 198 **Outcome measurement**

10 199 At baseline and at all follow-up visits range of motion including extension and flexion of the
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12 200 MCP and PIP joints of the fingers was measured with a goniometer. In the fasciectomy group
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14 201 the baseline measurements were done by the surgeons during the visit that resulted in the
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16 202 patient being scheduled for fasciectomy and the post-treatment measurements were done by
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18 203 six different therapists; these measurements were recorded in the patient's electronic medical
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20 204 records. In the CCH group all measurements (immediately before injection and at follow-up)
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22 205 were done by the same therapist, as part of a research project. The measurements recorded at
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24 206 baseline and at the final visit were used in the analysis.
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30 208 **Analysis**

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32 209 In 2 previous randomized trials the proportion of MCP joints that were reduced to 0 to 5
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34 210 degrees of extension deficit was 45% at 30 days after first CCH injection⁷ and 94% at 6
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36 211 weeks after fasciectomy.¹¹ To detect a difference of this magnitude between the 2 groups
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38 212 (80% power and 0.05 significance level) would require a sample of 13 patients in each group.
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40 213 The cost estimation of CCH was based on standard procedures independent of sample size.
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42 214 For the cost of fasciectomy, a random sample of 15% from 113 fasciectomy-treated patients
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44 215 was judged adequate to provide representative average procedure time estimates and number
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46 216 of visits to medical personnel, on which the total cost was based. Data are shown as mean and
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48 217 SD and/or median and interquartile range (IQR). We calculated the average total cost of
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50 218 treatment per patient when only 1 CCH injection is required. We also calculated the cost if
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52 219 20% of the patients would require 2 CCH injections given on separate sessions to obtain
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3 220 contracture reduction. Because some patients who developed skin tears during finger
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5 221 extension chose to have dressing change, when necessary, at home or at primary care, only 1
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7 222 nurse visit was recorded in the Patient Administrative System. We therefore made the
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9 223 calculations assuming 1 of 3 patients in the CCH group would require 1 nurse visit. We also
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11 224 conducted a sensitivity analysis with the conservative assumption of 1 nurse visit per patient.
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14 225 All costs were calculated in Swedish Kronor (SEK) and converted to USD using the rate of 1
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16 226 USD = 6.676 SEK (Sweden's Central Bank average for 2011). The within-group change in
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18 227 extension deficit was analyzed with the Wilcoxon test. We also compared the 2 groups with
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21 228 regard to improvement in total extension deficit using the Mann-Whitney test. A p value
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23 229 below 0.05 was used to indicate statistical significance.
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3 230 **RESULTS**
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7 232 The 16 patients in the CCH group and the 16 patients in the fasciectomy group had similar
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9 233 characteristics (Table 1). In the fasciectomy group half of the patients received general
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11 234 anaesthesia and the other half axillary block. The mean operating time was 62 (SD 27)
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13 235 minutes, mean total OR time 138 (SD 43) minutes, and mean postoperative time spent at the
14
15 236 day-surgery recovery room until discharge 215 (SD 41) minutes. The median time from
16
17 237 surgery to end of therapy was 6.3 weeks (IQR 4.0-11.5) and to the postoperative follow-up by
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19 238 the surgeon 7.5 weeks (IQR 6.0-12.0). None of the patients in the CCH group required further
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21 239 therapy than the standard visits. Of the 16 patients, 9 developed skin tears ranging from minor
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23 240 superficial skin breakage that did not require further wound care to deeper wound that
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25 241 required 1 or more dressing changes. All wounds had healed within 2 weeks after injection.
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32 243 **Costs**
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34 244 The cost specifications for the two treatments are shown in Table 2. The largest treatment cost
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36 245 for CCH injections was the cost of the injection itself (970.19 USD) and for fasciectomy the
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38 246 cost of personnel (783.97 USD) and other costs (380.81 USD) associated with the surgery in
39
40 247 the operating room. Compared to fasciectomy, treatment with CCH injections required fewer
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42 248 outpatient hospital visits to a nurse and a therapist (Table 3).
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47 250 The total treatment cost with 1 CCH injection was 33% lower than that for fasciectomy
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49 251 (1418.04 versus 2102.56 USD). The cost was still lower (1675.24 USD) if 20% of patients
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51 252 treated with CCH would require 2 injections in the same hand, given in separate sessions. In
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53 253 the sensitivity analysis the cost of CCH injections assuming an average of 1 nurse visit per
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3 254 patient was 1472.51 USD when 1 injection is given and 1696.79 USD when 20% would
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5 255 require 2 injections.

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10 257 **Outcomes**

11 258 Of the 16 patients in the CCH and fasciectomy groups, 7 and 9 patients respectively achieved
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13 259 an extension deficit of 0 to 5 degrees in the joint with the largest extension deficit. In both
14
15 260 groups the improvement in total extension deficit was statistically significant ($p < 0.001$) and
16
17 261 the extension deficits after CCH and fasciectomy were similar (median 10 degrees) (Table 3).
18
19 262 The median improvement in total extension deficit in the CCH group was 70 (IQR 55-85)
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21 263 degrees and in the fasciectomy group 50 (IQR 41-60) degrees ($p=0.006$).
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23 264 No complications were observed in any of the groups at the final follow-up.

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3 265 **DISCUSSION**
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7 267 Our study shows that treatment of DC with collagenase injections is associated with lower
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9 268 costs than surgery (fasciectomy) and results in similar short-term outcomes regarding
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11 269 reduction in finger joint contractures. The costs are still lower when assuming that 20% of the
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13 270 patients would require 2 injections in the same hand, but if more than 5 of 10 patients need 2
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15 271 or more injections the costs would exceed those of fasciectomy. Our estimates of the costs
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17 272 assuming 20% would require 2 injections were based on separate treatment sessions; the costs
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19 273 would be even lower if the 2 injections are given in the same session, which would probably
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21 274 become the usual practice.¹² Further, our results should be considered conservative since we
22
23 275 have not considered complications (such as wound infection and chronic regional pain
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25 276 syndrome) that are probably more frequent after surgery than after CCH injections and would
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27 277 therefore add to the total costs.
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34 279 For fasciectomy, the largest cost was represented by the various costs associated with a day-
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36 280 surgery procedure of approximately 1 hour duration in the operating room. The cost would be
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38 281 lower if the average operating time were shorter than our estimate of 62 minutes. In a recent
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40 282 study of DC in 12 European countries (based on a surgeon survey and patient chart review),
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42 283 the mean operating time for fasciectomy across all countries was 67 minutes (Nordic 63,
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44 284 Eastern 69, Western 66, and Mediterranean 68 minutes).⁴ A potential advantage with CCH
45
46 285 injections is the possibility to treat patients with bilateral disease in 1 stage, which is
47
48 286 uncommon with surgery considering the nature of the procedure. In contrast, patients with
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50 287 contractures involving 3 or more fingers can be treated with surgery in one session, but would
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52 288 need at least 2 CCH injections and, in more severe cases, 2 or more treatment sessions.
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291 Skin tears ranging from minor superficial skin breakage to deeper wounds occurred in more
292 than half the patients after CCH injections in our study. Skin tears following CCH injections
293 were reported in 11% in the multicenter randomized trial,⁷ and in up to 19% in other
294 studies.^{13,14} Skin tears are more likely to occur in severe contractures especially of the small
295 finger.⁹ Because the incidence and severity of skin tears (ie, need for wound care) may vary
296 we calculated the costs assuming that, on average, one third of the patients would require 1
297 nurse visit and also did a sensitivity analysis assuming an average of 1 nurse visit. We believe
298 these estimates cover the costs of wound care even if the true incidence of skin tears is higher
299 than previously reported.

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301 We only compared direct costs, and therefore did not include costs of lost productivity or sick
302 leave. Among employed patients, sick leave is more likely to be necessary and longer after
303 fasciectomy than after CCH injections. According to the Swedish Social Insurance Agency
304 the total cost of a 1-week sick leave based on the average salary in Sweden 2011 (including
305 sick-pay, general payroll tax, vacation-pay and overhead costs) exceeds 1300 USD
306 (www.scb.se). In addition, the direct costs of CCH injections and fasciectomy may differ
307 across countries and settings. In a Canadian study that estimated the cost (during 2005) of
308 open carpal tunnel release, a 10-minute procedure done under local anaesthesia, the total cost
309 (excluding surgeon's fee) was 137 CAD when done in the main operating room and 53 CAD
310 dollars when done in the office.¹⁵

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312 A limitation of our study is that only short-term outcomes were measured. The improvement
313 was high and the minor residual contracture was similar for CCH and fasciectomy.

314 Differences in long-term outcomes may change the cost-effectiveness of these treatments

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3 315 because if they differ substantially in the recurrence rate and the need for further treatments
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5 316 the cost of subsequent treatments should also be considered. According to the most recent
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7 317 estimate of recurrence following CCH injections, the rate at 5 years was 35% but in only 7%
8
9 318 the recurrence required treatment.¹⁶ Another limitation is that in the fasciectomy group the
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11 319 baseline range-of-motion measurements were done by different surgeons and the follow-up
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13 320 measurements by different therapists. The inter-observer reliability of these measurements is
14
15 321 unknown and there might be a risk that the surgeon overestimated the preoperative
16
17 322 contracture and the treating therapist underestimated residual contracture. However, we do not
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19 323 believe this issue has a substantial influence because fasciectomy was the only treatment
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21 324 option and the results of the post-treatment measurements, done by therapists, were similar in
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23 325 both groups.
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29 327 In conclusion, treatment of DC with CCH injections costs 33% less, in direct costs, than
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31 328 fasciectomy with equivalent short-term efficacy regarding reduction in contracture.
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3 330 **Funding**
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6

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8
9 333 had no role in the conduct of the study, data analysis and interpretation, or decision to submit
10
11 334 the article for publication. No commercial entities were involved at any stage.
12

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14 335 **Contributorship Statement**
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16 336 ES, AL, IA: Study conception and design, acquisition of data, analysis and interpretation of
17
18 337 data, and drafting of the article.
19

20
21 338 EA: Acquisition of data, and critical revision of the article for important intellectual content.
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23 339 MW: Analysis and interpretation of data and critical revision of the article for important
24
25 340 intellectual content.
26

27 341 All authors approved the final submitted version.
28

29 342 **Competing Interests**
30

31 343 Dr. Atroshi was a member of an Expert Group on Dupuytren's disease for Pfizer 2012. The
32
33 344 other authors have no competing interests.
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393 treatment with collagenase clostridium histolyticum (CORDLESS study): 3-year data. *J*
394 *Hand Surg Am* 2013;38:12-22.
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398 **Table 1.** Characteristics of the two samples of patients with Dupuytren's contracture treated
 399 with collagenase clostridium histolyticum injection or surgery (fasciectomy)

	CCH injection	Fasciectomy
Number of patients (men)	16 (11)	16 (13)
Age (yrs), mean (SD)	69 (4)	71 (5)
Number of fingers treated*		
Small	11	9
Ring	7	8
Middle	0	1
Total extension deficit (degrees) [†]		
mean (SD)	90 (39)	71 (28)
median (IQR)	70 (60-115)	75 (45-89)

400
 401 CCH, collagenase clostridium histolyticum; IQR, interquartile range

402 *2 patients in each group had 2 fingers treated.

403 [†] Metacarpophalangeal (MCP) plus proximal interphalangeal (PIP) joints (no MCP contracture
 404 in 1 patient in the CCH group and 2 patients in the fasciectomy group and no PIP contracture
 405 in 7 patients and 4 patients, respectively). In patients with 2 fingers treated the largest
 406 extension deficit was used.

407 **Table 2.** Cost specification for the various stages of treating Dupuytren's contracture
 408 with collagenase clostridium histolyticum injection or surgery (fasciectomy)

	Personnel costs [*]	Other costs [†]
	(USD)	(USD)
Doctor visit, CCH or fasciectomy (doctor and nurse)	65.80	16.78
Injection, CCH (doctor and nurse)	70.63	991.16
Finger extension, CCH (doctor and nurse)	70.63	20.97
Therapist visit, CCH	26.58	25.16
Surgery, fasciectomy (doctors and others)	783.97	380.81
Day surgery care, fasciectomy	88.10	52.41
Therapist visit, fasciectomy	39.88	37.77
Nurse visit, CCH or fasciectomy	43.51	37.77

409

410 CCH, collagenase clostridium histolyticum; USD, United States dollars

411 * Include average salary, social security contributions, vacation pay, sick pay, overhead costs,
 412 and the degree of capacity utilization.

413 † Include costs of surgical and other materials, injections, premises, etc.

414 Price of 1 CCH injection = 970.19 USD.

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3 415 **Table 3.** Number of visits to medical personnel, actual costs and outcomes of treating
4
5 416 Dupuytren's contracture with collagenase clostridium histolyticum injection or surgery
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7 417 (fasciectomy)
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10 418

	CCH injection	Fasciectomy
Mean, median (IQR) number of visits to:		
Doctor	3*	2*
Nurse	0.33*	3.0, 3.0 (2.0-3.8)
Therapist	3*	5.1, 4.0 (3.0-6.8)
Total cost per patient (USD)	1418.04	2102.56
Total cost per patient when 20% require 2 injections (USD)	1675.24	2102.56
Total extension deficit (degrees) [†]		
mean (SD)	20 (25)	19 (19)
median (IQR)	10 (0-30)	10 (0-34)

38 419

39 420 CCH, collagenase clostridium histolyticum; IQR, inter-quartile range; USD, United States

41 421 dollars

42 422 * Number of visits to a doctor in both groups and to a therapist in the CCH group was similar
43
44 423 for all patients (Figure 1); a third of CCH patients assumed to require 1 visit to a nurse.
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48 424 [†]Metacarpophalangeal plus proximal interphalangeal joints
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3 428 **Figure legend**

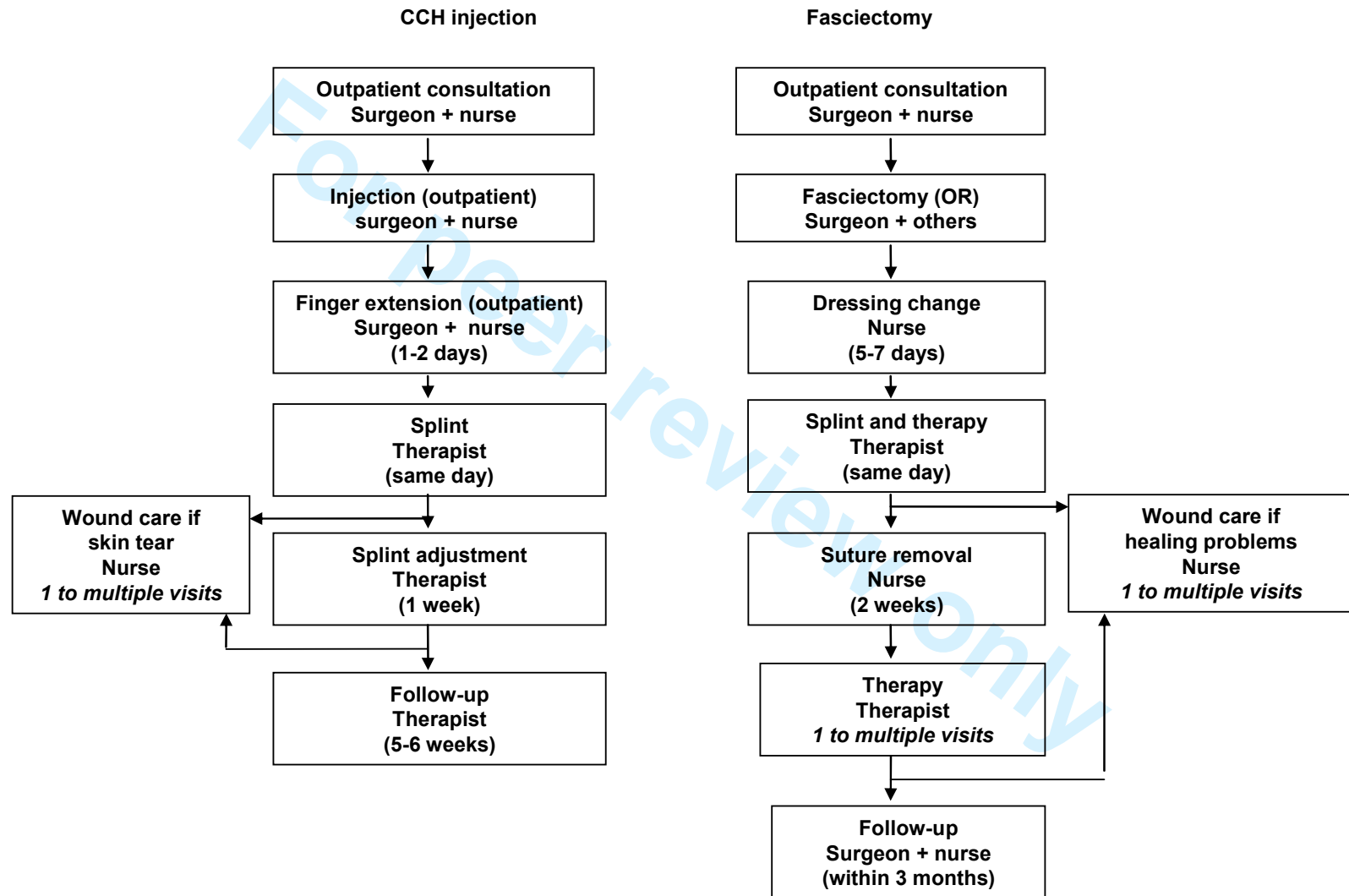
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7 430 **Figure 1.** Diagram showing the various stages of treating patients with Dupuytren's

8
9 431 contracture with collagenase clostridium histolyticum (CCH) injection or with fasciectomy as

10
11 432 a day-surgery procedure performed in the operating room (OR). The number of visits is 1

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13 433 unless specified otherwise.
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STROBE Statement—checklist of items that should be included in reports of observational studies

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

Continued on next page

Results

Participants	13*	(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 P 12 Figure 1
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders P 12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time P 12-13 Table 2 & 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(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 P 12-13 Table 2 & 3
		(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	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses P 12-13

Discussion

Key results	18	Summarise key results with reference to study objectives P 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias P 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence P 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results P 15

Other information

Funding	22	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 P 17
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*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.



**Costs of collagenase injections compared with fasciectomy
in the treatment of Dupuytren's contracture: A retrospective
cohort study**

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3 1 **Costs for collagenase injections compared with fasciectomy in the treatment**
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6 2 **of Dupuytren's contracture: A retrospective cohort study**
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2
3 19 **Abstract**

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5 20 **Objectives:** To compare collagenase injections and surgery (fasciectomy) for Dupuytren's
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7 21 contracture (DC) regarding actual total direct treatment costs and short-term outcomes.

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9 22 **Design:** Retrospective cohort study

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11 23 **Setting:** Orthopaedic department of a regional hospital in Sweden.

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13 24 **Participants:** Patients aged 65 years or older with previously untreated DC of 30 degrees or
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15 25 greater in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joints of the
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17 26 small, ring or middle finger. The collagenase group comprised 16 consecutive patients treated
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19 27 during the first 6 months following the introduction of collagenase as treatment for DC at the
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21 28 study centre. The controls were 16 patients randomly selected among those operated on with
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23 29 fasciectomy at the same centre during the preceding 3 years.

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25 30 **Interventions:** Treatment with collagenase was given during two standard outpatient clinic
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27 31 visits (injection of 0.9 mg, distributed at multiple sites in a palpable cord, and next-day finger
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29 32 extension under local anaesthesia) followed by night-time splinting. Fasciectomy was done in
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31 33 the operating room (day surgery) under general or regional anaesthesia using standard
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33 34 technique, followed by therapy and splinting.

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35 35 **Primary and secondary outcome measures:** Actual total direct costs (salaries of all medical
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37 36 personnel involved in care, medications, materials and other relevant costs), and total MCP
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39 37 and PIP extension deficit (degrees) measured by hand therapists at 6-12 weeks after treatment.

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41 38 **Results:** Collagenase injection required fewer hospital outpatient visits to a therapist and
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43 39 nurse than fasciectomy. Total treatment cost for collagenase injection was 1418.04 USD and
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45 40 for fasciectomy 2102.56 USD. The post-treatment median (interquartile range) total extension
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47 41 deficit was 10 (0-30) for the collagenase group and 10 (0-34) for the fasciectomy group.

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49 42 **Conclusions:** Treatment of Dupuytren's contracture with one collagenase injection costs 33%
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51 43 less than fasciectomy with equivalent efficacy at 6 weeks regarding reduction in contracture.
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3 44 **Strengths and limitations of this study**
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7 46 • This study presents previously unknown estimates of the actual costs of treating
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9 Dupuytren's contracture with Collagenase injections or fasciectomy
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11 48 • Comparison of the actual costs of the two treatments are based on detailed definition and
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13 49 measurement of all relevant costs
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15 50 • Outcomes of injections were prospectively measured but outcomes of surgery were based
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17 51 on medical records
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19 52 • Costs may vary across countries
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21 53 • Only short-term outcomes (6 weeks) were compared
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54 INTRODUCTION

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56 Dupuytren's contracture (DC) is a common hand disorder causing finger contractures that
57 may compromise hand function. Surgery in the form of limited fasciectomy has been the main
58 treatment option for reducing the contracture.¹ In Sweden (population 9.5 millions), more
59 than 3000 fasciectomy procedures are performed annually;² the actual number is probably
60 higher because procedures performed by surgeons in private practice, although constituting a
61 small proportion,³ may not always be reported to the national database. Surgery is usually
62 done in the main operating room under general or regional anaesthesia and the operating time
63 is on average about 1 hour,⁴ but can be substantially longer when severe contractures are
64 present in multiple fingers. After surgery many patients require therapy and splints. Although
65 surgery is often effective in reducing the contracture, postoperative complications such as
66 nerve injury and wound healing problems are common and patients may develop contracture
67 recurrence.^{5,6}

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69 Recently, injection with collagenase clostridium histolyticum (CCH) has been introduced as
70 the first pharmacological treatment for DC after it was shown in a randomized controlled trial
71 to be more effective than placebo injections in reducing contractures.⁷ The treatment is a
72 relatively simple procedure given in the outpatient clinic and rarely requires prolonged
73 therapy. The current price of a CCH injection (in Sweden) is almost one thousand US dollars
74 (USD) and one injection is used for each finger involved (unless contractures in 2 fingers are
75 caused by a common cord). Because of economic pressure to control health care expenditures,
76 the cost-effectiveness of surgical procedures has gained increased significance in hospital
77 decision making. The cost analysis of different treatment procedures such as fasciectomy and

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3 78 injection is therefore essential and the differences in short-term costs associated with these
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5 79 two techniques are important to consider.
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10 81 To our knowledge no previous study has compared the actual costs of CCH injections with
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12 82 those of fasciectomy. One study based on a cost-utility analysis model concluded that open
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14 83 partial fasciectomy did not meet the cost-effectiveness threshold and that CCH injections
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16 84 would be cost-effective when priced below 945 USD.⁸ Studies concerning costs of surgery
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18 85 have usually used reimbursement as a measure of costs,⁹ but reimbursement does not
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20 86 necessarily reflect the actual cost of a procedure. Reimbursement levels for a certain
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22 87 procedure may vary substantially across and even within countries. For cost comparison of
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24 88 CCH injections and fasciectomy in DC the actual cost of each procedure is therefore a more
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26 89 relevant measure. When comparing the costs of two treatment methods, the outcome of the
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28 90 treatments must also be taken into consideration. However, we could not find studies that
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30 91 have compared the outcomes of CCH and fasciectomy.
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36 93 The main aim of this retrospective cohort study was to compare CCH injections with
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38 94 fasciectomy regarding the actual total direct treatment costs. The secondary aim was to
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40 95 compare the short-term outcomes of these two treatment methods.
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3 97 **PATIENTS AND METHODS**
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7 99 **Study participants**

10 100 We conducted a retrospective cohort study at one orthopaedic department (Hässleholm,
11 101 Kristianstad and Ystad Hospitals) in southern Sweden. The department is the only centre that
12 102 treats patients with DC in a region with approximately 300,000 inhabitants.
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18 104 Data on CCH injections were collected prospectively starting September 2011 when CCH
19 105 was introduced as the main treatment option for DC at the department. The indication for
20 106 treatment with CCH injections was identical to that previously used for surgery at the study
21 107 centre, namely a palpable cord and contracture of 30 degrees or greater in the
22 108 metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joints. For this study we
23 109 included the first 16 consecutive patients, aged 65 years or older, treated with CCH injections
24 110 during the first 6 months (September 2011 through February 2012). We restricted the study to
25 111 patients of non-working age because we aimed to compare only direct costs.
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40 113 Data on fasciectomy were extracted from the medical records of patients treated at the
41 114 department before the introduction of CCH injections. The patients were chosen among those
42 115 aged 65 years or older, operated on with fasciectomy January 2009 through June 2011.

43 116 Patients with surgery on more than 2 fingers, previous surgery for DC in the same hand, and
44 117 additional procedures performed (e.g. skin graft or amputation) were excluded. A total of 113
45 118 patients were potentially eligible. Of these, a random sample of 15% was chosen by computer
46 119 (statistical software), yielding 18 patients; 2 were excluded (1 had surgery for DC in the
47 120 thumb and 1 chose to have postoperative therapy at another location). Thus, the fasciectomy
48 121 group included 16 patients.
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3 122 **Treatment and follow-up procedures**
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5 123 Both treatments required an initial standard outpatient consultation visit to a hand surgeon or
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7 124 an orthopaedic surgeon, usually as a referral from the patient's general practitioner. Each
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9 125 surgeon was assisted by a nurse at the outpatient clinic. During the visit the treatment decision
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11 126 was made and the patient was scheduled for treatment (Fig 1).
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16 128 **Collagenase injection:** Treatment with CCH required two standard outpatient visits to a hand
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18 129 surgeon: injection and next-day finger extension.⁷ During these visits the surgeon was assisted
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20 130 by a nurse (all treatments were given by the same hand surgeon). A modified injection
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22 131 method was used for all treated fingers; after reconstituting CCH with 0.39 ml of diluent,
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24 132 according to the standard procedure, all the reconstituted CCH (0.9 mg) was injected into the
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26 133 cord, distributed at multiple sites. The following day, finger manipulation (extension) was
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28 134 done under local anaesthesia. Immediately after finger extension the patient went to the
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30 135 therapist and received a splint for use at night for 8 weeks. A second visit to the therapist was
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32 136 done 1 week post-injection for splint adjustment and therapy instructions. Patients who during
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34 137 finger extension developed a skin tear that was judged to require dressing change were asked
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36 138 to visit a nurse within 2 to 3 days. Further visits to the nurse were done when necessary,
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38 139 depending on wound status. No routine post-treatment visits were scheduled to the treating
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40 140 surgeon and the final follow-up (usually at 5-6 weeks) was done by the therapist. If the patient
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42 141 was not satisfied with the degree of correction after the first injection, the therapist arranged a
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44 142 consultation to the treating surgeon for consideration of further treatment.
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52 144 **Fasciectomy:** Fasciectomy was done as a day-surgery procedure in the main operating room
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54 145 (OR). The surgery was done by one of six different surgeons (three experienced hand
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56 146 surgeons and three orthopaedic surgeons with experience in hand surgery) using standard
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3 147 technique for limited open fasciectomy.¹⁰ General anaesthesia or axillary block was used.
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5 148 According to routine procedures at the hospital general anaesthesia was administered by a
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7 149 nurse anaesthetist and axillary block was administered by an anaesthesiologist, after which
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9 150 the nurse anaesthetist was in charge of the patient's care with anaesthesiologist help obtained
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11 151 when needed. The surgery was done by a surgeon (no assistant) with a team consisting of an
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13 152 OR nurse, a nurse anaesthetist and 2 nurse assistants (1 participated only in the initial
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15 153 preparations). The electronic records for each surgical procedure include the exact start and
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17 154 finish times for the preparations before surgery, anaesthesia, the actual surgery (i.e. operating
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19 155 time from incision to dressing), and the work done after the surgeon has completed the
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21 156 operation and until the patient is taken back to the recovery room. After returning from the
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23 157 OR the patient stayed in the recovery room until discharge from the day-surgery unit. The
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25 158 time of discharge is documented in the electronic records. Thus, for each patient 3 times were
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27 159 recorded; the operating time, the total OR time (from start of preparations until room ready
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29 160 for next procedure), and the time at the recovery room until discharge.
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36 162 After fasciectomy all patients visited a nurse for dressing change after 5 to 7 days, followed
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38 163 immediately by a visit to a therapist for a splint and therapy instructions. A second visit to the
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40 164 nurse for wound inspection and suture removal was done at approximately 2 weeks. Further
41
42 165 visits to the nurse were done when necessary, depending on wound status. Patients also had
43
44 166 further visits to the therapist for scar management, splint adjustments and therapy instructions
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46 167 as required. The treating therapist decided on the frequency and duration of therapy. Patients
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48 168 had 1 postoperative follow-up visit to the surgeon timed according to surgeon preference.
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3 172 **Cost measurement**
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5 173 A detailed analysis of the salaries of physicians and non-physician medical personnel
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7 174 involved in the treatment of patients with DC was performed for CCH injection and
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9 175 fasciectomy. We identified the average salaries of individuals and used the average time units
10
11 176 to calculate the cost of manpower. The costs of all materials, premises and other costs were
12
13 177 calculated. We included fixed assets such as the costs of the premises and its expenses and the
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15 178 costs of surgical equipment. All costs were measured based on 2011 salaries/prices. These
16
17 179 costs include; salaries of all medical personnel involved in the direct care of the patients
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19 180 including social security contributions, vacation pay and sick pay (averaged for each category:
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21 181 specialist orthopaedic surgeon, anaesthesiologist, nurse, nurse assistant and therapist),
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23 182 hospital overhead costs, the degree of capacity utilization, medications, surgical and other
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25 183 material, premises and other costs. The average salaries were based on all respective medical
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27 184 personnel group in the public health care sector in the region. We did not include costs of
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29 185 non-medical personnel involved in the care (such as receptionists, secretaries, cleaners, etc).
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36 187 A standard outpatient visit to a doctor was 20 minutes. For the 2 CCH visits (injection and
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38 188 finger extension) we used the standard time for the surgeon and 25 minutes for the assisting
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40 189 nurse (to account for the time needed for preparations and work after the session had ended).
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42 190 For fasciectomy we used the mean operating time, total OR time and recovery time, according
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44 191 to the personnel involved and adjusted as required. For the operating surgeon we used the
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46 192 mean operating time plus 25 minutes needed for additional work (assessing the patient and
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48 193 marking the surgical site before surgery, scrubbing, writing the surgical notes and discharging
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50 194 the patient after surgery). For the non-physician personnel we used the mean total operating
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52 195 room time and for the anaesthesiologist we used half that time (one anaesthesiologist is
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54 196 usually assigned to 2 operating rooms simultaneously and the care of these patients after
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3 197 surgery). For recovery room personnel (a nurse and a nurse assistant are in charge of up to 5
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5 198 patients simultaneously), we used a fifth of the recovery time plus 5 minutes (preoperative
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7 199 preparations). A standard outpatient visit to a nurse (for wound care after CCH injection or
8
9 200 fasciectomy) was 45 minutes. A standard visit to therapist after CCH injection was 30
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11 201 minutes and after fasciectomy 45 minutes. For each patient the exact number of hospital
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13 202 outpatient visits to a doctor, nurse or therapist, related to the treatments, was retrieved from
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15 203 the Patient Administrative System.
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205 **Outcome measurement**

206 At baseline and at all follow-up visits range of motion including extension and flexion of the
207 MCP and PIP joints of the fingers was measured with a goniometer. In the fasciectomy group
208 the baseline measurements were done by the surgeons during the visit that resulted in the
209 patient being scheduled for fasciectomy and the post-treatment measurements were done by
210 six different therapists; these measurements were recorded in the patient's electronic medical
211 records. In the CCH group all measurements (immediately before injection and at follow-up)
212 were done by the same therapist, as part of a research project. The measurements recorded at
213 baseline and at the final visit were used in the analysis.
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215 **Analysis**

216 In 2 previous randomized trials the proportion of MCP joints that were reduced to 0 to 5
217 degrees of extension deficit was 45% at 30 days after first CCH injection⁷ and 94% at 6
218 weeks after fasciectomy.¹¹ To detect a difference of this magnitude between the 2 groups
219 (80% power and 0.05 significance level) would require a sample of 13 patients in each group.
220 The cost estimation of CCH was based on standard procedures independent of sample size.
221 For the cost of fasciectomy, a random sample of 15% from 113 fasciectomy-treated patients

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3 222 was judged adequate to provide representative average procedure time estimates and number
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5 223 of visits to medical personnel, on which the total cost was based. Data are shown as mean and
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7 224 SD and/or median and interquartile range (IQR). We calculated the average total cost of
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9 225 treatment per patient when only 1 CCH injection is given. We also calculated the cost if 20%
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11 226 of the patients would need 2 CCH injections given on separate sessions to obtain satisfactory
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13 227 contracture reduction. Because some patients who developed skin tears during finger
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15 228 extension chose to have dressing change, when necessary, at home or at primary care, only 1
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17 229 nurse visit was recorded in the Patient Administrative System. We therefore made the
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19 230 calculations assuming 1 of 3 patients in the CCH group would require 1 nurse visit. We also
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21 231 conducted a sensitivity analysis with the conservative assumption of 1 nurse visit per patient.
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23 232 All costs were calculated in Swedish Kronor (SEK) and converted to USD using the rate of 1
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25 233 USD = 6.676 SEK (Sweden's Central Bank average for 2011). The within-group change in
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27 234 extension deficit was analyzed with the Wilcoxon test. We also compared the 2 groups with
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29 235 regard to improvement in total extension deficit using the Mann-Whitney test. A p value
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31 236 below 0.05 was used to indicate statistical significance.
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3 237 **RESULTS**
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7 239 The 16 patients in the CCH group and the 16 patients in the fasciectomy group had similar
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9 240 characteristics (Table 1). In the fasciectomy group half of the patients received general
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11 241 anaesthesia and the other half axillary block. The mean operating time was 62 (SD 27)
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13 242 minutes, mean total OR time 138 (SD 43) minutes, and mean postoperative time spent at the
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15 243 day-surgery recovery room until discharge 215 (SD 41) minutes. The median time from
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17 244 surgery to end of therapy was 6.3 weeks (IQR 4.0-11.5) and to the postoperative follow-up by
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19 245 the surgeon 7.5 weeks (IQR 6.0-12.0). None of the patients in the CCH group required further
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21 246 therapy than the standard visits. Of the 16 patients, 9 developed skin tears ranging from minor
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23 247 superficial skin breakage that did not require further wound care to deeper wound that
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25 248 required 1 or more dressing changes. All wounds had healed within 2 weeks after injection.
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32 250 **Costs**
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34 251 The cost specifications for the two treatments are shown in Table 2. The largest treatment cost
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36 252 for CCH injections was the cost of the injection itself (970.19 USD) and for fasciectomy the
37
38 253 cost of personnel (783.97 USD) and other costs (380.81 USD) associated with the surgery in
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40 254 the operating room. Compared to fasciectomy, treatment with CCH injections required fewer
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42 255 outpatient hospital visits to a nurse and a therapist (Table 3).
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47 257 The total treatment cost with 1 CCH injection was 33% lower than that for fasciectomy
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49 258 (1418.04 versus 2102.56 USD). The cost was still lower (1675.24 USD) if 20% of patients
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51 259 treated with CCH would require 2 injections in the same hand, given in separate sessions. In
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53 260 the sensitivity analysis the cost of CCH injections assuming an average of 1 nurse visit per
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3 261 patient was 1472.51 USD when 1 injection is given and 1696.79 USD when 20% would
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5 262 require 2 injections.
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10 264 **Outcomes**

11 265 Of the 16 patients in the CCH and fasciectomy groups, 7 and 9 patients respectively achieved
12
13 266 an extension deficit of 0 to 5 degrees in the joint with the largest extension deficit. In both
14
15 267 groups the improvement in total extension deficit was statistically significant ($p < 0.001$) and
16
17 268 the extension deficits after CCH and fasciectomy were similar (median 10 degrees) (Table 3).
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19 269 The median improvement in total extension deficit in the CCH group was 65 (IQR 56-81)
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21 270 degrees and in the fasciectomy group 50 (IQR 41-60) degrees ($p=0.007$).
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25 271 No complications were observed in any of the groups at the final follow-up.
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3 272 **DISCUSSION**
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7 274 Our study shows that treatment of DC with a single collagenase injection is associated with
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9 275 lower costs than surgery (fasciectomy) and the short-term outcomes (6 weeks) regarding
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11 276 reduction in finger joint contractures are similar. The costs are still lower when assuming that
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13 277 20% of the patients would require 2 injections in the same hand, but if more than 5 of 10
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15 278 patients need 2 injections the costs would exceed those of fasciectomy. Our estimates of the
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17 279 costs assuming 20% would require 2 injections were based on separate treatment sessions; the
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19 280 costs would be even lower if the 2 injections are given in the same session, which would
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21 281 probably become the usual practice.¹² Further, our results should be considered conservative
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23 282 since we have not considered complications (such as wound infection and chronic regional
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25 283 pain syndrome) that are probably more frequent after surgery than after CCH injections and
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27 284 would therefore add to the total costs. The study by Hurst et al.⁷ reported use of an average of
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29 285 about 2 CCH injections per patient. However, in that study finger extension, which often is a
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31 286 painful procedure, was done without anaesthesia, which may have reduced the degree of
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33 287 initial contracture correction and thus necessitating a second injection. As in our study, use of
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35 288 local anaesthesia is currently the standard procedure. In addition, Hurst et al. injected 0.58 mg
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37 289 CCH into one part of the cord whereas our technique is to inject the whole content of a single
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39 290 CCH injection (0.9 mg) into the cord at multiple sites, which would probably increase the
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41 291 efficacy of a single injection.
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49 293 For fasciectomy, the largest cost was represented by the various costs associated with a day-
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51 294 surgery procedure of approximately 1 hour duration in the operating room. The cost would be
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53 295 lower if the average operating time were shorter than our estimate of 62 minutes. In a recent
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55 296 study of DC in 12 European countries (based on a surgeon survey and patient chart review),
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3 297 the mean operating time for fasciectomy across all countries was 67 minutes (Nordic 63,
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5 298 Eastern 69, Western 66, and Mediterranean 68 minutes).⁴ A potential advantage with CCH
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7 299 injections is the possibility to treat patients with bilateral disease in 1 stage, which is
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9 300 uncommon with surgery considering the nature of the procedure. In contrast, patients with
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11 301 contractures involving 3 or more fingers can be treated with surgery in one session, but would
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13 302 need at least 2 CCH injections and, in more severe cases, 2 or more treatment sessions.
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18 304 Skin tears ranging from minor superficial skin breakage to deeper wounds occurred in more
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20 305 than half the patients after CCH injections in our study. Skin tears following CCH injections
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22 306 were reported in 11% in the multicenter randomized trial,⁷ and in up to 19% in other
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24 307 studies.^{13,14} Skin tears are more likely to occur in severe contractures especially of the small
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26 308 finger.⁹ Because the incidence and severity of skin tears (ie, need for wound care) may vary
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28 309 we calculated the costs assuming that, on average, one third of the patients would require 1
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30 310 nurse visit and also did a sensitivity analysis assuming an average of 1 nurse visit. We believe
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32 311 these estimates cover the costs of wound care even if the true incidence of skin tears is higher
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34 312 than previously reported.
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38 314 We only compared direct costs, and therefore did not include costs of lost productivity or sick
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40 315 leave. Among employed patients, sick leave is more likely to be necessary and longer after
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42 316 fasciectomy than after CCH injections. According to the Swedish Social Insurance Agency
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44 317 the total cost of a 1-week sick leave based on the average salary in Sweden 2011 (including
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46 318 sick-pay, general payroll tax, vacation-pay and overhead costs) exceeds 1300 USD
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48 319 (www.scb.se). In addition, the direct costs of CCH injections and fasciectomy may differ
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50 320 across countries and settings. In a Canadian study that estimated the cost (during 2005) of
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52 321 open carpal tunnel release, a 10-minute procedure done under local anaesthesia, the total cost
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3 322 (excluding surgeon's fee) was 137 CAD when done in the main operating room and 53 CAD
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5 323 dollars when done in the office.¹⁵ Although the largest treatment cost for CCH injections was
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7 324 the cost of the injection itself, which may be substantially higher in some countries, the costs
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9 325 of surgery in these countries may also be higher. In a study involving 24 patients treated with
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11 326 fasciectomy at a single US hospital from 2008 to 2010 the average direct cost, defined as
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13 327 costs billed from hospital charges (facility fees) and professional charges (surgeon and
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15 328 anaesthesia fees) was estimated to be 11,240 USD.⁹
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21 330 A limitation of our study is that only very short-term outcomes were measured. The
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23 331 improvement was high and the minor residual contracture was similar for CCH and
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25 332 fasciectomy. Differences in long-term outcomes may change the cost-effectiveness of these
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27 333 treatments because if they differ substantially in the recurrence rate and the need for further
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29 334 treatments the cost of subsequent treatments should also be considered. According to the most
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31 335 recent published data regarding recurrence after CCH injections (defined as contracture
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33 336 increase of 20 degrees or greater in the presence of a palpable cord in joints initially corrected
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35 337 to a maximum of 5-degree contracture), the overall rate in 623 joints at 3 years was 35%
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37 338 (MCP 27% and PIP 56%) but the recurrence required treatment in only 7%.¹⁶ Following
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39 339 fasciectomy a 3-year recurrence rate of 12% has been reported in two studies; in the first
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41 340 study, 4 of 33 hands had more than 30 degrees increase in joint contracture compared to 6
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43 341 weeks,¹¹ and in the second study, 11 of 90 fingers showed progressive recurrence of PIP joint
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45 342 contracture but no specific definition of recurrence was stated.¹⁷ Thus, depending on the
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47 343 proportion of patients that subsequently need repeated treatment because of recurrent
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49 344 contracture in the treated fingers it is possible that in the long-term the direct costs of
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51 345 treatment with CCH may exceed those of fasciectomy.
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3 347 Another limitation is that in the fasciectomy group the baseline range-of-motion
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5 348 measurements were done by different surgeons and the follow-up measurements by different
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7 349 therapists. The inter-observer reliability of these measurements is unknown and there might
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9 350 be a risk that the surgeon overestimated the preoperative contracture and the treating therapist
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11 351 underestimated residual contracture. However, we do not believe this issue has a substantial
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13 352 influence because fasciectomy was the only treatment option and the results of the post-
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15 353 treatment measurements, done by therapists, were similar in both groups.
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21 355 In conclusion, treatment of DC with a single CCH injection costs 33% less, in direct costs,
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23 356 than fasciectomy with equivalent short-term efficacy (6 weeks) regarding reduction in
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25 357 contracture.
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6
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8
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10
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15

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19
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23 368 **Contributorship Statement**
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25 369 IA, ES, AL: Study conception and design, acquisition of data, analysis and interpretation of
26
27 370 data, and drafting of the article.
28

29 371 EA: Acquisition of data, and critical revision of the article for important intellectual content.
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31 372 MW: Analysis and interpretation of data and critical revision of the article for important
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33 373 intellectual content.
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35 374 All authors approved the final submitted version.
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38 375 **Competing Interests**
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40 376 Dr. Atroshi was a member of an Expert Group on Dupuytren's disease for Pfizer 2012. The
41
42 377 other authors have no competing interests.
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45 378 **Data Sharing Statement**
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47 379 **Data are available on request from Dr. Atroshi**
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437 **Table 1** Characteristics of the two samples of patients with Dupuytren's contracture treated with
 438 collagenase clostridium histolyticum injection or surgery (fasciectomy)

	CCH injection	Fasciectomy
Number of patients (men)	16 (11)	16 (13)
Age (yrs), mean (SD)	69 (4)	71 (5)
Number of fingers treated*		
Small	11	9
Ring	7	8
Middle	0	1
Extension deficit (degrees)		
Total [†] mean (SD)	90 (39)	71 (28)
median (IQR)	70 (60-115)	75 (45-89)
MCP [‡] mean (SD)	64 (16)	60 (17)
median (IQR)	65 (60-75)	60 (41-80)
PIP [‡] mean (SD)	55 (22)	46 (18)
median (IQR)	55 (43-70)	40 (35-48)

439
 440 CCH, collagenase clostridium histolyticum; IQR, interquartile range

441 *2 patients in each group had 2 fingers treated.

442 [†] Metacarpophalangeal (MCP) plus proximal interphalangeal (PIP) joints in all treated fingers (in
 443 patients with 2 fingers treated the finger with largest extension deficit was used).

444 [‡] The values showing MCP and PIP extension deficits separately include only joints with contracture
 445 (no MCP contracture in 1 patient in the CCH group and 2 patients in the fasciectomy group and no
 446 PIP contracture in 7 patients in each group).

447 **Table 2** Cost specification for the various stages of treating Dupuytren's contracture
 448 with collagenase clostridium histolyticum injection or surgery (fasciectomy)

	Personnel costs [*]	Other costs [†]
	(USD)	(USD)
Doctor visit, CCH or fasciectomy (doctor and nurse)	65.80	16.78
Injection, CCH (doctor and nurse)	70.63	991.16
Finger extension, CCH (doctor and nurse)	70.63	20.97
Therapist visit, CCH	26.58	25.16
Surgery, fasciectomy (doctors and others)	783.97	380.81
Day surgery care, fasciectomy	88.10	52.41
Therapist visit, fasciectomy	39.88	37.77
Nurse visit, CCH or fasciectomy	43.51	37.77

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 450 CCH, collagenase clostridium histolyticum; USD, United States dollars

451 *Include average salary, social security contributions, vacation pay, sick pay, overhead costs, and the
 452 degree of capacity utilization.

453 †Include costs of surgical and other materials, injections, premises, etc.

454 Price of 1 CCH injection = 970.19 USD.

455 **Table 3** Number of visits to medical personnel, actual costs and short-term outcomes of treating
 456 Dupuytren's contracture with collagenase clostridium histolyticum injection or surgery (fasciectomy)

	CCH injection	Fasciectomy
Mean, median (IQR) number of visits to:		
Doctor	3*	2*
Nurse	0.33*	3.0, 3.0 (2.0-3.8)
Therapist	3*	5.1, 4.0 (3.0-6.8)
Total cost per patient (USD)	1418.04	2102.56
Total cost per patient when 20% require 2 injections (USD)	1675.24	2102.56
Extension deficit (degrees) [†]		
Total	mean (SD)	20 (25)
	median (IQR)	10 (0-30)
MCP	mean (SD)	10 (17)
	median (IQR)	0 (0-15)
PIP	mean (SD)	23 (18)
	median (IQR)	20 (8-35)

457
 458 CCH, collagenase clostridium histolyticum; IQR, interquartile range; USD, United States dollars

459 * Number of visits to a doctor in both groups and to a therapist in the CCH group was similar for all
 460 patients (Figure 1); a third of CCH patients assumed to require 1 visit to a nurse.

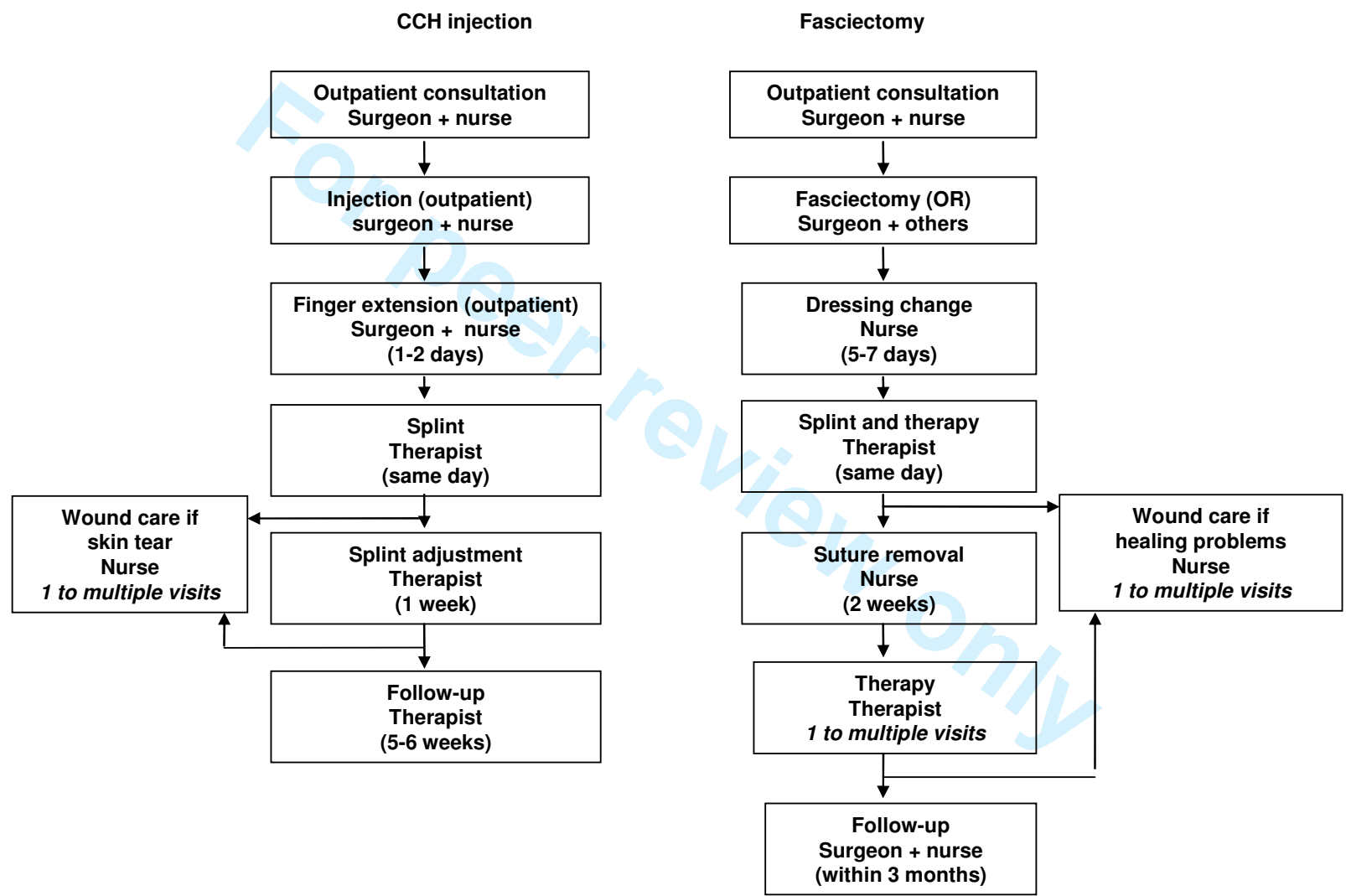
461 [†] Metacarpophalangeal (MCP) plus proximal interphalangeal (PIP) joints in all treated fingers. The
 462 values showing MCP and PIP extension deficits separately include only joints with pretreatment
 463 contracture (see footnote in Table 1).

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3 464 **Figure legend**
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7 466 **Figure 1.** Diagram showing the various stages of treating patients with Dupuytren's
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9 467 contracture with collagenase clostridium histolyticum (CCH) injection or with fasciectomy as
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11 468 a day-surgery procedure performed in the operating room (OR). The number of visits is 1
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13 469 unless specified otherwise.
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3 1 **Costs for collagenase injections compared with fasciectomy in the treatment**
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5 2 **of Dupuytren's contracture: A retrospective cohort study**
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3 19 **Abstract**

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5 20 **Objectives:** To compare collagenase injections and surgery (fasciectomy) for Dupuytren's
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7 21 contracture (DC) regarding actual total direct treatment costs and short-term outcomes.

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10 22 **Design:** Retrospective cohort study

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12 23 **Setting:** Orthopaedic department of a regional hospital in Sweden.

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14 24 **Participants:** Patients aged 65 years or older with previously untreated DC of 30 degrees or
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16 25 greater in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joints of the
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18 26 small, ring or middle finger. The collagenase group comprised 16 consecutive patients treated
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20 27 during the first 6 months following the introduction of collagenase as treatment for DC at the
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22 28 study centre. The controls were 16 patients randomly selected among those operated on with
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24 29 fasciectomy at the same centre during the preceding 3 years.

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27 30 **Interventions:** Treatment with collagenase was given during two standard outpatient clinic
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29 31 visits (injection of 0.9 mg, distributed at multiple sites in a palpable cord, and next-day finger
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31 32 extension under local anaesthesia) followed by night-time splinting. Fasciectomy was done in
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33 33 the operating room (day surgery) under general or regional anaesthesia using standard
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35 34 technique, followed by therapy and splinting.

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38 35 **Primary and secondary outcome measures:** Actual total direct costs (salaries of all medical
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40 36 personnel involved in care, medications, materials and other relevant costs), and total MCP
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42 37 and PIP extension deficit (degrees) measured by hand therapists at 6-12 weeks after treatment.

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44 38 **Results:** Collagenase injection required fewer hospital outpatient visits to a therapist and
45
46 39 nurse than fasciectomy. Total treatment cost for collagenase injection was 1418.04 USD and
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48 40 for fasciectomy 2102.56 USD. The post-treatment median (interquartile range) total extension
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50 41 deficit was 10 (0-30) for the collagenase group and 10 (0-34) for the fasciectomy group.

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52 42 **Conclusions:** Treatment of Dupuytren's contracture with one collagenase injection costs 33%
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54 43 less than fasciectomy with equivalent efficacy at 6 weeks regarding reduction in contracture.
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3 44 **Strengths and limitations of this study**
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- 7 46 • This study presents previously unknown estimates of the actual costs of treating
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9 Dupuytren's contracture with Collagenase injections or fasciectomy
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11 47
12 48 • Comparison of the actual costs of the two treatments are based on detailed definition and
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14 49 measurement of all relevant costs
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16 50 • Outcomes of injections were prospectively measured but outcomes of surgery were based
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18 51 on medical records
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20 52 • Costs may vary across countries
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22 53 • Only short-term outcomes (6 weeks) were compared
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54 INTRODUCTION

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56 Dupuytren's contracture (DC) is a common hand disorder causing finger contractures that
57 may compromise hand function. Surgery in the form of limited fasciectomy has been the main
58 treatment option for reducing the contracture.¹ In Sweden (population 9.5 millions), more
59 than 3000 fasciectomy procedures are performed annually;² the actual number is probably
60 higher because procedures performed by surgeons in private practice, although constituting a
61 small proportion,³ may not always be reported to the national database. Surgery is usually
62 done in the main operating room under general or regional anaesthesia and the operating time
63 is on average about 1 hour,⁴ but can be substantially longer when severe contractures are
64 present in multiple fingers. After surgery many patients require therapy and splints. Although
65 surgery is often effective in reducing the contracture, postoperative complications such as
66 nerve injury and wound healing problems are common and patients may develop contracture
67 recurrence.^{5,6}

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69 Recently, injection with collagenase clostridium histolyticum (CCH) has been introduced as
70 the first pharmacological treatment for DC after it was shown in a randomized controlled trial
71 to be more effective than placebo injections in reducing contractures.⁷ The treatment is a
72 relatively simple procedure given in the outpatient clinic and rarely requires prolonged
73 therapy. The current price of a CCH injection (in Sweden) is almost one thousand US dollars
74 (USD) and one injection is used for each finger involved (unless contractures in 2 fingers are
75 caused by a common cord). Because of economic pressure to control health care expenditures,
76 the cost-effectiveness of surgical procedures has gained increased significance in hospital
77 decision making. The cost analysis of different treatment procedures such as fasciectomy and

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3 78 injection is therefore essential and the differences in short-term costs associated with these
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5 79 two techniques are important to consider.
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10 81 To our knowledge no previous study has compared the actual costs of CCH injections with
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12 82 those of fasciectomy. One study based on a cost-utility analysis model concluded that open
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14 83 partial fasciectomy did not meet the cost-effectiveness threshold and that CCH injections
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16 84 would be cost-effective when priced below 945 USD.⁸ Studies concerning costs of surgery
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18 85 have usually used reimbursement as a measure of costs,⁹ but reimbursement does not
19
20 86 necessarily reflect the actual cost of a procedure. Reimbursement levels for a certain
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22 87 procedure may vary substantially across and even within countries. For cost comparison of
23
24 88 CCH injections and fasciectomy in DC the actual cost of each procedure is therefore a more
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26 89 relevant measure. When comparing the costs of two treatment methods, the outcome of the
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28 90 treatments must also be taken into consideration. However, we could not find studies that
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30 91 have compared the outcomes of CCH and fasciectomy.
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36 93 The main aim of this retrospective cohort study was to compare CCH injections with
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38 94 fasciectomy regarding the actual total direct treatment costs. The secondary aim was to
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40 95 compare the short-term outcomes of these two treatment methods.
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3 97 **PATIENTS AND METHODS**
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7 99 **Study participants**
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10 100 We conducted a **retrospective** cohort study at one orthopaedic department (Hässleholm,
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12 101 Kristianstad and Ystad Hospitals) in southern Sweden. The department is the only centre that
13
14 102 treats patients with DC in a region with approximately 300,000 inhabitants.
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18 104 Data on CCH injections were collected prospectively starting September 2011 when CCH
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20 105 was introduced as the main treatment option for DC at the department. The indication for
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22 106 treatment with CCH injections was identical to that previously used for surgery at the study
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24 107 centre, namely a palpable cord and contracture of 30 degrees or greater in the
25
26 108 metacarpophalangeal (MCP) **and/or** proximal interphalangeal (PIP) joints. For this study we
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28 109 included the first 16 consecutive patients, aged 65 years or older, treated with CCH injections
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30 110 during the first 6 months (September 2011 through February 2012). We restricted the study to
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32 111 patients of non-working age because we aimed to compare only direct costs.
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38 113 Data on fasciectomy were extracted from the medical records of patients treated at the
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40 114 department before the introduction of CCH injections. The patients were chosen among those
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42 115 aged 65 years or older, operated on with fasciectomy January 2009 through June 2011.
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44 116 Patients with surgery on more than 2 fingers, previous surgery for DC in the same hand, and
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46 117 additional procedures performed (e.g. skin graft or amputation) were excluded. A total of 113
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48 118 patients were potentially eligible. Of these, a random sample of 15% was chosen by computer
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50 119 (statistical software), yielding 18 patients; 2 were excluded (1 had surgery for DC in the
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52 120 thumb and 1 chose to have postoperative therapy at another location). Thus, the fasciectomy
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54 121 group included 16 patients.
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3 122 **Treatment and follow-up procedures**
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5 123 Both treatments required an initial standard outpatient consultation visit to a hand surgeon or
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7 124 an orthopaedic surgeon, usually as a referral from the patient's general practitioner. Each
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9 125 surgeon was assisted by a nurse at the outpatient clinic. During the visit the treatment decision
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11 126 was made and the patient was scheduled for treatment (Fig 1).
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16 128 **Collagenase injection:** Treatment with CCH required two standard outpatient visits to a hand
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18 129 surgeon: injection and next-day finger extension.⁷ During these visits the surgeon was assisted
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20 130 by a nurse (all treatments were given by the same hand surgeon). A modified injection
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22 131 method was used for all treated fingers; after reconstituting CCH with 0.39 ml of diluent,
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24 132 according to the standard procedure, all the reconstituted CCH (0.9 mg) was injected into the
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26 133 cord, distributed at multiple sites. The following day, finger manipulation (extension) was
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28 134 done under local anaesthesia. Immediately after finger extension the patient went to the
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30 135 therapist and received a splint for use at night for 8 weeks. A second visit to the therapist was
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32 136 done 1 week post-injection for splint adjustment and therapy instructions. Patients who during
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34 137 finger extension developed a skin tear that was judged to require dressing change were asked
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36 138 to visit a nurse within 2 to 3 days. Further visits to the nurse were done when necessary,
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38 139 depending on wound status. No routine post-treatment visits were scheduled to the treating
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40 140 surgeon and the final follow-up (usually at 5-6 weeks) was done by the therapist. If the patient
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42 141 was not satisfied with the degree of correction after the first injection, the therapist arranged a
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44 142 consultation to the treating surgeon for consideration of further treatment.
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52 144 **Fasciectomy:** Fasciectomy was done as a day-surgery procedure in the main operating room
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54 145 (OR). The surgery was done by one of six different surgeons (three experienced hand
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56 146 surgeons and three orthopaedic surgeons with experience in hand surgery) using standard
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3 147 technique for limited open fasciectomy.¹⁰ General anaesthesia or axillary block was used.
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5 148 According to routine procedures at the hospital general anaesthesia was administered by a
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7 149 nurse anaesthetist and axillary block was administered by an anaesthesiologist, after which
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9 150 the nurse anaesthetist was in charge of the patient's care with anaesthesiologist help obtained
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11 151 when needed. The surgery was done by a surgeon (no assistant) with a team consisting of an
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13 152 OR nurse, a nurse anaesthetist and 2 nurse assistants (1 participated only in the initial
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15 153 preparations). The electronic records for each surgical procedure include the exact start and
16
17 154 finish times for the preparations before surgery, anaesthesia, the actual surgery (i.e. operating
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19 155 time from incision to dressing), and the work done after the surgeon has completed the
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21 156 operation and until the patient is taken back to the recovery room. After returning from the
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23 157 OR the patient stayed in the recovery room until discharge from the day-surgery unit. The
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25 158 time of discharge is documented in the electronic records. Thus, for each patient 3 times were
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27 159 recorded; the operating time, the total OR time (from start of preparations until room ready
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29 160 for next procedure), and the time at the recovery room until discharge.
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36 162 After fasciectomy all patients visited a nurse for dressing change after 5 to 7 days, followed
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38 163 immediately by a visit to a therapist for a splint and therapy instructions. A second visit to the
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40 164 nurse for wound inspection and suture removal was done at approximately 2 weeks. Further
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42 165 visits to the nurse were done when necessary, depending on wound status. Patients also had
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44 166 further visits to the therapist for scar management, splint adjustments and therapy instructions
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46 167 as required. The treating therapist decided on the frequency and duration of therapy. Patients
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48 168 had 1 postoperative follow-up visit to the surgeon timed according to surgeon preference.
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3 172 **Cost measurement**
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5 173 A detailed analysis of the salaries of physicians and non-physician medical personnel
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7 174 involved in the treatment of patients with DC was performed for CCH injection and
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9 175 fasciectomy. We identified the average salaries of individuals and used the average time units
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11 176 to calculate the cost of manpower. The costs of all materials, premises and other costs were
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13 177 calculated. We included fixed assets such as the costs of the premises and its expenses and the
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15 178 costs of surgical equipment. All costs were measured based on 2011 salaries/prices. These
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17 179 costs include; salaries of all medical personnel involved in the direct care of the patients
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19 180 including social security contributions, vacation pay and sick pay (averaged for each category:
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21 181 specialist orthopaedic surgeon, anaesthesiologist, nurse, nurse assistant and therapist),
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23 182 hospital overhead costs, the degree of capacity utilization, medications, surgical and other
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25 183 material, premises and other costs. The average salaries were based on all respective medical
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27 184 personnel group in the public health care sector in the region. We did not include costs of
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29 185 non-medical personnel involved in the care (such as receptionists, secretaries, cleaners, etc).
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36 187 A standard outpatient visit to a doctor was 20 minutes. For the 2 CCH visits (injection and
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38 188 finger extension) we used the standard time for the surgeon and 25 minutes for the assisting
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40 189 nurse (to account for the time needed for preparations and work after the session had ended).
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42 190 For fasciectomy we used the mean operating time, total OR time and recovery time, according
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44 191 to the personnel involved and adjusted as required. For the operating surgeon we used the
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46 192 mean operating time plus 25 minutes needed for additional work (assessing the patient and
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48 193 marking the surgical site before surgery, scrubbing, writing the surgical notes and discharging
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50 194 the patient after surgery). For the non-physician personnel we used the mean total operating
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52 195 room time and for the anaesthesiologist we used half that time (one anaesthesiologist is
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54 196 usually assigned to 2 operating rooms simultaneously and the care of these patients after
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3 197 surgery). For recovery room personnel (a nurse and a nurse assistant are in charge of up to 5
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5 198 patients simultaneously), we used a fifth of the recovery time plus 5 minutes (preoperative
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7 199 preparations). A standard outpatient visit to a nurse (for wound care after CCH injection or
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9 200 fasciectomy) was 45 minutes. A standard visit to therapist after CCH injection was 30
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11 201 minutes and after fasciectomy 45 minutes. For each patient the exact number of hospital
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13 202 outpatient visits to a doctor, nurse or therapist, related to the treatments, was retrieved from
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15 203 the Patient Administrative System.
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21 **Outcome measurement**

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23 206 At baseline and at all follow-up visits range of motion including extension and flexion of the
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25 207 MCP and PIP joints of the fingers was measured with a goniometer. In the fasciectomy group
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27 208 the baseline measurements were done by the surgeons during the visit that resulted in the
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29 209 patient being scheduled for fasciectomy and the post-treatment measurements were done by
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31 210 six different therapists; these measurements were recorded in the patient's electronic medical
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33 211 records. In the CCH group all measurements (immediately before injection and at follow-up)
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35 212 were done by the same therapist, as part of a research project. The measurements recorded at
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37 213 baseline and at the final visit were used in the analysis.
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43 **Analysis**

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45 216 In 2 previous randomized trials the proportion of MCP joints that were reduced to 0 to 5
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47 217 degrees of extension deficit was 45% at 30 days after first CCH injection⁷ and 94% at 6
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49 218 weeks after fasciectomy.¹¹ To detect a difference of this magnitude between the 2 groups
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51 219 (80% power and 0.05 significance level) would require a sample of 13 patients in each group.
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53 220 The cost estimation of CCH was based on standard procedures independent of sample size.
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55 221 For the cost of fasciectomy, a random sample of 15% from 113 fasciectomy-treated patients
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3 222 was judged adequate to provide representative average procedure time estimates and number
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5 223 of visits to medical personnel, on which the total cost was based. Data are shown as mean and
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7 224 SD and/or median and interquartile range (IQR). We calculated the average total cost of
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9 225 treatment per patient when only 1 CCH injection is given. We also calculated the cost if 20%
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11 226 of the patients would need 2 CCH injections given on separate sessions to obtain satisfactory
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13 227 contracture reduction. Because some patients who developed skin tears during finger
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15 228 extension chose to have dressing change, when necessary, at home or at primary care, only 1
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17 229 nurse visit was recorded in the Patient Administrative System. We therefore made the
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19 230 calculations assuming 1 of 3 patients in the CCH group would require 1 nurse visit. We also
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21 231 conducted a sensitivity analysis with the conservative assumption of 1 nurse visit per patient.
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23 232 All costs were calculated in Swedish Kronor (SEK) and converted to USD using the rate of 1
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25 233 USD = 6.676 SEK (Sweden's Central Bank average for 2011). The within-group change in
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27 234 extension deficit was analyzed with the Wilcoxon test. We also compared the 2 groups with
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29 235 regard to improvement in total extension deficit using the Mann-Whitney test. A p value
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31 236 below 0.05 was used to indicate statistical significance.
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3 237 **RESULTS**

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7 239 The 16 patients in the CCH group and the 16 patients in the fasciectomy group had similar
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9 240 characteristics (Table 1). In the fasciectomy group half of the patients received general
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11 241 anaesthesia and the other half axillary block. The mean operating time was 62 (SD 27)
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13 242 minutes, mean total OR time 138 (SD 43) minutes, and mean postoperative time spent at the
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15 243 day-surgery recovery room until discharge 215 (SD 41) minutes. The median time from
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17 244 surgery to end of therapy was 6.3 weeks (IQR 4.0-11.5) and to the postoperative follow-up by
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19 245 the surgeon 7.5 weeks (IQR 6.0-12.0). None of the patients in the CCH group required further
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21 246 therapy than the standard visits. Of the 16 patients, 9 developed skin tears ranging from minor
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23 247 superficial skin breakage that did not require further wound care to deeper wound that
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25 248 required 1 or more dressing changes. All wounds had healed within 2 weeks after injection.
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32 250 **Costs**

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34 251 The cost specifications for the two treatments are shown in Table 2. The largest treatment cost
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36 252 for CCH injections was the cost of the injection itself (970.19 USD) and for fasciectomy the
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38 253 cost of personnel (783.97 USD) and other costs (380.81 USD) associated with the surgery in
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40 254 the operating room. Compared to fasciectomy, treatment with CCH injections required fewer
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42 255 outpatient hospital visits to a nurse and a therapist (Table 3).
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47 257 The total treatment cost with 1 CCH injection was 33% lower than that for fasciectomy
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49 258 (1418.04 versus 2102.56 USD). The cost was still lower (1675.24 USD) if 20% of patients
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51 259 treated with CCH would require 2 injections in the same hand, given in separate sessions. In
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53 260 the sensitivity analysis the cost of CCH injections assuming an average of 1 nurse visit per
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3 261 patient was 1472.51 USD when 1 injection is given and 1696.79 USD when 20% would
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5 262 require 2 injections.
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9 264 **Outcomes**

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11 265 Of the 16 patients in the CCH and fasciectomy groups, 7 and 9 patients respectively achieved
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13 266 an extension deficit of 0 to 5 degrees in the joint with the largest extension deficit. In both
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15 267 groups the improvement in total extension deficit was statistically significant ($p < 0.001$) and
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17 268 the extension deficits after CCH and fasciectomy were similar (median 10 degrees) (Table 3).
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19 269 The median improvement in total extension deficit in the CCH group was 65 (IQR 56-81)
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21 270 degrees and in the fasciectomy group 50 (IQR 41-60) degrees ($p=0.007$).
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25 271 No complications were observed in any of the groups at the final follow-up.
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3 272 **DISCUSSION**

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7 274 Our study shows that treatment of DC with a single collagenase injection is associated with
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9 275 lower costs than surgery (fasciectomy) and the short-term outcomes (6 weeks) regarding
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11 276 reduction in finger joint contractures are similar. The costs are still lower when assuming that
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13 277 20% of the patients would require 2 injections in the same hand, but if more than 5 of 10
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15 278 patients need 2 injections the costs would exceed those of fasciectomy. Our estimates of the
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17 279 costs assuming 20% would require 2 injections were based on separate treatment sessions; the
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19 280 costs would be even lower if the 2 injections are given in the same session, which would
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21 281 probably become the usual practice.¹² Further, our results should be considered conservative
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23 282 since we have not considered complications (such as wound infection and chronic regional
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25 283 pain syndrome) that are probably more frequent after surgery than after CCH injections and
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27 284 would therefore add to the total costs. The study by Hurst et al.⁷ reported use of an average of
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29 285 about 2 CCH injections per patient. However, in that study finger extension, which often is a
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31 286 painful procedure, was done without anaesthesia, which may have reduced the degree of
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33 287 initial contracture correction and thus necessitating a second injection. As in our study, use of
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35 288 local anaesthesia is currently the standard procedure. In addition, Hurst et al. injected 0.58 mg
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37 289 CCH into one part of the cord whereas our technique is to inject the whole content of a single
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39 290 CCH injection (0.9 mg) into the cord at multiple sites, which would probably increase the
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41 291 efficacy of a single injection.

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45 293 For fasciectomy, the largest cost was represented by the various costs associated with a day-
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47 294 surgery procedure of approximately 1 hour duration in the operating room. The cost would be
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49 295 lower if the average operating time were shorter than our estimate of 62 minutes. In a recent
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51 296 study of DC in 12 European countries (based on a surgeon survey and patient chart review),
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3 297 the mean operating time for fasciectomy across all countries was 67 minutes (Nordic 63,
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5 298 Eastern 69, Western 66, and Mediterranean 68 minutes).⁴ A potential advantage with CCH
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7 299 injections is the possibility to treat patients with bilateral disease in 1 stage, which is
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9 300 uncommon with surgery considering the nature of the procedure. In contrast, patients with
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11 301 contractures involving 3 or more fingers can be treated with surgery in one session, but would
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13 302 need at least 2 CCH injections and, in more severe cases, 2 or more treatment sessions.
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18 304 Skin tears ranging from minor superficial skin breakage to deeper wounds occurred in more
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20 305 than half the patients after CCH injections in our study. Skin tears following CCH injections
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22 306 were reported in 11% in the multicenter randomized trial,⁷ and in up to 19% in other
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24 307 studies.^{13,14} Skin tears are more likely to occur in severe contractures especially of the small
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26 308 finger.⁹ Because the incidence and severity of skin tears (ie, need for wound care) may vary
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28 309 we calculated the costs assuming that, on average, one third of the patients would require 1
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30 310 nurse visit and also did a sensitivity analysis assuming an average of 1 nurse visit. We believe
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32 311 these estimates cover the costs of wound care even if the true incidence of skin tears is higher
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34 312 than previously reported.
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39 314 We only compared direct costs, and therefore did not include costs of lost productivity or sick
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41 315 leave. Among employed patients, sick leave is more likely to be necessary and longer after
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43 316 fasciectomy than after CCH injections. According to the Swedish Social Insurance Agency
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45 317 the total cost of a 1-week sick leave based on the average salary in Sweden 2011 (including
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47 318 sick-pay, general payroll tax, vacation-pay and overhead costs) exceeds 1300 USD
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49 319 (www.scb.se). In addition, the direct costs of CCH injections and fasciectomy may differ
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51 320 across countries and settings. In a Canadian study that estimated the cost (during 2005) of
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53 321 open carpal tunnel release, a 10-minute procedure done under local anaesthesia, the total cost
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3 322 (excluding surgeon's fee) was 137 CAD when done in the main operating room and 53 CAD
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5 323 dollars when done in the office.¹⁵ Although the largest treatment cost for CCH injections was
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7 324 the cost of the injection itself, which may be substantially higher in some countries, the costs
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9 325 of surgery in these countries may also be higher. In a study involving 24 patients treated with
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11 326 fasciectomy at a single US hospital from 2008 to 2010 the average direct cost, defined as
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13 327 costs billed from hospital charges (facility fees) and professional charges (surgeon and
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15 328 anaesthesia fees) was estimated to be 11,240 USD.⁹
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21 330 A limitation of our study is that only very short-term outcomes were measured. The
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23 331 improvement was high and the minor residual contracture was similar for CCH and
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25 332 fasciectomy. Differences in long-term outcomes may change the cost-effectiveness of these
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27 333 treatments because if they differ substantially in the recurrence rate and the need for further
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29 334 treatments the cost of subsequent treatments should also be considered. According to the most
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31 335 recent published data regarding recurrence after CCH injections (defined as contracture
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33 336 increase of 20 degrees or greater in the presence of a palpable cord in joints initially corrected
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35 337 to a maximum of 5-degree contracture), the overall rate in 623 joints at 3 years was 35%
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37 338 (MCP 27% and PIP 56%) but the recurrence required treatment in only 7%.¹⁶ Following
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39 339 fasciectomy a 3-year recurrence rate of 12% has been reported in two studies; in the first
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41 340 study, 4 of 33 hands had more than 30 degrees increase in joint contracture compared to 6
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43 341 weeks,¹¹ and in the second study, 11 of 90 fingers showed progressive recurrence of PIP joint
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45 342 contracture but no specific definition of recurrence was stated.¹⁷ Thus, depending on the
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47 343 proportion of patients that subsequently need repeated treatment because of recurrent
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49 344 contracture in the treated fingers it is possible that in the long-term the direct costs of
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51 345 treatment with CCH may exceed those of fasciectomy.
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3 347 Another limitation is that in the fasciectomy group the baseline range-of-motion
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5 348 measurements were done by different surgeons and the follow-up measurements by different
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7 349 therapists. The inter-observer reliability of these measurements is unknown and there might
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9 350 be a risk that the surgeon overestimated the preoperative contracture and the treating therapist
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11 351 underestimated residual contracture. However, we do not believe this issue has a substantial
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13 352 influence because fasciectomy was the only treatment option and the results of the post-
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15 353 treatment measurements, done by therapists, were similar in both groups.
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21 355 In conclusion, treatment of DC with a single CCH injection costs 33% less, in direct costs,
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23 356 than fasciectomy with equivalent short-term efficacy (6 weeks) regarding reduction in
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25 357 contracture.
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8
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422 recurrence after surgery for Dupuytren's contracture?: a prospective, randomised trial. *J*
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427 **Table 1** Characteristics of the two samples of patients with Dupuytren's contracture treated with
 428 collagenase clostridium histolyticum injection or surgery (fasciectomy)

	CCH injection	Fasciectomy
Number of patients (men)	16 (11)	16 (13)
Age (yrs), mean (SD)	69 (4)	71 (5)
Number of fingers treated*		
Small	11	9
Ring	7	8
Middle	0	1
Extension deficit (degrees)		
Total [†] mean (SD)	90 (39)	71 (28)
median (IQR)	70 (60-115)	75 (45-89)
MCP [‡] mean (SD)	64 (16)	60 (17)
median (IQR)	65 (60-75)	60 (41-80)
PIP [‡] mean (SD)	55 (22)	46 (18)
median (IQR)	55 (43-70)	40 (35-48)

429
 430 CCH, collagenase clostridium histolyticum; IQR, interquartile range

431 * 2 patients in each group had 2 fingers treated.

432 [†] Metacarpophalangeal (MCP) plus proximal interphalangeal (PIP) joints in all treated fingers (in
 433 patients with 2 fingers treated the finger with largest extension deficit was used).

434 [‡] The values showing MCP and PIP extension deficits separately include only joints with contracture
 435 (no MCP contracture in 1 patient in the CCH group and 2 patients in the fasciectomy group and no
 436 PIP contracture in 7 patients in each group).

437 **Table 2** Cost specification for the various stages of treating Dupuytren's contracture
 438 with collagenase clostridium histolyticum injection or surgery (fasciectomy)

	Personnel costs [*]	Other costs [†]
	(USD)	(USD)
Doctor visit, CCH or fasciectomy (doctor and nurse)	65.80	16.78
Injection, CCH (doctor and nurse)	70.63	991.16
Finger extension, CCH (doctor and nurse)	70.63	20.97
Therapist visit, CCH	26.58	25.16
Surgery, fasciectomy (doctors and others)	783.97	380.81
Day surgery care, fasciectomy	88.10	52.41
Therapist visit, fasciectomy	39.88	37.77
Nurse visit, CCH or fasciectomy	43.51	37.77

439
 440 CCH, collagenase clostridium histolyticum; USD, United States dollars

441 *Include average salary, social security contributions, vacation pay, sick pay, overhead costs, and the
 442 degree of capacity utilization.

443 †Include costs of surgical and other materials, injections, premises, etc.

444 Price of 1 CCH injection = 970.19 USD.

445 **Table 3** Number of visits to medical personnel, actual costs and short-term outcomes of treating
 446 Dupuytren's contracture with collagenase clostridium histolyticum injection or surgery (fasciectomy)

	CCH injection	Fasciectomy
Mean, median (IQR) number of visits to:		
Doctor	3*	2*
Nurse	0.33*	3.0, 3.0 (2.0-3.8)
Therapist	3*	5.1, 4.0 (3.0-6.8)
Total cost per patient (USD)	1418.04	2102.56
Total cost per patient when 20% require 2 injections (USD)	1675.24	2102.56
Extension deficit (degrees) [†]		
Total	mean (SD)	20 (25)
	median (IQR)	19 (19)
		10 (0-30)
		10 (0-34)
MCP	mean (SD)	10 (17)
	median (IQR)	8 (10)
		0 (0-15)
		0 (0-20)
PIP	mean (SD)	23 (18)
	median (IQR)	21 (13)
		20 (8-35)
		25 (8-33)

447 CCH, collagenase clostridium histolyticum; IQR, interquartile range; USD, United States dollars
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449 * Number of visits to a doctor in both groups and to a therapist in the CCH group was similar for all
 450 patients (Figure 1); a third of CCH patients assumed to require 1 visit to a nurse.

451 [†] Metacarpophalangeal (MCP) plus proximal interphalangeal (PIP) joints in all treated fingers. The
 452 values showing MCP and PIP extension deficits separately include only joints with pretreatment
 453 contracture (see footnote in Table 1).

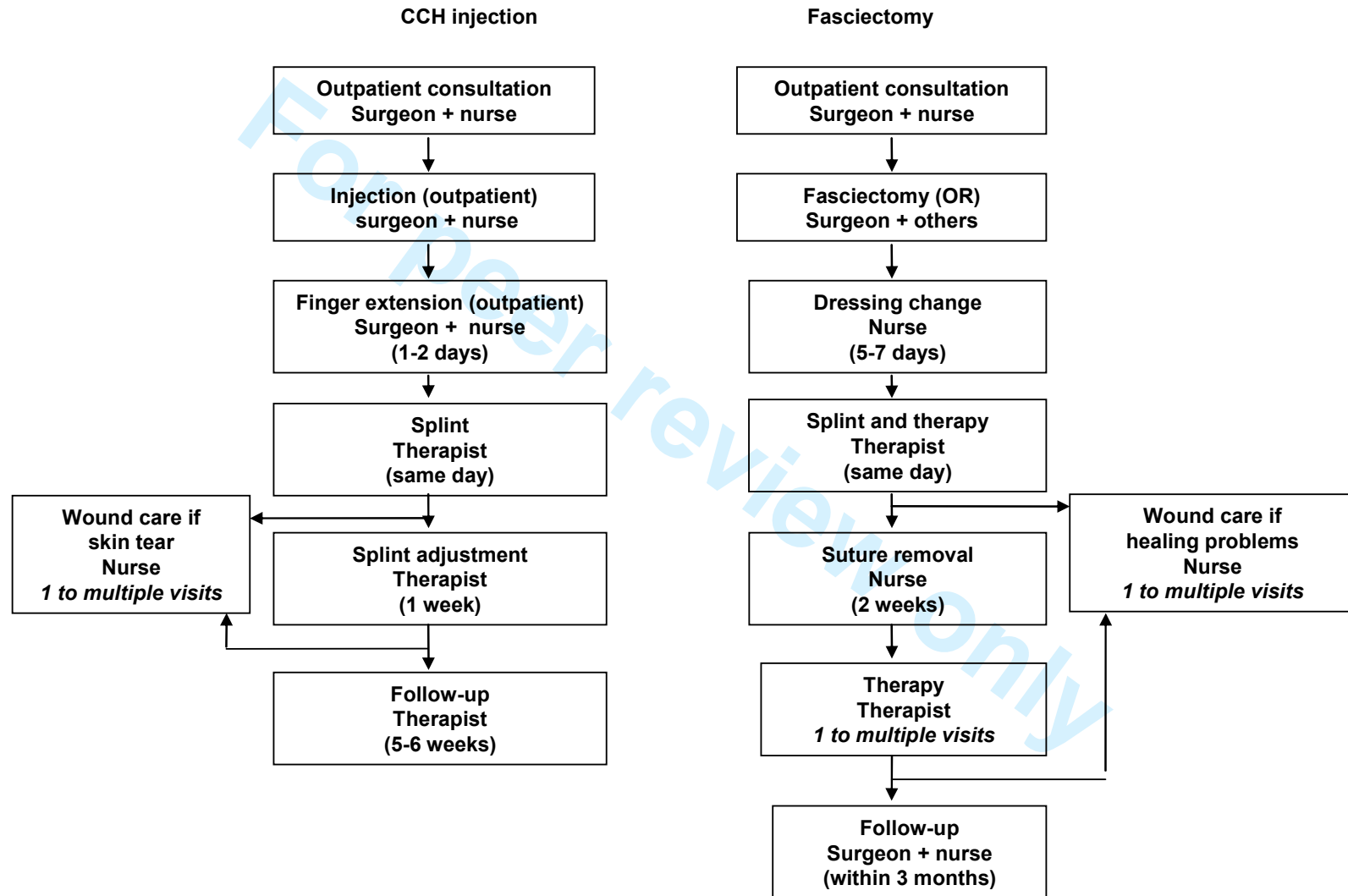
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3 454 **Figure legend**

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7 456 **Figure 1.** Diagram showing the various stages of treating patients with Dupuytren's
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10 457 contracture with collagenase clostridium histolyticum (CCH) injection or with fasciectomy as
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12 458 a day-surgery procedure performed in the operating room (OR). The number of visits is 1
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14 459 unless specified otherwise.

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For peer review only



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

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

Continued on next page

Results

Participants	13*	(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 P 12 Figure 1
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders P 12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time P 12-13 Table 2 & 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(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 P 12-13 Table 2 & 3
		(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	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses P 12-13

Discussion

Key results	18	Summarise key results with reference to study objectives P 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias P 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence P 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results P 15

Other information

Funding	22	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 P 17
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*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.