■ SYSTEMATIC REVIEW

Treatment of Dupuytren's contracture

A SYSTEMATIC REVIEW

E. Soreide,
M. H. Murad,
J. M. Denbeigh,
E. A. Lewallen,
A. Dudakovic,
L. Nordsletten,
A. J. van Wijnen,
S. Kakar

From Mayo Clinic, Rochester, Minnesota, United States

■ E. Soreide, MD, Orthopaedic Surgeon
Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA and Department of Orthopedic Surgery, Oslo University Hospital, Oslo, Norway.

■ M. H. Murad, MD, Professor of Medicine
Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota, USA.

■ J. M. Denbeigh, PhD, Post-Doctoral Research Fellow
■ A. Dudakovic, PhD, Post-Doctoral Research Fellow
■ S. Kakar, MD, FAOA, Orthopaedic and Hand Surgeon, Professor of Orthopaedic Surgery
Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA.

■ E. A. Lewallen, PhD, Assistant Professor
Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA and Department of Biological Sciences, Hampton University, Hampton, Virginia, USA.

■ L. Nordsletten, MD, PhD, Orthopaedic Surgeon, Professor of Orthopaedic Surgery
Department of Orthopedic Surgery, Oslo University Hospital, Oslo, Norway.

■ A. J. van Wijnen, PhD, Professor of Orthopaedic Surgery and Professor of Molecular Biology and Biochemistry
Department of Orthopedic Surgery and Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota, USA.

Correspondence should be sent to S. Kakar; email: kakar.sanjeev@mayo.edu

doi:10.1302/0301-620X.100B9.BJJ-2017-1194.R2 $2.00

Bone Joint J 2018;100-B:1138–45.

Aims

Dupuytren's contracture is a benign, myoproliferative condition affecting the palmar fascia that results in progressive contractures of the fingers. Despite increased knowledge of the cellular and connective tissue changes involved, neither a cure nor an optimum form of treatment exists. The aim of this systematic review was to summarize the best available evidence on the management of this condition.

Materials and Methods

A comprehensive database search for randomized controlled trials (RCTs) was performed until August 2017. We studied RCTs comparing open fasciectomy with percutaneous needle aponeurotomy (PNA), collagenase clostridium histolyticum (CCH) with placebo, and CCH with PNA, in addition to adjuvant treatments aiming to improve the outcome of open fasciectomy. A total of 20 studies, involving 1584 patients, were included.

Results

PNA tended to provide higher patient satisfaction with fewer adverse events, but had a higher rate of recurrence compared with limited fasciectomy. Although efficacious, treatment with CCH had notable recurrence rates and a high rate of transient adverse events. Recent comparative studies have shown no difference in clinical outcome between patients treated with PNA and those treated with CCH.

Conclusion

Currently there remains limited evidence to guide the management of patients with Dupuytren's contracture.

Cite this article: *Bone Joint J* 2018;100-B:1138–45.

Dupuytren's contracture is a benign fibroproliferative condition affecting the palmar fascia of the hand. The differentiation of fibroblasts to myofibroblasts, with contractile properties and excessive collagen deposition of less organized cross-linked extracellular matrix, may cause progressive contractures of the fingers.[1] It is most prevalent in the ulnar rays of the hand, but can involve all the fingers.[2,3]

The gold-standard treatment for Dupuytren's contracture has involved surgery, ranging from percutaneous release to dermatofasciectomy.[4,5] Despite short-term success, there is a high rate of recurrent contracture with additional comorbidities such as wound-healing complications and neurovascular injury.[6] This has led to the pursuit of minimally invasive options, including percutaneous needle aponeurotomy (PNA) and collagenase clostridium histolyticum (CCH) injections. These have gained popularity among both patients and surgeons given their relative simplicity and the rapid return of function.[7-12] Both these treatments aim to weaken and disrupt the cord, enabling improved extension of the affected finger. The optimal form of treatment for Dupuytren's contracture should allow correction of the deformity with minimal complications and rehabilitation, maintain the correction with the passage of time, and be cost-effective.

The aim of this systematic review was to summarize the best available evidence on the management of Dupuytren's contracture comparing PNA, CCH injections, and surgery.

Material and Methods

A comprehensive search of Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and

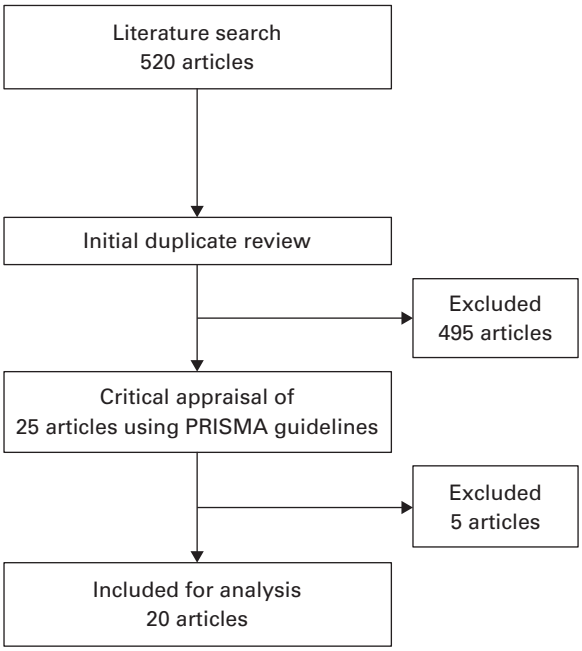

Fig. 1

A literature search of Dupuytren's contracture. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Scopus (supplementary material), from their inception to 2 August 2017, in all languages, was conducted. Controlled vocabulary based on the assessment of the patient, intervention, comparison, and outcome (PICO) was used to search for studies involving the treatment of Dupuytren's contracture, including randomized controlled trials (RCTs) in humans. Case control studies, case reports, and basic science research studies were excluded. The investigators' initial review of the literature was independently conducted by two investigators (ES and SK) and repeated to reduce the intra- and interobserver variability with study selection. The Cochrane Risk of Bias tool was used to assess the methodological quality of the studies.[13] The Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) was used to report the findings.

Statistical analysis. Relative risk (RR), confidence intervals (CIs), and p-values have been calculated for studies reporting the incidence. Mean and standard deviation were used for those reporting continuous data. Statistical significance was set at $p < 0.05$. If data were available with reasonable homogeneity of the design and outcomes of the trials, a network meta-analysis following a Bayesian approach was planned.

Results

The initial search generated 520 articles (Fig. 1), from which 25 were chosen by two investigators (ES and SK) for full text review. A further five articles were excluded due to low patient numbers ($n < 20$),[14] dealing with the prevention rather than the treatment of Dupuytren's contracture,[15] being an abstract,[16] or having a follow-up of < 30 days.[17,18] Thus 20 articles, involving a total of 1584 patients, were ultimately included in the study.

The methodological quality of the studies was adequate, with a moderate risk of bias (Table I).[7-12,19-32] All studies were RCTs published in peer-reviewed journals. Four were multicentre studies; there was one phase II clinical trial and two phase III clinical trials.[7,8] The follow-up ranged from 30 days to five years. There were inconsistencies in the inclusion criteria and outcome parameters in the studies.

The variation of outcome parameters combined with the heterogeneity in study design represent a break of the comparison chain needed to conduct a true meta-analysis (Fig. 2).[33]

Percutaneous needle aponeurotomy *versus* limited fasciectomy. In a RCT involving 121 patients, van Rijssen et al[10] reported a better correction of contracture from limited fasciectomy (LF) compared with PNA (79% *vs* 62%), at six weeks' follow-up (Table II). Patients undergoing PNA reported a higher level of satisfaction and subjective function. However, this difference was not confirmed by the Disability of the Arm, Shoulder and Hand (DASH) questionnaire.[34] Major adverse effects, including infection, haematoma, and digital nerve injury, were less common in patients undergoing PNA (relative risk (RR) 0.14; 95% CI 0.01 to 2.57). In a second, longer follow-up of 93 patients, at five years, these authors[11] noted an increased risk of recurrence in those treated with PNA compared with those treated with LF ($p = 0.0001$).

Kan et al[29] described a RCT involving 80 patients, comparing percutaneous needle aponeurotomy with lipofilling (PALF) to LF. The correction of the contracture was similar at follow-up of 12 months, but the rehabilitation time was significantly shorter in the PALF group. There was no difference in the recurrence or complication rates between the groups, although two patients in the LF group had persistent symptoms.

Table I. Assessment of the quality of the methodology of the studies (The Cochrane Collaboration's tool for assessing risk of bias)

Author (year)	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Badalamente et al[7] (2002)	Unclear	Yes	Yes	Unclear	Unclear	Yes
Citron and Nunez[19] (2005)	Yes	Yes	Yes	Yes	Unclear	Unclear
van Rijssen et al[10] (2006)	Yes	Yes	No	Yes	Unclear	Yes
Badalamente and Hurst[8] (2007)	Unclear	Unclear	Yes	Yes	Unclear	Yes
Hurst et al[9] (2009)	Yes	Yes	Yes	Yes	Unclear	Yes
Ullah et al[20] (2009)	Yes	Yes	No	Unclear	Unclear	Yes
Gilpin et al[12] (2010)	Yes	No	Yes	Unclear	Unclear	Unclear
Jerosch-Herold et al[21] (2011)	Yes	Yes	No	Unclear	Unclear	Unclear
Kemler et al[22] (2012)	Yes	Yes	No	Unclear	Unclear	Yes
McMillan and Binhammer[23] (2012)	Unclear	Unclear	No	Yes	Unclear	Unclear
van Rijssen et al[11] (2012)	Yes	Yes	Unclear	Unclear	Unclear	Unclear
Collis et al[24] (2013)	Yes	Yes	No	Unclear	Unclear	Unclear
McMillan and Binhammer[25] (2014)	Unclear	Unclear	No	No	Unclear	Unclear
Degreef et al[26] (2014)	Yes	Yes	Yes	Yes	Unclear	Yes
Mickelson et al[27] (2014)	Yes	Yes	Yes	Yes	Unclear	Yes
Kaplan et al[28] (2015)	Yes	Yes	Unclear	Yes	Unclear	Unclear
Kan et al[29] (2016)	Yes	Yes	Incomplete	Yes	Unclear	Unclear
Strömberg et al[30] (2016)	Yes	Yes	Yes	Yes	Yes	Yes
Scherman et al[31] (2016)	Yes	Unclear	No	Unclear	Unclear	No
Skov et al[32] (2017)	Yes	Yes	Incomplete	Yes	Unclear	Yes

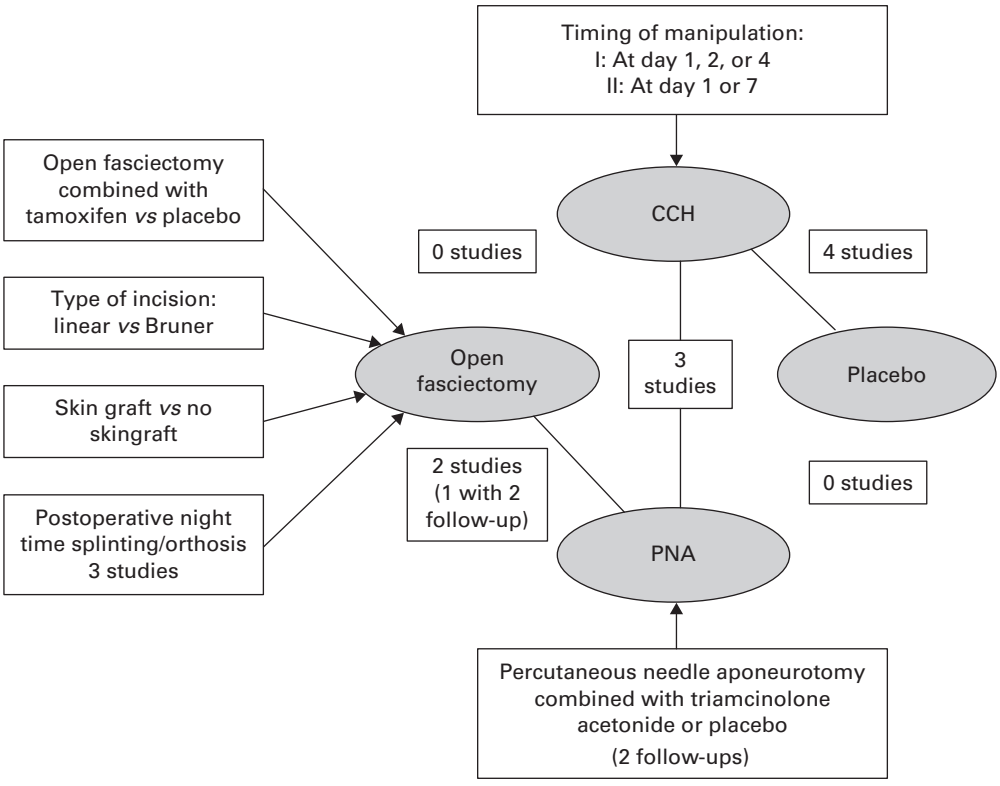

Fig. 2

An overview of the literature on Dupuytren's contracture. CCH, collagenase clostridium histolyticum; PNA, percutaneous needle aponeurotomy.

Adjuvant treatment to PNA. One RCT compared PNA alone *versus* PNA combined with injections of triamcinolone acetonide (TA) into the cords, which were undertaken immediately after PNA, three weeks later, and six weeks later.[23] A total of 47 patients with contractures of > 20° were included. There were no differences in baseline contractures and no difference in total active extension deficit (TAED) at six months ($p = 0.08$). However, patients in the TA group had better

Table II. Percutaneous needle aponeurotomy (PNA) *versus* limited fasciectomy (LF)

Author (year)	n	Comparison	Follow-up	Primary outcome	Effect estimate outcome, RR (95% CI)	Secondary outcome	Effect estimate secondary outcome, RR (95% CI)	Recurrence definition	Effect estimate recurrence, RR (95% CI)	Effect estimate adverse events, RR (95% CI)
van Rijssen et al[10] (2006)	121	PNA *vs* LF	6 wks	TPED	Incidence not reported	DASH, Satisfaction (VAS)	Incidence not reported	Not reported		0.14 (0.01 to 2.57), p = 0.18
van Rijssen et al[11] (2012)	93	PNA *vs* LF	5 yrs	Recurrence	4.06 (2.24 to 7.33), p < 0.0001	TPED	Incidence not reported	Increase in contracture > 30°	4.06 (2.24 to 7.33), p < 0.0001	Not reported
Kan et al[29] (2016)	80	PALF *vs* LF	1 yr	Contracture correction and convalescence time	Incidence not reported	DASH, TPED	Incidence not reported	Not defined	2.05 (0.79 to 5.32), p = 0.14	0.53 (0.09 to 3.00), p = 0.47

RR, relative risk; CI, confidence interval; TPED, total passive extension deficit; DASH, The Disability of the Arm, Shoulder and Hand questionnaire; VAS, visual analogue scale; PALF, percutaneous aponeurotomy and lipofilling

Table III. Collagenase injection treatment *versus* placebo

Author (year)	n	Comparison	Follow-up	Primary outcome	Effect estimate outcome, RR (95% CI)	Secondary outcome	Effect estimate secondary outcome, RR (95% CI)	Recurrence definition	Effect estimate recurrence, RR (95% CI)	Effect estimate major adverse events, RR (95% CI)
Badalamente et al[7] (2002)	IIA, 49; IIB, 80	CCH *vs* placebo; IIA, single dose *vs* placebo; IIB, dose response	12 mths	Clinical success*	IIA: all joints: 9.12 (2.38 to 35.01), p = 0.001	IIB: Dose response, 10 000 *vs* 5000 *vs* 2500 U injected	10 000 U *vs* low dose, 1.65 (1.12 to 2.44), p = 0.012	Not reported	Not reported for blind phase	No major adverse events reported
Badalamente and Hurst[8] (2007)	33	CCH *vs* placebo	12 mths DB and 12 mths OL	Clinical success*	CCH *vs* placebo, 23.29 (1.53 to 354.09), p = 0.023			Increase in joint contracture > 20°	Not reported recurrence rate for follow-up for the double-blinded phase only	No major adverse events reported
Hurst et al[9] (2009)	308	CCH *vs* placebo	90 days	Clinical success*	CCH *vs* placebo, 9.42 (4.48 to 19.40), p < 0.0001	Clinical improvement at 30 days†	CCH *vs* placebo, 7.27 (4.26 to 12.42), p < 0.0001	Increase in joint contracture > 20°	No recurrence reported at 90 days	CCH *vs* placebo, 5.09 (1.21 to 21.399), p = 0.026
Gilpin[12] (2010)	66	CCH *vs* placebo	90 days DB and 12 mths OL	Clinical success*	CCH *vs* placebo, 12.00 (1.73 to 83.02), p = 0.012	Clinical improvement at 30 days†	CCH *vs* placebo, 5.44 (1.89 to 15.70), p = 0.002	Increase in joint contracture > 20°	No recurrence at 90 days or 12 mths	CCH *vs* placebo at 90 days, 1.44 (0.06 to 33.82), p = 0.82

*Clinical success: reduction in contracture to < 5° extension at 30 days
†Clinical improvement: reduction of contracture > 50% of baseline 30 days following last injection
RR, relative risk; CI, confidence interval; CCH, collagenase clostridium histolyticum; DB, double-blinded; OL, open-label

correction: 87% compared with 64% (p = 0.003). No major adverse events were reported. The rate of recurrence was not reported for either group. In a subsequent follow-up of the same cohort, including 44 patients with a follow-up of between seven and 53 months, TA injections was associated with better correction (TAED) up to 24 months, but this difference did not persist over time.[25] They also noted a higher rate of further treatment in patients without adjuvant steroid injections up to 24 months; however, this was not present at 36 months.

Collagenase clostridium histolyticum (CCH) *versus* placebo. Four RCTs compared CCH injections with placebo (Table III), using a contracture of > 20° in at least one joint in one finger as the inclusion criterion. Collectively, they showed an improvement in correction to < 5° of extension for CCH injections compared with saline injections.[7-9,12] Hurst et al[9] and Gilpin et al[12] also recorded an increased relative risk for clinical improvement, defined as a reduction in the contracture by > 50%, for CCH compared with saline (p = 0.002 and p < 0.001, respectively). No recurrences were reported at 90 days in either study. Badalamente et al[7] reported a rate of recurrence in four of 34 metacarpophalangeal (MP) joints at four years, and four of ten proximal interphalangeal (PIP) joints at 3.8 years in previously successfully treated joints, representing a total recurrence rate of 21%. Minor transient and self-limiting adverse events, most commonly injection-related, are frequent following CCH treatment.[7-9,12] Hurst et al[9] reported three serious adverse events, in 204 patients treated with CCH, while Gilpin et al[12] reported one major adverse event in 45 patients.

CCH injection and the timing of manipulation. In the protocols for CCH injections used by Hurst et al,[9] the cords were manipulated on the day after the injection. Mickelson et al[27] compared manipulation on the first day compared with the seventh day after injection and found no difference in the outcomes, (defined as success with extension deficit < 5°, RR, 1.05, 95% CI 0.68 to 1.62; p = 0.84). In addition, there was no difference in RR for skin tears between manipulation at these two times (RR 0.73, 95% CI 0.31 to 1.71; p = 0.47). Kaplan et al[28] compared manipulation on the first, second, and fourth days, and noted no differences between manipulation on the first day or delayed (the second or fourth days) at 30 days' follow-up, (RR 1.1, 95% CI 0.87 to 1.41; p = 0.40). The timing of

Table IV. Collagenase injection treatment *versus* percutaneous needle fasciectomy (PNF)

Author (year)	n	Comparison	Follow-up	Primary outcome	Effect estimate outcome, RR (95% CI)	Secondary outcome	Effect estimate secondary outcome, RR (95% CI)	Recurrence definition	Effect estimate recurrence, RR (95% CI)	Effect estimate major adverse events, RR (95% CI)
Scherman et al[31] (2016)	93	CCH *vs* PNF	12 mths	Total extension deficit	Incidence not reported	QuickDASH, URAM score	Incidence not reported	Increase in joint contracture > 20	CCH *vs* PNF, 0.86 (0.25 to 2.98), p = 0.81	CCH *vs* PNF, 2.15 (0.70 to 6.59), p = 0.18
Strömberg et al[30] (2016)	140	CCH *vs* PNF	1 yr	Contracture correction	CCH *vs* PNF, 0.98 (0.87 to 1.10), p = 0.74	URAM, patient satisfaction	Incidence not reported	Increase in joint contracture > 20	CCH *vs* PNF, 1.06 (0.07 to 16.6), p = 0.97	CCH *vs* PNF, 4.67 (2.97 to 7.32), p < 0.001
Skov et al[32] (2017)	50	CCH *vs PNF*	2 yrs	Clinical improvement*	CCH *vs* PNF, 0.24 (0.06 to 1.16), p = 0.08	DASH, clinical success†	Incidence not reported	Increase in joint contracture > 20	CCH *vs* PNF, 1.18 (0.85 to 1.65), p = 0.32	No major adverse event reported

*Clinical improvement: reduction of contracture > 50% of baseline
†Clinical success: < 5° passive extension deficit
RR, relative risk; CI, confidence interval; DASH, The Disability of the Arm, Shoulder and Hand questionnaire; URAM, Unité Rhumatologique des Affections de la Main; CCH, collagenase clostridium histolyticum

Table V. Adjunctive treatments with open fasciectomy

Author (year)	n	Comparison	Follow-up	Primary outcome	Effect estimate outcome, RR (95% CI)	Secondary outcome	Effect estimate secondary outcome, RR (95% CI)	Recurrence definition	Effect estimate recurrence, RR (95% CI)	Effect estimate major adverse events, RR 95% CI)
Citron and Nunez[19] (2005)	79	Type of incision, Bruner *vs* longitudinal	2 yrs	ROM	Incidence not reported			Any new nodules of disease in the operating field	Bruner *vs* longitudinal: 3.19 (1.01 to 10.09), p = 0.048	Bruner *vs* longitudinal: 1.26 (0.47 to 3.43), p = 0.65
Ullah et al[20] (2009)	79	Skin graft or not in fasciectomy	3 yrs	ROM	Incidence not reported	Grip strength	Incidence not reported	Not defined	Skin graft *vs* fasciectomy: 1.25 (0.41 to 3.82), p = 0.69	CRPS 1 per group: 1.03 (0.07 to 15.83), p = 0.99
Jerosch-Herold et al[21] (2011)	146	Postoperative night time splinting *vs* splinting on indication*	12 mths	DASH	Incidence not reported	Patient satisfaction	Incidence not reported	Not reported	Not reported	Not reported
Collis et al[24] (2013)	53	Extension orthoses or not following surgical release	3 mths	TAE	Incidence not reported	TAF, grip strength, and DASH	Incidence not reported	Not reported	Not reported	Not reported
Kemler et al[22] (2012)	54	Postoperative splinting and HT *vs* HT only following limited fasciectomy	12 mths	Extension deficit of the PIP joint	Incidence not reported	Patient-reported global perceived effect	Splinting and HT *vs* HT: 0.88 (0.61 to 1.26), p = 0.49	Not reported	Not reported	Splinting and HT *vs* HT only: 1.55 (0.75 to 3.04), p = 0.25
Degreef et al[26] (2014)	26	High-dose tamoxifen postoperatively fasciectomy compared with placebo	2 yrs	TAED	Incidence not reported	Patient satisfaction	Incidence not reported	Development of recurring contraction	Not reported	No major adverse events reported

*Development of contractures
RR, relative risk; CI, confidence interval; ROM, range of movement; CRPS, complex regional pain syndrome; DASH, The Disability of the Arm, Shoulder and Hand questionnaire; TAE, total active extension; TAF, total active flexion; PIP, proximal interphalangeal; HT, hand therapy; TAED, total active extension deficit

manipulation did not affect the ability to maintain the success until the 90th day (RR 1.10, 95% CI 0.85 to 1.43; p = 0.45).

CCH injection treatment *versus* percutaneous needle aponeurotomy. Three recently published Scandinavian studies have compared CCH treatment and PNA (Table IV). Scherman et al[31] followed 93 patients for 12 months and did not find any difference in total passive extension deficit between CCH treatment and PNA. Subjective outcomes as evaluated by QuickDASH[35] and Unité Rhumatologique des Affections de la Main (URAM)[36] score did not differ. Recurrence, defined as increase of joint contracture by > 20°, was similar in the two groups at 12 months (RR 2.15, 95% CI 0.70 to 6.59; p = 0.18). Strömberg et al[30] also found no difference in the correction of contractures, functional outcome assessed by the URAM score, and recurrence rate at one year. There was a significantly increased relative risk of adverse events in the CCH group (p < 0.001); however, most resolved without treatment, and no severe adverse events were noted.

Skov et al[32] reported, in a study involving 50 patients, an increased ability of PNA to maintain a reduction of contractures by > 50% at two years, although this did not reach statistical significance (RR 0.24, 95% CI 0.06 to 1.16; p = 0.08). DASH scores were low, regardless of the form of treatment, throughout the study. They also noted recurrence, as defined by a passive extension deficit of > 20°, in 20 of 24 patients (83%) treated with CCH and 13 of 19 patients (68%) treated with PNA at two years (RR 1.18, 95% CI 0.85 to 1.65; p = 0.32).

Adjunctive treatments with open fasciectomy. Given the risk of recurrence, several attempts have been made to improve the clinical outcome following open fasciectomy (Table V). Degreef et al[26] investigated the effects of a high dose of tamoxifen (80 mg/day) given from six weeks preoperatively to 12 weeks

following open fasciectomy in patients with a high risk of recurrence. They noted a significant improvement in the passive extension deficit ($p = 0.0176$) and patient satisfaction ($p = 0.0319$) with tamoxifen treatment, three months postoperatively. This gain was, however, lost at two years postoperatively.

Citron and Nunez[19] compared the efficacy of a modified Bruner incision with VY closure to a longitudinal incision with Z-plasty and found no difference in the primary outcome measure of range of movement (ROM) of the finger. The modified Brunner incision with VY closure resulted in an increased risk of recurrence, defined as any new nodule formation in the operative field (RR 3.19, 95% CI 1.01 to 10.09; $p = 0.048$). The rate of adverse events, including digital nerve injuries and algodystrophy, did not differ between the types of incision (RR 2.11, 95% CI 0.23 to 19.38; $p = 0.37$).

Another RCT studied the effects of wound closure with a Z-plasty compared with a dermatofasciectomy and full-thickness 'firebreak' skin graft after correction of the contracture.[20] The authors reported an overall recurrence rate of 12.2% at three years, with no difference between the groups.

Three RCTs have investigated the effect of postoperative night-time splinting or orthosis in addition to hand therapy following open fasciectomy, and neither showed an improvement in the functional outcome, range of movement, or recurrence rate.[21,22,24]

Discussion

This systematic literature review highlights the high level of heterogeneity among study designs and treatments in the management of Dupuytren's contracture. The results of CCH treatment have shown early promise but have not been superior to PNA. PNA shows good short-term results with a higher rate of satisfaction than limited open fasciectomy, but with a higher recurrence rate. Although adequate randomization and concealment of allocation reduces the risk of selection bias, inclusion and exclusion criteria of a study limit the generalizability of the results, as one particular presentation of the condition could be more suitable for one form of treatment rather than another. In addition, patient and surgeon preference, the skill of the surgeon, and the learning curves of the various forms of treatment should be considered when interpreting the clinical applicability of the data.[37]

In reviewing the literature, the definition of deformity and a threshold of range of movement to which an intervention is indicated, or beneficial, is not consistent. This variability of definitions must be considered when comparing the results, as differences in the severity of contracture may represent differences in resistance to treatment and may affect the recurrence rate.

The length of follow-up ranged from 30 days to five years, making comparison between studies difficult. It is thus not possible to compare outcomes, such as the ability to maintain the correction of contracture, rates of recurrence, and patient satisfaction, satisfactorily.

We confirmed that many different outcome measurements are used for the assessment of treatment of Dupuytren's contracture, as previously noted by others.[38,39] Range of movement (ROM), 'clinical success' (extension deficit of < 5°), clinical improvement (reduction of a contracture by > 50%), satisfaction, patient-reported outcome measurements (e.g. DASH, Michigan Hand Questionnaire, MHQ),[40] and recurrence rate (without agreement about the definition of recurrence) are frequently used as outcome parameters. Many of these are based on the evaluation of ROM, which can be difficult as the endpoint may be elastic, the angulation of the joint may rely on the applied force and the position of the adjacent joints may alter the measurements.[41,42]

The DASH questionnaire is commonly used to assess function in Dupuytren's contracture. However, its sensitivity and specificity may not be sufficient to monitor the functional limitations associated with this condition.[21,34,41] This may explain the tendency of low baseline DASH scores in patients with Dupuytren's contracture,[32,41,43] comparable with the normative values in the general population.[44] Thus, the minimal clinically important difference (MCID) of DASH[45] should be taken into account when assessing the outcome of treatment in these patients. Given these deficiencies, other hand-specific outcome measures such as the MHQ, URAM, and the Southampton Dupuytren's Scoring Scheme (SDSS)[46] may be more appropriate for monitoring the impairment related to this condition. The MHQ has been shown to be a reliable and valid tool to assess changes in these patients.[47] The URAM scale has been verified for the assessment of Dupuytren's contracture and has been shown to be a superior functional outcome measure compared with other tools and self-assessed disability, such as a visual analogue scale (VAS).[36] The SDSS quantifies functional impairment and has been shown to have better sensitivity than the Quick-DASH.[46] Future studies should consider using these Dupuytren's-specific outcome tools, as well as patient expectations and experiences, and regain of function, to assess the efficacy of different forms of treatment.[48]

In reviewing the literature, a consistent definition of recurrence does not exist, nor does a threshold for intervention following recurrence. These inconsistencies make meaningful comparisons between studies difficult. In addition, as the rate of recurrence usually increases after one year, follow-up should be at least two years.[31] In a prospective cohort study, including 644 patients who underwent CCH treatment, a cumulative recurrence rate of 47% of previously successfully treated joints at five years was reported,[49] 34% presenting within three years. Using the same definition of a successfully treated joint and recurrence, van Rijseen et al[11] reported a recurrence rate of 22% after PNA treatment and 5% after LF in previously successfully treated joints, at five years' follow-up. They also noted that recurrence appeared significantly sooner in patients treated with PNA. Skov et al[32] did not, at any time up to two years, find a difference in recurrence rate comparing treatment with PNA and CCH. However, previous authors have reported recurrence rates following LF ranging from 12% to 73% and

following PNA of 33% to 100%, reflecting the importance of the length of follow-up.[39,50]

Given the increasing focus on quality, the cost of care needs to be considered when deciding on treatment. For CCH, the cost of the drug and the number of injections needed to achieve an acceptable result, need to be considered. In contradistinction, the cost of PNA will include the cost of anaesthesia and operating theatre time if the procedure is not undertaken in the clinic. For limited fasciectomy, in addition to operating theatre time, details about hand therapy and time off work should be considered. Using a cost-utility analysis for a public healthcare system and accounting for the probability of complications such as complex regional pain syndrome and nerve injury, as well as recurrence, Baltzer et al[51] noted that PNA would be the preferred form of treatment. CCH would be feasible if the cost is < $475 for a complete series of injections.[52,53] LF was not shown to be cost-effective. Skov et al[32] reported inferior functional results of CCH compared with PNA at two years' follow-up, further reducing the cost-effectiveness of CCH.

Three recent RCTs showed a higher incidence of transient adverse events such as pruritus, swelling, skin rupture pain, and bruising in patients treated with CCH compared with PNA.[32] This finding has also been confirmed in a recent meta-analysis.[54] Peimer et al,[49] in a study involving 644 patients treated with CCH with follow-up of five years, reported only one persistent adverse event. Furthermore, a combined analysis of four clinical trials dealing with CCH treatment in 506 patients revealed six major adverse events, including two tendon ruptures.[55] LF has a higher incidence of nerve injuries, neuropraxia, arterial injuries, and complex regional pain syndrome than CCH.[56]

Postoperative splinting at night has not yet been shown to be beneficial for all patients in the management of this condition.[21,22,24,57] It may be useful for a select group of patients with early postoperative persistent contracture.[58] Splinting after manipulation has been part of the regimen following treatment with CCH.[9] To our knowledge, there are no comparative studies assessing the functional outcome after CCH treatment without night-time splinting. Thus, the efficacy of splinting after treatment needs further investigation to include the rate of compliance and which patients may benefit from this regimen.

Despite the increased numbers of recent RCTs, we were not able to identify a superior form of treatment for the management of Dupuytren's contracture. The results do not demonstrate a superior clinical outcome for patients treated with CCH compared with PNA.[30-32]

For future studies, information about preoperative evaluation, including the assessment of risk factors for recurrence, would be valuable. We favour the assessment of both pre- and postoperative total active and passive flexion and extension of the fingers. Outcome parameters should also include functional assessment as measured by more disease-specific tools, such as the URAM scale or the SDSS, in order to allow comparison between studies and increase the generalizability of the data. The definition of recurrence needs to be clarified and preferably reported at specific timepoints with follow-up of five years, to quantify the true rate of recurrence.

Take home message:

- There is a paucity of data to recommend one treatment outcome over another in the management of Dupuytren's disease.
- In the era of value-based healthcare, the long-term efficacy of collagenase compared with the other treatments needs further validation.

Supplementary material (available online)

The search strategy of Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus.

References

1. **Huang C, Ogawa R.** Fibroproliferative disorders and their mechanobiology. *Connect Tissue Res* 2012;53:187–196.
2. **Wolfe S, Pederson W, Kozin SH, Cohen M.** *Green's Operative Hand Surgery*. Two-Volume Set. Seventh ed. Philadelphia, PA: Elsevier, 2016.
3. **Worrell M.** Dupuytren's disease. *Orthopedics* 2012;35:52–60.
4. **Swartz WM, Lalonde DH.** MOC-PS(SM) CME article: Dupuytren's disease. *Plast Reconstr Surg* 2008;121(Suppl):1–10.
5. **Hueston JT.** Limited fasciectomy for Dupuytren's contracture. *Plast Reconstr Surg Transplant Bull* 1961;27:569–585.
6. **Chen NC, Srinivasan RC, Shauver MJ, Chung KC.** A systematic review of outcomes of fasciotomy, aponeurotomy, and collagenase treatments for Dupuytren's contracture. *Hand (N Y)* 2011;6:250–255.
7. **Badalamente MA, Hurst LC, Hentz VR.** Collagen as a clinical target: nonoperative treatment of Dupuytren's disease. *J Hand Surg Am* 2002;27:788–798.
8. **Badalamente MA, Hurst LC.** Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg Am* 2007;32:767–774.
9. **Hurst LC, Badalamente MA, Hentz VR, et al.** Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med* 2009;361:968–979.
10. **van Rijssen AL, Gerbrandy FSJ, ter Linden H, Klip H, Werker PMN.** A comparison of the direct outcomes of percutaneous needle fasciotomy and limited fasciectomy for Dupuytren's disease: a 6-week follow-up study. *J Hand Surg Am* 2006;31:717–725.
11. **van Rijssen AL, ter Linden H, Werker PMN.** Five-year results of a randomized clinical trial on treatment in Dupuytren's disease: percutaneous needle fasciotomy versus limited fasciectomy. *Plast Reconstr Surg* 2012;129:469–477.
12. **Gilpin D, Coleman S, Hall S, et al.** Injectable collagenase Clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. *J Hand Surg Am* 2010;35:2027–2038.
13. **Higgins JP, Altman DG, Gøtzsche PC, et al.** The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:5928.
14. **Bulstrode NW, Bisson M, Jemec B, et al.** A prospective randomised clinical trial of the intra-operative use of 5-fluorouracil on the outcome of dupuytren's disease. *J Hand Surg Br* 2004;29:18–21.
15. **Seegenschmiedt MH, Olschewski T, Guntrum F.** Radiotherapy optimization in early-stage Dupuytren's contracture: first results of a randomized clinical study. *Int J Radiat Oncol Biol Phys* 2001;49:785–798.
16. **Kaplan FT, Badalamente MA, Hurst LC, Merrell GA, Pahk R.** Delayed manipulation following clostridial collagenase histolyticum injection for Dupuytren contracture. *Hand (N Y)* 2013;10:52–53.
17. **Bhatia R, Blackshaw G, Barr V, Savage R.** Comparative study of "staples versus sutures" in skin closure following Dupuytren's surgery. *J Hand Surg Br* 2002;27:53–54.
18. **Howard K, Simison AJ, Morris A, Bhalaik V.** A prospective randomised trial of absorbable versus non-absorbable sutures for wound closure after fasciectomy for Dupuytren's contracture. *J Hand Surg Eur Vol* 2009;34:618–620.
19. **Citron ND, Nunez V.** Recurrence after surgery for Dupuytren's disease: a randomized trial of two skin incisions. *J Hand Surg Br* 2005;30:563–566.
20. **Ullah AS, Dias JJ, Bhowal B.** Does a 'firebreak' full-thickness skin graft prevent recurrence after surgery for Dupuytren's contracture?: a prospective, randomised trial. *J Bone Joint Surg [Br]* 2009;91-B:374–378.

21. **Jerosch-Herold C, Shepstone L, Chojnowski AJ, et al.** Night-time splinting after fasciectomy or dermo-fasciectomy for Dupuytren's contracture: a pragmatic, multi-centre, randomised controlled trial. *BMC Musculoskelet Disord* 2011;12:136.
22. **Kemler MA, Houpt P, van der Horst CM.** A pilot study assessing the effectiveness of postoperative splinting after limited fasciectomy for Dupuytren's disease. *J Hand Surg Eur Vol* 2012;37:733–737.
23. **McMillan C, Binhammer P.** Steroid injection and needle aponeurotomy for Dupuytren contracture: a randomized, controlled study. *J Hand Surg Am* 2012;37:1307–1312.
24. **Collis J, Collocott S, Hing W, Kelly E.** The effect of night extension orthoses following surgical release of Dupuytren contracture: a single-center, randomized, controlled trial. *J Hand Surg Am* 2013;38:1285–1294.
25. **McMillan C, Binhammer P.** Steroid injection and needle aponeurotomy for Dupuytren disease: long-term follow-up of a randomized controlled trial. *J Hand Surg Am* 2014;39:1942–1947.
26. **Degreef I, Tejpar S, Sciot R, De Smet L.** High-dosage tamoxifen as neoadjuvant treatment in minimally invasive surgery for Dupuytren disease in patients with a strong predisposition toward fibrosis: a randomized controlled trial. *J Bone Joint Surg [Am]* 2014;96-A:655–662.
27. **Mickelson DT, Noland SS, Watt AJ, et al.** Prospective randomized controlled trial comparing 1- versus 7-day manipulation following collagenase injection for dupuytren contracture. *J Hand Surg Am* 2014;39:1933–1941.
28. **Kaplan FTD, Badalamente MA, Hurst LC, Merrell GA, Pahk R.** Delayed manipulation after collagenase clostridium histolyticum injection for Dupuytren contracture. *Hand (N Y)* 2015;10:578–582.
29. **Kan HJ, Selles RW, van Nieuwenhoven CA, et al.** Percutaneous aponeurotomy and lipofilling (PALF) versus limited fasciectomy in patients with primary dupuytren's contracture: a prospective, randomized, controlled trial. *Plast Reconstr Surg* 2016;137:1800–1812.
30. **Strömberg J, Ibensen-Sörensen A, Fridén J.** Comparison of treatment outcome after collagenase and needle fasciotomy for Dupuytren contracture: A randomized, single-blinded, clinical trial with a 1-year follow-up. *J Hand Surg Am* 2016;41:873–880.
31. **Scherman P, Jenmalm P, Dahlin LB.** One-year results of needle fasciotomy and collagenase injection in treatment of Dupuytren's contracture: A two-centre prospective randomized clinical trial. *J Hand Surg Eur Vol* 2016;41:577–582.
32. **Skov ST, Bisgaard T, Sondergaard P, Lange J.** Injectable collagenase versus percutaneous needle fasciotomy for Dupuytren contracture in proximal interphalangeal joints: a randomized controlled trial. *J Hand Surg Am* 2017;42:321–328.
33. **Benkhadra K, Wang Z, Murad MH.** Network meta-analysis: introduction and an example that compares devices for PFO closure. *Eur Heart J* 2015;36:80–82.
34. **Hudak PL, Amadio PC, Bombardier C, et al.** Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. *Am J Ind Med* 1996;29:602–608.
35. **Beaton DE, Wright JG, Katz JN, Upper Extremity Collaborative Group.** Development of the QuickDASH: comparison of three item-reduction approaches. *J Bone Joint Surg [Am]* 2005;87:1038–1046.
36. **Beaudreuil J, Allard A, Zerkak D, et al.** Unité Rhumatologique des Affections de la Main (URAM) scale: development and validation of a tool to assess Dupuytren's disease-specific disability. *Arthritis Care Res* 2011;63:1448–1455.
37. **Warwick D.** Dupuytren's disease: my personal view. *J Hand Surg Eur Vol* 2017;42:665–672.
38. **Akhavani MA, McMurtrie A, Webb M, Muir L.** A review of the classification of Dupuytren's disease. *J Hand Surg Eur Vol* 2015;40:155–165.
39. **Becker GW, Davis TR.** The outcome of surgical treatments for primary Dupuytren's disease—a systematic review. *J Hand Surg Eur Vol* 2010;35:623–626.
40. **Chung KC, Pillsbury MS, Walters MR, Hayward RA.** Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. *J Hand Surg Am* 1998;23:575–587.
41. **Ball C, Pratt AL, Nanchahal J.** Optimal functional outcome measures for assessing treatment for Dupuytren's disease: a systematic review and recommendations for future practice. *BMC Musculoskelet Disord* 2013;14:131.
42. **Eaton C.** Evidence-based medicine: Dupuytren contracture. *Plast Reconstr Surg* 2014;133:1241–1251.
43. **Engstrand C, Krevers B, Nylander G, Kvist J.** Hand function and quality of life before and after fasciectomy for Dupuytren contracture. *J Hand Surg Am* 2014;39:1333–1343.
44. **Hunsaker FG, Cioffi DA, Amadio PC, Wright JG, Caughlin B.** The American academy of orthopaedic surgeons outcomes instruments: normative values from the general population. *J Bone Joint Surg [Am]* 2002;84-A:208–215.
45. **Voineskos SH, Coroneos CJ, Thoma A, Bhandari M.** Measuring and understanding treatment effectiveness in hand surgery. *Hand Clin* 2014;30:285–292.
46. **Mohan A, Vadher J, Ismail H, Warwick D.** The Southampton Dupuytren's Scoring Scheme. *J Plast Surg Hand Surg* 2014;48:28–33.
47. **Thoma A, Kaur MN, Ignacy TA, et al.** Psychometric properties of health-related quality of life instruments in patients undergoing palmar fasciectomy for dupuytren's disease: a prospective study. *Hand (N Y)* 2014;9:166–174.
48. **Bernabé B, Lasbleiz S, Gerber RA, et al.** URAM scale for functional assessment in Dupuytren's disease: a comparative study of its properties. *Joint Bone Spine* 2014;81:441–444.
49. **Peimer CA, Blazar P, Coleman S, et al.** Dupuytren contracture recurrence following treatment with collagenase clostridium histolyticum (CORDLESS [Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study]): 5-year data. *J Hand Surg Am* 2015;40:1597–1605.
50. **Werker PM, Pess GM, van Rijssen AL, Denkler K.** Correction of contracture and recurrence rates of Dupuytren contracture following invasive treatment: the importance of clear definitions. *J Hand Surg Am* 2012;37:2095–2105.
51. **Baltzer H, Binhammer PA.** Cost-effectiveness in the management of Dupuytren's contracture. A Canadian cost-utility analysis of current and future management strategies. *Bone Joint J* 2013;95-B:1094–1100.
52. **Brazzelli M, Cruickshank M, Tassie E, et al.** Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. *Health Technol Assess* 2015;19:1–202.
53. **Chen NC, Shauver MJ, Chung KC.** Cost-effectiveness of open partial fasciectomy, needle aponeurotomy, and collagenase injection for dupuytren contracture. *J Hand Surg Am* 2011;36:1826–1834.
54. **Sanjuan-Cerveró R, Carrera-Hueso FJ, Vazquez-Ferreiro P, Ramon-Barrios MA.** Efficacy and adverse effects of collagenase use in the treatment of Dupuytren's disease: a meta-analysis. *Bone Joint J* 2018;100-B:73–80.
55. **Badalamente MA, Hurst LC, Benhaim P, Cohen BM.** Efficacy and safety of collagenase clostridium histolyticum in the treatment of proximal interphalangeal joints in dupuytren contracture: combined analysis of 4 phase 3 clinical trials. *J Hand Surg Am* 2015;40:975–983.
56. **Peimer CA, Wilbrand S, Gerber RA, Chapman D, Szczypa PP.** Safety and tolerability of collagenase Clostridium histolyticum and fasciectomy for Dupuytren's contracture. *J Hand Surg Eur Vol* 2015;40:141–149.
57. **Jerosch-Herold C, Shepstone L, Chojnowski AJ, Larson D.** Splinting after contracture release for Dupuytren's contracture (SCoRD): protocol of a pragmatic, multi-centre, randomized controlled trial. *BMC Musculoskelet Disord* 2008;9:62.
58. **Larson D, Jerosch-Herold C.** Clinical effectiveness of post-operative splinting after surgical release of Dupuytren's contracture: a systematic review. *BMC Musculoskelet Disord* 2008;9:104.

Author contributions:

E. Soreide: Designing the study, Literature search, Reviewing and critically appraising the literature, Statistical analysis, Interpreting the data, Preparing, critically revising, and approving the manuscript.

M. H. Murad: Reviewing and critically appraising the literature, Statistical analysis, Interpreting the data, Revising and approving the manuscript.

J. M. Denbeigh: Critically appraising the literature, Statistical analysis, Critically revising and approving the manuscript.

E. A. Lewallen: Critically appraising the literature, Statistical analysis, Critically revising and approving the manuscript.

A. Dudakovic: Critically appraising the literature, Critically revising and approving the manuscript.

L. Nordsletten: Designing the study, Statistical analysis, Interpreting the data, Critically revising and approving the manuscript.

A. J. van Wijnen: Designing the study, Interpreting the data, Critically revising and approving the manuscript.

S. Kakar: Designing the study, Literature search, Reviewing and critically appraising the literature, Statistical analysis, Interpreting the data, Preparing, critically revising, and approving the manuscript.

Funding statement:

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Acknowledgement:

We would like to express our appreciation to Larry Prokop for providing valuable assistance in setting up and conducting the extensive search of the literature.

This article was primary edited by J. Scott.