Current concepts in Dupuytren's disease

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Abstract The last few years have seen a number of significant studies in Dupuytren's disease that may result in a paradigm shift in the management of this condition. This review article assesses recent therapeutic studies from January 2010 to August 2012. These were rated for levels of evidence, trial quality using the Jadad and Detsky scales, and graded by strength of recommendation. Significant studies include the success of Phase III trials of injectable collagenase (CORD I and II), that may radically alter the practice of Dupuytren's. Other highlights include randomized controlled trials that address the ongoing debate on needle fasciotomy vs limited fasciectomy, and also the utility of night-time post-operative splinting. Furthermore, the concept of "clinically important differences" in Dupuytren's outcomes research is considered in the context of the CORD I trial. The implications of these studies for current practice and future research are discussed.

Keywords Dupuytren's · Randomized trials · Quality

Introduction

This article focuses specifically on advances in the understanding of the pathophysiology and management of Dupuytren's disease that have been published in the last 2½ years, and presupposes background knowledge of the condition. It is therefore intended as a review of current concepts only, rather than as a general overview of the

condition, of which there are a multitude of such articles. A limited systematic review of this nature is required to update the reader on rapidly evolving research and novel techniques in Dupuytren's, that may not be yet incorporated into national guidelines, and for which consensus opinion has yet to be established. Furthermore, to limit personal bias in the analysis of these trials, established criteria for levels of evidence and quality scoring systems have been used.

A number of significant studies have been published in recent years, which may result in a paradigm shift in the management of Dupuytren's disease. Foremost of these are the Phase III Trials of injectable collagenase in the CORD 1 and 2 studies, which may well radically alter the management of Dupuytren's disease. Other highlights include randomized controlled trials that address the ongoing debate on needle fasciotomy vs limited fasciectomy, and also the utility of night-time post-operative splinting. Furthermore, the concept of "clinically important differences" with respect to Dupuytren's outcome research is considered in the context of the CORD I Trial Results.

Literature search

Method

Pubmed/Medline search using the terms Dupuytren contracture/ Dupuytren's disease retrieved 184 articles. Inclusion criteria included meta-analyses, randomized controlled trials, comparative cohort, and single cohort studies (Level I to IV evidence) in the last 2.5 years (January 2010 - August 2012). Scope of articles was limited to therapeutic clinical studies, and excluded epidemiological, basic science, and economic analyses. Levels of evidence were rated according to the criteria from the JBJS [1], quality of RCTs assessed using the Jadad and Detsky quality scales [2, 3], and grades of recommendation for therapeutic trials rated according to Harbour et al. [4].

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Results

Level I and II evidence

7 articles labeled as randomized controlled trials were retrieved - 4 of these were original RCTs whilst 3 were secondary analyses of previously published RCTs. The average Jadad score was 3.5 with most trials failing the double-blind scoring element. A score of 3 or more is broadly regarded as a high quality trial. The average transformed Detsky quality score was 79 % (Table 1). Problems identified included; inconsistent blinding of assessment, a failure to describe un-enrolled patients (rather than exclusion criteria), and a lack of A-priori power analysis. High quality trials are those given a Detsky quality score of greater than 75 %, a result that was achieved by 2 of the published studies, with a further 2 trials scored at 75 % exactly [5]. This compares favorably with the quality of trials in aesthetic surgery (11 RCTs in 4 years, 68 % score) and orthopaedic surgery (43 RCTs in 12 years, 68 % score) [5, 6].

Level III evidence

Two comparative studies were retrieved, 1 concerning the economic analysis of techniques (not discussed [7]), and the other concerning the use of cellulose in segmental fasciectomy [8].

Level IV evidence

Eleven therapeutic single cohort studies were identified, but are not discussed further in this article. Most of these concerned techniques on which data has been previously published such as needle fasciotomy and external fixator devices [9–11], although there are also some novel techniques such as lipofilling in needle fasciotomy [12]. However, without comparison with a control group these more novel techniques should be considered preliminary in nature. It has been well demonstrated that non-randomized trials are significantly more likely to show that novel treatments are superior to traditional treatments [13].

Outcomes research

Difficulties in interpretation of outcome studies

There are a number of problems with outcome measurements in Dupuytren's disease. Most studies use 2 forms of outcome assessment, first - objective clinical measurements of contractures, and second - functional assessment scales such as the DASH score. Heterogeneity of these outcome

measurements, and a lack of consensus on definitions of endpoints such as “success” and “recurrence”, often make valid comparison of different trials impossible.

Problems with objective outcome measurements

Most trials use the terms “passive extension deficit” when referring to true extension deficit, and “active extension deficit” when referring to extensor lag. All such measurements are prone to user bias as it is often impossible to blind rater measurements, for example when comparing non-surgical and surgical treatments where scars are typically obvious. Only 1 out of the 4 RCTs studied in this article had appropriate blinding of user measurements.

Some caution should be applied to the interpretation of results reflecting active mobility, for example active extension deficit may be compromised in cases with advanced contractures due to secondary attenuation of the extensor central slip. For this reason assessment of active and passive ranges of motion may provide a better insight in to the effects of treatment for Dupuytren's disease. We would therefore suggest that trials utilize goniometer based, blinded, and independent measurements of the active and passive extension deficit. Goniometer measured extension deficits have a high degree of inter-rater reliability (intra-class co-efficient 0.83–0.97) and low standard error of the mean (<3 degrees) [14].

The degree of extension deficit may be quantified in degrees of motion or with the use of grading systems such as described by Tubiana [15]. However, in using grading systems there is inevitably loss of data when converting from an exact measure to a limited range, and therefore a reduction in sensitivity. For example, a pre-operative PIPJ contracture of 40 degrees and post-operative of 0 degrees, are both Tubiana Grade 1 (defined as a total extensor deficit of 0 to 45 degrees). Furthermore, grading systems may create artificial statistical boundaries (eg, Grade 1 vs Grade 2). The use of statistical methods on the raw data in degrees is a more valid method of analysis.

Definitions of endpoints: “successful outcomes” and “recurrence”

“Successful endpoints” often differ between studies, making valid comparisons about “success” difficult. Some use Tubiana Grade 1 as a successful endpoint [12], whilst others use a more exact measurement such as that employed in the CORD studies - “a reduction in primary joint contracture (MCP or PIPJ) to 0 to 5 degrees of normal” [16•]. An additional difficulty in comparing studies on Dupuytren's disease is the difference in definitions of “recurrence” [17•]. Historical definitions are insufficiently exact to be used in clinical trials, with McFarlane and McGrouther

Table 1 Average Detsky Quality Score of RCTs in Dupuytren's disease 2010–2012

Category	Subcategory	Average transformed score	Comments
Randomization	Randomly assigned	100 %	
	Method randomization	87.5 %	Only partial description of randomization in 1 trial
	Concealment of randomization	75 %	
Outcomes	Criteria of outcome measurements	100 %	
	Objective outcome measurements	100 %	
	Blinding of assessment	25 %	No blinding of assessor or not stated in 3 trials
Patient Eligibility	Inclusion/exclusion criteria	87.5 %	
	Unenrolled patients described (eg, not eligible)	0 %	Patient numbers not enrolled or not eligible to enter, is not mentioned in any study
Therapy and control groups	Therapeutic treatment described	100 %	
	Control treatment described	87.5 %	Control group only partially described in 1 trial
Statistics	Test stated	100 %	
	<i>P</i> values	100 %	
	Appropriate analysis	100 %	
	Power analysis	50 %	In 1 trial the description of power analysis is incomplete
Total		79 %	Overall the scores are above 75 %, considered high quality

stating that it is “*recurrent joint contracture sufficient to require further operation*” and Hueston defining it as “*the appearance of new Dupuytren's tissue within the area previously cleared at operation*”. More exact definitions include those used by Van Rijssen et al. who define recurrence as a total passive extension deficit of 30 degrees [17••]. However, this definition fails to distinguish recurrence within a previously treated joint, as it may inadvertently include “recurrence” when the contracture occurs in another previously unaffected joint. Hurst and Badalamente therefore defined recurrence in the CORD 1 Trial as a return of *joint specific* contracture of greater than 20° in a previously successfully treated joint (ie, released to 0–5° from normal) [16••].

These differences in measurements of endpoints serves to highlight the difficulty in making valid comparisons of outcomes in single cohort studies. Furthermore, as PIPJ or MCPJ disease may have differing clinical courses and implications, measurements should be applied in a joint-specific manner rather than on total range of motion. The definitions developed and used in the CORD trials are the most exact in the literature, are joint-specific, less prone to bias, and are advocated for use in future studies.

Functional outcome measurements analyses

The second form of outcome measure used in many studies is the functional assessment scale, such as the DASH score. Although these have been clinically validated, they pose a number of problems in relation to Dupuytren's disease. First, studies suggest that they do not necessarily correlate with disease severity, and second, their relevance to patient

reported outcomes is questionable. The latter problem has been addressed recently using the concept of the “Clinically Important Difference” (CID) in disease states. This concept attempts to correlate objective measurements such as contracture angle, with subjective measures of patient outcomes, such as perceived benefit or satisfaction. It therefore gives the patient tangible answers to previously abstract concepts such as contracture angle.

Utility of the DASH score

Study: Jerosch-Herold et al. 2011 [18]

Summary: This study was a secondary analysis of a RCT, which demonstrated that the DASH score has none, or a very weak association with flexion contractures of the digits. The correlation between Total Range of Motion (using active extension deficit) and the DASH score was studied in 154 patients undergoing limited or dermo-fasciectomy. They found a statistically significant but weak positive correlation between range of motion and DASH score in the index, middle, and ring fingers ($r=0.21$ to 0.28 , $P=0.01$ to 0.001). Interestingly, no significant correlation was found for the little finger, which had the greatest degree of flexion contracture ($r=0.07$, $P=0.41$). Other trials on the DASH score have also demonstrated a weak or absent correlation with flexion contracture [19, 20]. Reasons for the lack of utility of the DASH score are that it is not disease-specific and excludes many of the tasks that Dupuytren's patients have difficulty with, such as putting on gloves and shaking hands. Also the DASH score emphasizes tripod grip rather than ulnar sided

grip, with tasks such as writing and turning a key. This may explain the greater degree of correlation with the radial sided digits in Dupuytren's, and absence of correlation with the little finger [18]. The same research group has also found no correlation of extension deficit with the Quick DASH score, an abbreviated version of the DASH [21].

Recommendation: The DASH score cannot be used as a reliable comparator between trials on Dupuytren's due to its weak or absent correlation with objective measures of flexion contracture. Alternative functional outcome scales should be considered.

Level of Evidence: Original trial II, secondary analysis IV.

“Clinically important differences” in Dupuytren's

Study: Witthaut et al. 2011 [22•]

Summary: This study was a secondary analysis of the 308 patients enrolled in the CORD I trial, and is one of the first to meaningfully assess the concept of the “Clinically Important Difference”. This study had 2 main aims. First, to correlate meaningful changes in patient's perceptions of their condition (ie, mild, moderate, good improvements) with the corresponding changes in contracture angle. Second, to determine what is a clinically important baseline level of contracture at which intervention is necessary from a patient's perspective. This study was performed by regression modeling of patient reported outcomes with objective measures such as the contracture angle. The results suggested that the minimum “Clinically Important Difference” in contracture angle for a patient to perceive a benefit was 13.5 degrees. This equates to a 33.3 % patient reported improvement, and also an improvement in physician ratings of disease severity (see Table 2). The baseline level of contracture at which patients felt intervention was necessary was a ROM of less than 54 degrees (“normal” corresponded to a ROM of >67, “mild” 54–67, “moderate” 41.6–54.3 and “severe” <46 degrees).

Recommendation: This study suggests that a 13.5 degree post-operative correction is the minimum “Clinically

Important Difference”, ie, the minimum required for patients to perceive a functional benefit. It also suggests that from a patient's perspective, the minimum baseline level of contracture that requires intervention is equivalent to a ROM<54 degrees. These findings have particularly important implications for patient counseling, as they convert rather abstract notions for the patient into more tangible expressions (ie, “27 degrees straighter means that you will be much improved”), and may establish the baseline level of contracture that warrants intervention from a patient's rather than physician's view.

Level of Evidence: Original study I, secondary analysis IV

Surgical trials

Only Level I to III evidence from 2010–2012 is presented here and the quality of these trials is assessed with the Jadad and Detsky Quality Scales where applicable. Only 1 surgical RCT was noted in this time period.

Needle aponeurotomy vs limited fasciectomy

Study: Van Rijssen et al. 2012, University Medical Centre Groningen, Netherlands [17]

Summary: This was a prospective randomized controlled trial of needle fasciotomy vs limited fasciectomy in 111 patients with a 5-year follow-up. Patients with a total passive extension deficit of greater than 30 degrees in a single ray were included. The Abe diathesis score was assessed for each patient pre-operatively. 84 % completed follow-up. The primary endpoint in this study was recurrence, defined as an increase in total passive extension deficit of more than 30 degrees (in comparison to the 6 week post-operative measurements). They also analyzed post-operative success rates using the endpoints defined by the CORD 1 study (correction of individual joint contracture to within 0 degrees to 5 degrees of normal). This indicated that the initial success rates for the MCP joint were 94 % for limited fasciectomy and 55 % for needle fasciotomy, and for the PIP joint were 47 % and 26 % respectively. Satisfaction scores were also assessed using their own scoring system. The results of this study suggested that limited fasciectomy group had a significantly lower recurrence rate at 5 years (20.9 %) compared with the needle fasciotomy group (84.9 %, $P<0.001$). Furthermore, recurrences in the needle fasciotomy group occurred significantly earlier than for limited fasciectomy ($P=0.001$). The Abe diathesis score did not correlate with an increased risk of recurrence with either technique. Interestingly, older age groups were also associated with a decreased risk of recurrence with both

Table 2 “Clinically important difference” in Dupuytren's: correlation of objective measures of contracture with patient and physician reported subjective outcomes

Correction of contracture in degrees	Patient rated improvement	Physician rating improvement
<13.5	0 %	None
13.5–27	33 %	Minimal improvement
27–43.5	66 %	Much improved
>43.5	100 %	Very much improved

techniques. Patient satisfaction was significantly higher in the limited fasciectomy group compared with needle fasciotomy ($P<0.001$).

Validity: This randomized controlled trial was well designed with a long follow-up period. However, blinding of measurements is not clear from this study, with surgical scars possibly making it obvious to the assessor what form of treatment has been performed.

Jadad Score: 3/5 not double blind.

Detsky score: 75 % (borderline high quality trial). Main methodological limitations included lack of blinding, description of unenrolled patients, and power analysis.

Recommendation: The level of evidence and quality of this trial supersedes that of other previous single cohort studies in the literature, and provides the best evidence that limited fasciectomy is superior to needle fasciotomy, when recurrence and initial success of contracture release are used as clinical endpoints. However, these are not the only considerations when evaluating treatment options, and complication rates and time off work need to be factored into the evaluation. This study also suggests that needle fasciotomy may have a more significant role in the older patient group who may have a lower long-term recurrence rate.

Level of Evidence: II

Strength of recommendation: B

Trials on adjuncts to surgery

3 trials of level I-III evidence were included from 2010–2012, on the adjunctive use of steroid injection, night-time splinting, and cellulose implants.

Needle fasciotomy with or without steroids

Study: McMillan et al. 2012, Sunnybrook Health Science Centre, Toronto [23]

Summary: 47 patients undergoing needle fasciotomy were randomized to steroids or no steroids treatment arms. Steroids were given as an injection immediately at time of surgery (8–48 mg per digit), and at 6 weeks and 3 months after surgery, with follow-up for a total of 6 months. No placebo injections were used in the control group, and therefore this study was not adequately controlled or blinded. Change in total active extension deficit (TAED) compared with pre-operative baseline was used as the primary outcome measure. Results indicated that correction of contractures was statistically significantly better in the steroid injection group at 3 months post-operative (87 % steroid group vs 64 % no steroids, $P=0.003$). No complications were reported in either group.

Validity: The authors note that the short term follow-up of only 6 months may not reflect changes in the ongoing pathofibrosis of Dupuytren's. Longer follow-up would be required to confirm this as a valid adjunct to surgery. Furthermore, no blinding was performed, with all surgery, injections and measurements performed by a single operator, thereby providing a source of potential bias.

Jadad score: 3/5, not double blind.

Detsky score: 75 % (borderline high quality trial). Main methodological limitations included lack of blinding of assessment, control group, description of unenrolled patients, and power analysis.

Recommendation: Steroids may be of benefit as a post-operative adjunct to needle fasciotomy to minimize early recurrence at 3 months. There are some methodological concerns regarding these outcomes and further studies would be suggested before recommending steroids as an adjunctive treatment.

Level of Evidence: II

Strength of Recommendation: B

Postoperative nocturnal splinting after limited or dermo-fasciectomy

Study: Jerosch-Herold et al. 2011, University of East Anglia, UK [24]

Summary: 154 patients were enrolled into a multi-center randomized trial of nocturnal splint (77 patients) vs no splintage groups (69 patients). The nocturnal splints were worn for 6 months, whilst the no splintage group underwent hand therapy alone. However, splintage could be used as a 'per protocol' deviation if recurrent contractures occurred within the study period, defined as a 15-degree loss at the PIPJ and 20-degree loss at the MCPJ (13 patients "per protocol" deviation). Outcome measures were measured at 1 year follow-up on an "intention to treat" basis, using the DASH score, total active extension deficit, and patient satisfaction. Results indicated that there was no statistical difference at 1-year follow-up between the 2 groups for DASH score, total active extension deficit (Splint group 33 degrees, no splint 30 degrees, $P=0.17$) or patient satisfaction.

Validity: Randomized controlled trial with appropriate methodology including power analysis.

Jadad: 3/5, not double blind.

Detsky: 80 % - high quality trial. Few methodological limitations included lack of blinding, and no description of unenrolled patients.

Recommendation: The efficacy of routine post-operative night splinting has not been demonstrated. Night splinting therefore does not need to be performed on a routine basis post-operatively, with early recurrent contractures treated on a reactive basis with splinting.

Level of Evidence: II

Strength of recommendation: B

Cellulose implants in segmental fasciectomy

Study: Degreef et al. 2011, University Hospitals Leuven, Belgium [8]

Summary: Single center, prospective case control study involving 29 patients, 15 received a cellulose implant, and 14 without. Segmental fasciectomy was performed and a commercially available cellulose implant was interposed in the residual space. All patients were fully corrected after surgery with full extension. Outcomes at 3 months indicated that the cellulose implant group performed significantly better than the group without cellulose. Total extension deficit was 12 degrees and 38 degrees respectively ($P<0.0001$).

Validity: This study uses a pseudo case-control technique, without true matching of patients. Blinding of assessment is not clearly explained in this paper.

Jadad and Detsky scores: N/A

Recommendations: This trial suggests that cellulose implants may be of benefit in preventing rapid recurrence at 3 months in segmental fasciectomy. A randomized trial would be suggested to confirm these findings.

Level of Evidence: III

Strength of Recommendation: C

Trials of non-surgical interventions

2 trials of non-surgical interventions were initially rated as Level I–III, with 1 later downgraded to level IV.

Injectable collagenase

Although the concept of enzymatic fasciotomy was originally described by Bassot in 1969 [25], the recent published results of Phase 3 Trials of Clostridial Collagenase published in 2009 in the New England Journal of Medicine seem likely to stimulate renewed interest in this treatment option for patients with Dupuytren's disease [16•]. More recent studies have focused on secondary analysis of the original Collagenase Option for Reduction of Dupuytren's (CORD) I trial, long term follow-ups of previous collagenase trials, and the CORD II trial. As the CORD I study was published in 2009, it precedes the inclusion date of the articles included for this review. However, in brief, the CORD I study was a randomized, placebo controlled, multicenter trial in the United States involving 308 patients. Patients with MCPJ or PIPJ contractures of > 20 degrees were enrolled in a randomized, controlled, double-blind trial. The treatment arm was collagenase clostridium histolyticum (0.58 mg), of up to 3 injections over

a 30-day period, with manipulation the day after injection. Post-operative night splints were used for up to 4 months but no formal hand therapy instituted. The primary endpoint was a reduction in contracture to 0–5 degrees from normal. Although 96.6 % patients reported adverse events, these were mostly minor in nature, such as pain, pruritus, and transient lymphadenopathy. Serious adverse events occurred in 3 cases - 2 tendon ruptures and 1 chronic regional pain syndrome. The primary endpoint or overall success rate was achieved in 64 % of primary joints compared with 6.8 % in placebo treated joints. The primary endpoint was achieved on average at day 56. The change in MCPJ flexion contracture was 48 to 7 degrees and the PIPJ was 55 to 22 degrees. Although no recurrences in successfully treated joints were noted at the 90 day follow-up period, the time frame was insufficient to assess for true recurrence. The CORD II study addresses this shortcoming, with a significantly longer follow-up period than the CORD I study.

CORD II study

Study: Gilpin et al. 2010, Brisbane Hand and Upper Limb Clinic, Australia [26].

Summary: This study was performed separately to the CORD I study, with near identical trial protocols but much longer follow-up period. This was a prospective randomized controlled trial with 2 phases over 1 year. The first phase was a 90 day double blind phase followed by a 9 month open label phase. 66 patients (with 66 cords, MCPJ or PIPJ >20 degrees) were randomized to collagenase or to placebo. Up to 6 injections were allowed in the study period. Primary endpoint was defined as release of contracture to 0–5 degrees from normal, 30 days after the last injection. Results indicated that the primary endpoint was achieved in 44.4 % of collagenase patients vs 4.8 % of placebo patients ($P<0.001$). Increase in range of motion from baseline of the primary joint (35 vs 8 degrees) and patient satisfaction were higher in the collagenase group. Serious adverse events included 1 allergic reaction and 1 flexor tendon pulley rupture in the collagenase group. In terms of immunogenicity, all patients developed antibodies to class I and II clostridium histolyticum after 3 injections. Significantly, no joints that were successfully treated with collagenase developed recurrence at 12 months follow-up. Subgroup analysis indicated some interesting findings. First, when MCPJ contractures were compared with the PIPJ, a statistical difference in contracture release was only noted in the MCPJ group, and *not with the PIPJ contractures*. Second, those with a higher baseline contracture responded more poorly than those with a lower baseline contracture (defined as MCPJ <50 or PIPJ <40). Validity: Well-designed trial with good follow-up (97 %), and is the only double blind RCT reviewed in this article.

Table 3 Recent higher level evidence trials on outcomes research, surgical and non-surgical techniques in Dupuytren's disease (Jan 2010–Aug 2012)

Topic	Technique	Institution, patients and study design	Primary outcomes	Level of evidence	Jadad score	Detsky quality score
Outcomes research	DASH score	Secondary analysis of data from previous RCT	DASH weakly correlated with flexion contracture of radial digits No correlation with contracture of little finger	II original IV secondary analysis	NA	NA
	Clinically important differences	Secondary analysis of data from the CORD 1 trial	13.5° contracture release equates to a “clinically important difference” for patients	I original IV secondary analysis	NA	NA
Surgical Trial	Needle fasciotomy vs limited fasciectomy	Van Rijssen et al. 2012. University Medical Centre Groningen, The Netherlands RCT, 111 patients (115 hands)	5-y follow up recurrence rates: fasciectomy 85 % fasciectomy 21 % ($P<0.001$)	II (unblinded RCT)	3/5 Not double blind	75 %
Trials on adjuncts to surgery	Needle fasciotomy with steroids	McMillan et al. 2012 Sunnybrook Health Science Centre, Toronto RCT, 47 patients	6 mo follow-up correction of total active extension deficit Steroids – 87 % No steroids – 64 %	II (unblinded RCT)	3/5 Not double blind	75 %
	Segmental fasciectomy with cellulose	Degreef et al. 2011, University Hospitals Leuven, Belgium. Comparative study – cellulose vs no implant	Reduction in recurrent contractures at 3 mo with cellulose implants	III	NA	NA
	Postoperative nocturnal splinting	Jerosch-Herold et al. 2011, multi-centre trial, East Anglia, UK. Multi-centre RCT. 154 patients, 5 hospitals	1-y follow-up DASH score, total extension deficit and patient satisfaction. No difference in outcomes between splint and no-splint	II (unblinded RCT)	3/5 Not double blind	80 %
Nonsurgical trials	Collagenase	CORD II trial Gilpin et al. 2010, Brisbane, Australia. Multicentre, RCT double blind trial 66 patients	1-y follow-up Initial success rates 44 % with collagenase Successfully treated joints had no recurrence	I (double blind RCT)	5/5 Double blind phase (then changed to open label)	85 %
	Collagenase	Watt et al. 2010. Stanford University Hospitals, USA Secondary analysis of Phase II trial 8 patients	8-y follow-up Recurrent contractures in 67 % MCPJ and 100 % PIPJ	I (original trial) IV (secondary analysis)	NA	NA

DASH disability of the arm, shoulder, and hand; *RTC* randomized controlled trial

Jadad: 5/5 blind phase.

Detsky: 85 % - high quality trial. No major methodological limitations.

Recommendation: The efficacy (44 % success rates) and longevity of collagenase was demonstrated in the CORD II study, and supports data from the CORD I study. Successfully treated joints do not appear to recur at 1 year. Subgroup analysis suggests that collagenase may be more beneficial in early disease, particularly of the MCPJ.

Level of Evidence: I

Strength of recommendation: A

Long term follow-up of injectable collagenase

Study: Watt et al. 2010. Stanford University Hospitals and Clinics, USA [27]

Summary: Long term follow-up of a small subset of 8 patients from a previous Phase II clinical trial of collagenase. The original Phase II trial was designed to determine dose response, efficacy and safety, with patients randomized to a single injection of placebo, 2,500 units, 5,000 units, or 10,000 units of collagenase. 23 patients were included in the original study from 1999–2001, and of these, 8 patients were available for 8 year follow-up (6 MCPJ and 2 PIPJ), and had not received further therapeutic interventions. Recurrence was defined in this study as any increase in joint contracture, compared with maximal extension achieved after injection. Using this definition, 67 % of MCP joint and 100 % of PIP joint contractures recurred at long term follow-up. For the MCPJ the pre-injection contractures were on average 57 degrees, at post-injection 3 degrees and at 8 year follow-up 22 degrees. For the PIPJ the pre-injection contractures were 45 degrees, post-injection 6 degrees, and 8 year follow-up 60 degrees.

Validity: Small study size with differing amounts of collagenase at primary treatment, no statistical analysis possible. The definition of recurrence in this trial is not standard, and may be too strict. If the CORD trial definitions of recurrence are used, only 2/6 of MCPJ recurred. Jadad and Detsky scores: N/A

Recommendation: This small dataset suggests that recurrent contractures will occur in the majority of patients treated with collagenase at 8 years.

Level of Evidence: I (original trial), IV for secondary analysis

Strength of recommendation: C (Table 3)

Conclusions

The last couple of years have produced a number of landmark articles in Dupuytren's research, both in terms of

innovation and in degree of quality. Recently, there has been a drive to increase the level of evidence in surgical journals, without adequately addressing the quality of trials. It is therefore encouraging to note that the quality of randomized controlled trials is universally high in Dupuytren's.

In outcomes research, the limited applicability of traditional functional outcome scores such as the DASH score in Dupuytren's disease, suggests that alternative scales be explored. The concept of "Clinically Important Differences" holds promise in this regard by directly correlating objective measurements with patient reported outcomes. Furthermore, outcomes research requires standardization, with the CORD trial definitions of "successful endpoints" and "recurrence", suggested for use in future studies.

Future directions in clinical research may need to address the role of collagenase further. Although the efficacy of collagenase has been demonstrated against placebo, and FDA approval granted, this does not equate to superiority over traditional surgical techniques. More data on longevity, recurrence rates, comparison to needle fasciotomy, and limited fasciectomy, is required before endorsing this as a more effective and safer alternative to surgery.

As such, the authors' own approach at present remains relatively traditional and does not incorporate needle fasciotomy or collagenase to a great extent, except in minor cases or contractures of the MCP joints. Our approach is broadly in line with the guidelines established by the British Society for Surgery of the Hand [28]. Notably, these are in conflict with those established by other clinical bodies such as the National Institute for Clinical Excellence (NICE) [29], particularly concerning treatments that lack high levels and quality of evidence, such as radiotherapy. This serves to highlight the importance of transparent assessment of treatments against established quality criteria such as the Detsky scale, and standardization of outcome measures, in order to minimize personal bias in the interpretation of evidence.

Summary

Highlights from high-level evidence trials in Dupuytren's from 2010–2012 include:

- Limited fasciectomy has a lower 5-year recurrence rate and higher satisfaction rate than needle fasciotomy. Level II evidence. Recommendation B
- Night splinting does not confer additional benefit post-contracture release. Level II evidence. Recommendation B.
- The use of steroids may be of benefit as an adjunct to needle fasciotomy. Level II evidence. Recommendation B.
- Cellulose implants may reduce early recurrence after segmental fasciectomy. Level III evidence. Recommendation C.

- Collagenase - release of contractures may be achieved in 44 % of patients without recurrence at 1 year. Collagenase may be more beneficial in early disease, particularly of the MCPJ. Level I evidence. Recommendation A

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- Of importance
- Of major importance

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