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Does collagenase injection disrupt or digest the Dupuytren's cord: a magnetic resonance imaging study

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Abstract

Collagenase *clostridium histolyticum* has been extensively studied as a treatment modality for Dupuytren's contracture. Its mechanism of action has been documented. It is unknown whether injected collagenase weakens the Dupuytren's cord sufficiently to cause failure during manipulation or if there is digestion and reduction in cord volume. We examined five patients with isolated contractures of the ring or middle metacarpalphalangeal (MP) joint using magnetic resonance imaging (MRI) prior to injection with collagenase and again 1 month following injection. All patients had full correction after manipulation which was maintained at follow-up. The Dupuytren's cord was evaluated with respect to volume, signal intensity, inflammatory changes and continuity. Additionally, signal intensity changes of the flexor tendons and neurovascular structures were recorded. MRI demonstrated cord discontinuity, significant reduction of cord volume and a significant increase in cord signal intensity after treatment with collagenase. There was a slight increase in flexor tendon signal intensity that was not significant. These findings suggest that there may be local chemical dissolution of the cord. Future studies may establish whether or not this will have prognostic implications in terms of correction and recurrence following collagenase injection.

Level of evidence: IV

Keywords

Clostridium histolyticum, Xiaflex, collagenase, Dupuytren's contracture, enzymatic fasciotomy, magnetic resonance imaging (MRI)

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Introduction

Dupuytren's disease is a chronic condition caused by the pathologic production and deposition of collagen in the hand (Brickley-Parsons et al., 1981; Murrell et al., 1991). Without intervention, the condition results in continued flexion deformity of the digits and impaired hand function. Traditionally, surgery has been the standard treatment for advanced contractures (Coert et al., 2006; Sennwald, 1990; Stewart et al., 2014). Despite resection of the diseased tissue, the condition may recur and often requires repeat surgery (Tonkin et al., 1984). Surgical intervention carries associated risks of substantial morbidity including skin complications, pain, infection, neurovascular injury, hematoma and complex regional pain syndrome (Black and Blazar, 2011). Complications can be debilitating for patients when they occur. As a result of the associated risks of surgical intervention, there is increased interest in alternative treatment options including injectable collagenase *clostridium histolyticum* (Auxilium Pharmaceuticals, Inc., Malvern, PA, USA).

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Magnetic resonance imaging (MRI) has successfully been used to characterize and define the Dupuytren's cord (Yacoe et al., 1993). Moreover, MRI signal intensity has been shown to correlate with the degree of cellularity seen histologically (Yacoe et al., 1993). The purpose of this study is to determine if collagenase injection *in vivo* weakens the Dupuytren's cord sufficiently to cause simple cord rupture during manipulation or if there is digestion and reduction in cord volume as would be indicated by decreased cellularity. A secondary goal is to determine if collagenase causes damage to the flexor tendons or digital neurovascular bundles. Because there have been soft-tissue complications of collagenase injection including skin tears and tendon rupture, we were interested in determining whether there are MRI signal changes in the neighbouring structures that might herald a risk for injury.

The aims of our study were to test the hypotheses that post-injection MRI will demonstrate a reduction in cord volume and show negligible signal changes in the adjacent soft tissue structures.

Methods

Approval for a five-patient pilot study was obtained through our institutional review board prior to conducting this study and informed consent was obtained for all participants. Patients with isolated 25° or greater contractures of a single metacarpalphalangeal (MP) joint of either the ring or middle finger were considered for enrolment in the study. These digits were chosen as the ring and middle fingers are the most similar in size and Dupuytren's pathology. The little finger was excluded because of the nearly universal presence of the ADM cord and its confounding effects. We excluded patients that had previous treatment with collagenase, had a PIP contracture, were pregnant or nursing, had a neuromuscular disorder that affected the hands, previous surgery in that hand or had medical co-morbidities that would disrupt the treatment plan.

Qualified patients were offered enrolment in the study, which consisted of MRI scans of the hand pre-injection and at 30 days post-injection. Pre-injection scans were performed within 7 days of the injection. Enrolled patients were examined at baseline to document the degree of contracture of the MP joint using a digital goniometer. Each patient then received one collagenase injection, following the recommended dosing instructions included on the package insert. Manipulation was performed under local anaesthetic 24 h later. The joint ranges of motion were documented by the senior author (S. W. W.) following the manipulation and at the first follow-up examination (average, 34 days; range, 35–55 days). The post-injection MRI was obtained immediately preceding the first follow-up visit using the identical MRI protocol. Clinical assessment at both visits included an assessment of sensory and vascular status, FDS and FDP integrity, and the presence of any complications. All patients were contacted by telephone by the senior author (S. W. W.) at 3 years following injection to inquire as to cord recurrence, satisfaction, functional deficits, adverse events and nerve or tendon dysfunction.

Quantitative MRI analysis

MRI scanning of the affected hand was performed in a 1.5T imaging system (General Electric HDX, Waukesha, WI, USA) using a quadrature receive-only dedicated wrist and hand coil (Medical Advances). Coronal and sagittal images were obtained utilizing a field of view of 10–11 cm (depending on the patient size), matrix 512 × 320, 2 excitations, receiver bandwidth of 31.25–42 kHz, repetition time (TR) of 3500–5600 ms, echo time (TE) of 26–32 ms and a slice thickness of 1.2–1.5 mm with no interslice gap. In the axial plane, matrix was 512 × 320 with 2 excitations, and a slice thickness of 2.5–4 mm with no interslice gap. An additional axial inversion recovery sequence was performed using the following parameters: TR, 3500–5000; effective echo time, 17 ms; field of view, 10 mm; bandwidth, 31.25–42 kHz; slice thickness, 2.5–4 mm with no gap; and matrix of 256 × 192 at 2 excitations.

Quantitative soft-tissue MRI analysis was performed by a senior radiologist according to a previously published and reproducibility-assessed protocol to quantify tissue on moderate echo time MR images (Nawabi et al., 2013). The criteria utilized to evaluate the Dupuytren's cord included cord volume and signal intensity measured by using a standardized region of interest placed on the axial MR images and recorded using standardized software available in the Advantage Windows workstation (GE Healthcare, Waukesha, WI, USA). Anatomic markers of the metacarpal base proximally and the middle phalangeal base distally were utilized to standardize measurements pre and post injection, thus capturing the entire cord and assuring that volume measurements were independent of extent of correction or MP joint angle. Cord volume measurements were obtained on sequential axial proton density-weighted images with the same pulse sequence parameters replicated between the two examinations. Similar coil, field strength and patient positioning were used. The number of images included for measurement depended on the length of the cord, which was variable between patients,

Table 1. Signal intensity and volume of Dupuytren's cord and flexor tendons.

Dupuytren's cord						
Signal intensity			Cord volume (mm^3)			
Pre	Post	*p*-value	Pre	Post	Percent change	*p*-value
631	2021	0.022	670	188	72%	0.0013
Flexor tendon signal intensity						
Profundus			Superficialis			
Pre	Post	*p*-value	Pre		Post	*p*-value
191	223	0.455	235		342	0.069

Post, post-injection; Pre, pre-injection.

but consistent within each patient pre and post injection. Conversion of image pixels to cubic millimetres was performed using modified MATLAB 6.2 software (Applied Science Laboratory General Electric Medical Systems). Signal intensity was compared pre- and post-injection using a consistent number of pixels in the region of interest for each patient. Inflammatory changes were characterized as either baseline, moderate or severe based on the amount of fluid signal around the cord. Trace amounts of fluid were labelled baseline, whereas fluid extending down the cord for <2 cm were moderate and >2 cm severe. Inflammatory changes of the superficial and deep flexor tendons were also scored as baseline, moderate or severe depending on the amount of fluid in the flexor tendon sheath using the same classification for signal around the cord, as noted above. The digital nerves and vessels were also examined for abnormalities and peri-neural inflammation.

Statistical methods used for this study included descriptive statistics and paired t-tests using an alpha value of less than or equal to 0.05. In addition, the data were evaluated with a non-parametric Wilcoxon Signed Ranks test and a McNemar's test. The statistical conclusions were unchanged by the results of the non-parametric studies.

Results

Five men with a mean age of 68 years (range, 59–72 years) were enrolled in the study. Four ring fingers and one middle finger had mean contractures of 33° (range, 25–40°). All patients had full correction with zero residual MP joint contracture following manipulation. This correction was maintained at a mean of 39 days (range, 34–55 days) later. There were no flexor tendon ruptures, skin tears, changes in digital sensation, loss of digital flexion, neuropathic pain or vascular compromise in the cohort.

The Dupuytren's cord was disrupted in all five cases. In addition, there was a significant reduction in Dupuytren's cord volume on post-injection MRI from 670 mm^3 to 188 mm^3 ($p<0.01$) (Table 1). This represents a mean 72% reduction in cord volume. The reduction in cord volume was easily appreciated on both axial and coronal images (Figure 1A and B). There was also a significant increase in cord signal intensity seen on post-injection MRI (Figure 2A–D). Signal intensity in the cord increased from a mean of 631 to 2021 (320%) following treatment with collagenase ($p<0.02$) (Table 1).

Tendon signal intensity for the flexor digitorum superficialis (FDS) and profundus (FDP) tendons also increased slightly but were not significant (Table 1). The FDS tendon signal intensity increased from 235 to 342 ($p<0.07$) and the FDP tendon signal intensity increased from 191 to 223 ($p<0.46$).

Increased inflammatory changes, as defined by the amount of fluid around the cord, were identified in all five patients (Table 2). In three cases, inflammatory changes about the flexor tendons progressed by one stage from baseline to moderate. No patients were identified as having severe inflammatory changes about the flexor tendons (Table 2).

Although no formal measurements were taken of the neurovascular bundles, the digital nerves and vessels had no signs of injury or surrounding signal/inflammatory changes.

At the 3-year telephone follow-up four of the five patients had no evidence of recurrence. One patient reported approximately 5° loss of extension since treatment. A second patient noted loss of approximately 15° of flexion following a bicycle accident that occurred 2 years after treatment with collagenase. One patient complained of mild swelling in the hand

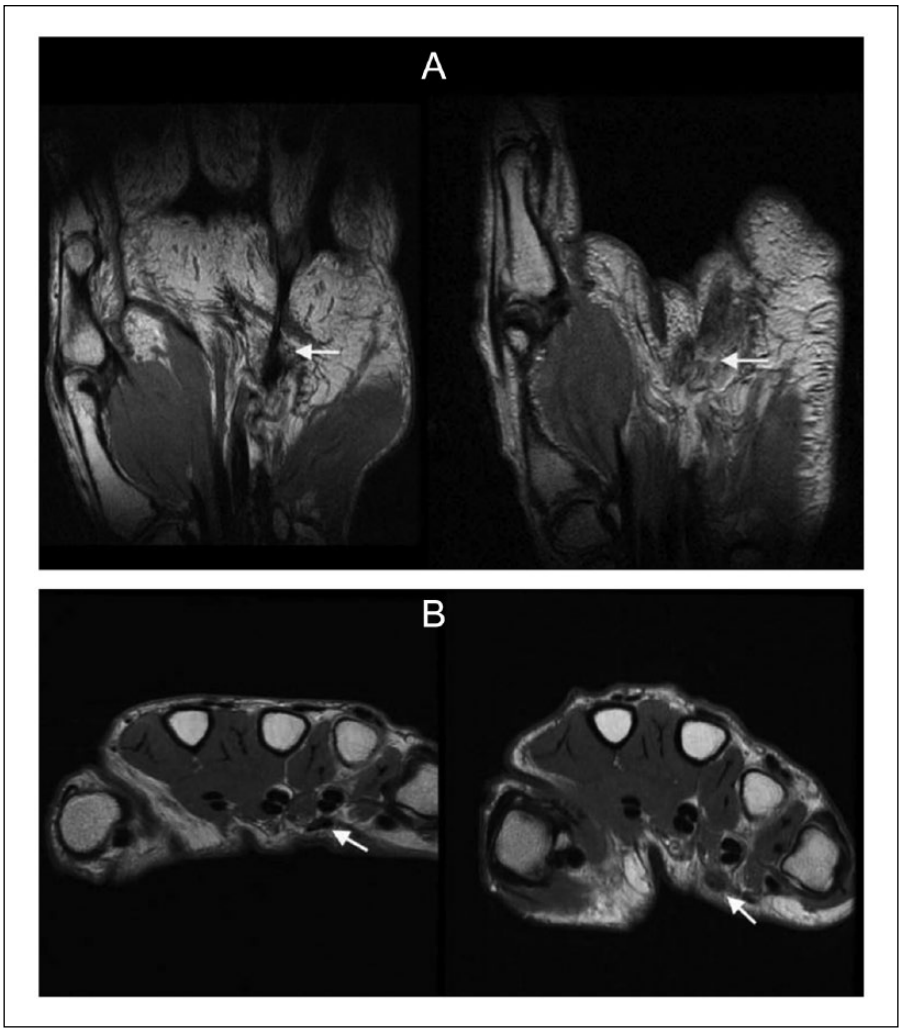

Figure 1. (A) Coronal MRI image demonstrating appearance of Dupuytren's cord before (left) and after (right) collagenase injection and manipulation. (B) Axial MRI image demonstrating appearance of Dupuytren's cord before (left) and after (right) collagenase injection and manipulation.

for 2 months after treatment, which resolved completely. No patients reported any adverse effect on the tendons, nerves or vascularity of the digit. All patients stated that they were satisfied with their result and had no functional problems with their hands.

Discussion

Collagenase *clostridium histolyticum* is a matrix metalloproteinase enzyme that breaks down collagen (Syed et al., 2012). The enzyme is produced by the bacterium *Clostridium histolyticum.* The two collagenase enzymes used in the preparation cleave different portions of the collagen molecule and then digest the collagen fragments. After initial lytic cleavages of the native collagen triple helix, the smaller fragments are subsequently digested by gelatinases and eventually non-selective proteases. Collagenase injections have been shown to cause a downregulation of collagen and other proteins at the transcriptional level (Syed et al., 2012), and to decrease fibroblast proliferation *in vitro*.

Treatment of Dupuytren's contracture with collagenase is an attractive option for hand surgeons because it avoids the substantial morbidity associated with open surgery (McFarlane, 1974; Peimer et al., 2015; Rodrigo et al., 1976; Warwick et al., 2015). Understanding the *in vivo* effects of collagenase on the Dupuytren's cord has important prognostic implications that may guide choice of treatment. *In vitro* studies have shown that a 3600-unit dose of collagenase resulted in a 93% decrease in the tensile modulus of the Dupuytren's cord (Starkweather et al., 1996). Histologic exam of *in vitro* specimens after

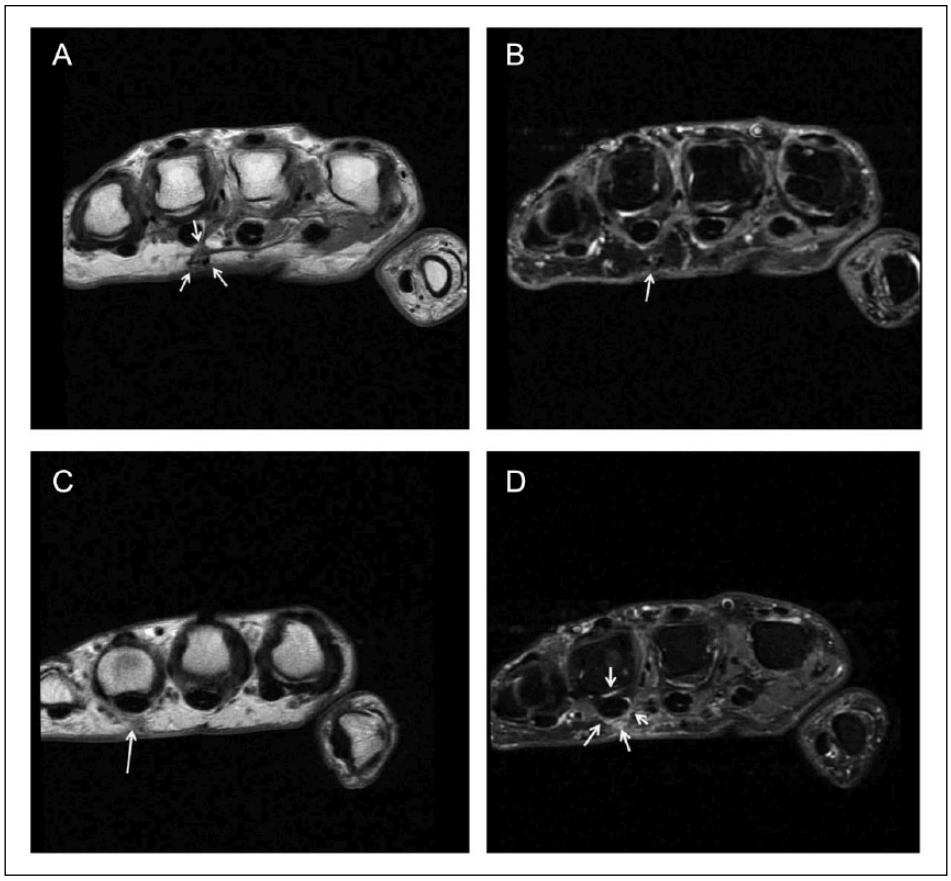

Figure 2. (A) Axial fast spin echo image demonstrates well-defined intermediate signal intensity surrounding a hypointense cord (arrows), extending to the palmar radial margin of the flexor tendon of the fourth digit, consistent with a Dupuytren's contracture. (B) Corresponding axial inversion recovery sequence demonstrates hypointense signal surrounding the supressed fat with no soft tissue oedema surrounding the hypointense cord (arrow). (C) Follow-up axial fast spin echo proton density weighted image following injection demonstrates dissolution of the hypointense cord with intermediate signal intensity in the subcutaneous fat (arrow). (D) Corresponding axial inversion recovery following injection demonstrates hyperintense soft tissue oedema (arrows) at the site of the prior cord, as well as in the palmar, and to a lesser extent, dorsal margin of the flexor tendon sheath (arrows).

Table 2. Inflammatory changes about cord and flexor tendons.

Patient	Dupuytren's cord		Flexor tendon	
	Pre	Post	Pre	Post
1	Baseline	Moderate	Baseline	Moderate
2	Baseline	Severe	Baseline	Baseline
3	Moderate	Severe	Moderate	Moderate
4	Baseline	Severe	Baseline	Moderate
5	Baseline	Moderate	Baseline	Moderate

Post, post-injection; Pre, pre-injection.

treatment with collagenase suggested there was lysis of collagen near the rupture site. Our study suggests that treatment with collagenase may cause not only a local disruption of the cord but also a significant reduction in the overall cord volume. The significant increase in signal intensity within the cord, although multi-factorial, is a reflection of the increased mobility of water and collagen disorganization.

It is important to understand the effect of collagenase on the neighbouring soft tissues. Previous authors have commented on the possible spread of enzymatic processes to nearby flexor tendons or pulleys dependent upon injection technique (Verheyden, 2015). Signal hyperintensity about the cord was noted in each patient in this cohort, and was seen in three of the five patients in the underlying flexor tendons. No changes were seen in the neurovascular bundles. *In vitro* wound models have shown an increase in the migration of inflammatory cells with the introduction of lower doses of collagenase, when compared with controls (Syed et al., 2012). Higher concentrations of collagenase have been shown to cause a reversal of this effect. The margins of the injections may reflect

this lower dose effect and could possibly explain the inflammatory effects seen on MRI. In addition, individual patients' metabolism of the enzyme will affect the relative dose present and thus, potentially modulate the signal changes present on MRI. Signal intensity changes were also identified in the FDS and FDP tendons, but the changes were nearly an order of magnitude less than the increase seen in the cord and did not reach statistical significance. While it is important to note the three cases of peri-tendinous signal changes, no definitive conclusions can be made with respect to potential tendon injury. Clinically, there were no cases of tendon rupture, tendinopathy or loss of digital flexion.

Comparison of needle aponeurotomy and collagenase injection for treatment of Dupuytren's is relevant because both methods represent less invasive alternatives to open surgery. Collagenase appears to act as a chemical fasciectomy; thus, its effects may be more similar to open surgery where diseased tissue is removed, rather than local needle aponeurotomy where tissue is simply divided (Desai and Hentz, 2011). Whether or not dissolution of the diseased tissue will lead to longer periods without disease recurrence and decreased severity of contracture as compared to simple cord division cannot be stated without a larger randomized study.

We acknowledge several limitations to the current study. Statistically, there is a lack of statistical power with only five patients enrolled. Although our sample size was small, the effect seen on post-injection MRI was large enough to detect significant differences in cord volume, fluid changes and signal intensity. We recognize that MRI is only a representation of the tissue level changes occurring *in vivo* which are best determined histologically. However, high resolution MRI allows us to interpret soft tissue images with great detail and accuracy. The use of MRI to quantify changes in volume and signal intensity of soft tissue structures has been previously validated in other anatomic regions such as the hip and the knee (Berns et al., 1992; Potter et al., 2004). Moreover, signal intensity has been shown to correlate with histologic cellularity of lesions in Dupuytren's disease (Yacoe et al., 1993). Signal intensity is a function of many different variables, including the internal relaxation properties of the soft tissue, but can also be affected by regional B1 variations and factors such as eddy currents. Quantitative evaluation of tendons is only feasible, given the short inherent T2* relaxation times, using an ultrashort TE pulse sequence that was not a part of this particular project. Signal intensity has previously been applied as a measure of inherent tissue characteristics, provided that it is compared to the 'normal' tendon at that same time, thus accounting for potential diurnal variations and day-to-day alterations between longitudinal studies (Rodeo et al., 2007). Signal intensity was measured not only in the affected tendon but also in the 'normal' unaffected tendon, which was used as an internal 'control'. We used the signal intensity as a semi-quantitative marker of relative variation between normal and abnormal tendon. The signal intensity changes identified represent increased water mobility within the structure and may be related to an inflammatory effect of the injection. We recognize that MRI is an expensive technology and the present study is not advocating routine use of MRI in diagnosis and treatment of Dupuytren's contractures. In this case MRI was necessary to determine if cord dissolution had occurred.

The study may also have been strengthened by a direct, postoperative MRI comparison with patients undergoing a limited incision fasciotomy or needle aponeurotomy. This would allow the investigators to compare the changes in the tissue after each of the treatment modalities and, perhaps, better answer the question of tissue dissolution following collagenase injection.

Ultimately the long-term results of treatment with collagenase will determine its role in the treatment of Dupuytren's disease. This can only be considered a pilot study. Collagenase injection appears to reduce the quantity of diseased tissue and in this sense, may be similar to a limited fasciectomy. This notion has been previously supported by *in vitro* studies looking at the effects of collagenase at the molecular and cellular level (Syed et al., 2012).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients prior to inclusion in the study.

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