Clinical outcomes following collagenase injections compared to fasciectomy in the treatment of Dupuytren's contracture

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Abstract

Introduction The aim of this study is to compare the efficacy of collagenase injections with that of fasciectomy in the treatment of Dupuytren's contracture.

Methods This is a case–control retrospective study. We reviewed the electronic medical records from January 2009 through January 2013, identifying 142 consecutive patients who underwent either fasciectomy or collagenase injection. Exclusion criteria for both groups were age <18 years, pregnant women, and arthroplasty or arthrodesis of the treated joint. Follow-up data beyond 1-year duration was available for 117 of the patients: 44 patients who had undergone fasciectomy, and 73 patients who had received collagenase injection. The primary outcome measure in this study was resolution of joint contracture to 0–5° deficit of full extension. Data was analyzed using two-sample t tests for continuous data and chi-square test for categorical data. A significant P value was set at <0.05.

Results At the latest follow-up, significantly more joints treated with fasciectomy met the primary outcome measure. Metacarpophalangeal (MP) joints responded better than the proximal interphalangeal (PIP) joints for both treatments. At the latest follow-up (14.2 months for collagenase, 16.3 months for fasciectomy), 46 % of MP joints treated with collagenase and 68 % of MP joints treated with fasciectomy maintained resolution of joint contracture. Sub-analysis of the affected joints based on the severity of initial contracture demonstrated that MP and PIP joints with contractures <45° responded better than more severely contracted joints (>45°).

Conclusions Fasciectomy yields a greater mean magnitude of correction for digital contractures at the latest follow-up when compared to collagenase. Both treatments were more effective for treatment of MP joint contracture compared to PIP joint contracture.

Level of Evidence Level III, therapeutic.

Keywords Dupuytren's disease · Collagenase · Xiaflex · Faciectomy · Finger joint contracture

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Introduction

Dupuytren's disease is a progressive fibroproliferative disorder of the palmar fascia. Flexion contractures caused by pathologic collagen cords result in loss of hand function and impact on quality of life. Contractures occur most commonly in the ring and little fingers, although all digits including the thumb may be involved [20]. The collagen cords may affect both the metacarpophalangeal (MP) and proximal

interphalangeal (PIP) joints. Men are affected more commonly than women [9].

Fasciectomy remains the most widely used procedure [4, 22] to address MP and PIP joint contractures. The correction of contracture of the PIP joint is less predictable than the MCP joint, regardless of technique (fasciectomy, needle fasciotomy, enzymatic treatment) [21, 24–26]. While fasciectomy often yields significant deformity correction and functional gains, recurrence rates as high as 71 % have been reported [3]. Additionally, major complications following fasciectomy have been reported in approximately 15 % of cases [6]. These complications include digital nerve injury (3.4 %), digital artery injury (2 %), infection (2.4 %), and complex regional pain syndrome (5.5 %). Finger stiffness, paraesthesia, and wound healing complications may also occur. As the incidence of Dupuytren's disease increases with advancing age [9], so do with the comorbidities of patients seeking treatment for disabling hand contractures. For patients with significant comorbidities, open surgical fasciectomy may represent a suboptimal option.

Collagenase enzymatic fasciotomy has become an accepted nonsurgical treatment alternative to the traditional fasciectomy or fasciotomy (needle and/or open) for significant digital contractures due to Dupuytren's disease [1, 2, 8]. Collagenase clostridium histolyticum (CCH) is a bacterial protein, made-up of two collagenases isolated from Clostridium histolyticum [13]. The collagenases are zinc-dependent matrix metalloproteinases which cleave the triple helical structure of collagen molecules [27]. Commonly known as Xiaflex® (Auxilium Pharmaceuticals Inc., Malvern, PA, USA), CCH was approved for use in patients with Dupuytren's contractures by the FDA in February 2010, following several prospective, multicenter clinical trials, which demonstrated its short-term efficacy [7, 8]. Patients treated with collagenase in these studies had superior outcomes in joint range of motion compared to placebo at 90 day follow-up. Post-marketing surveillance data suggests that collagenase has a favorable safety profile, with <0.6 severe adverse events per 1000 injections [17].

The purposes of this study were to compare the two treatment modalities as used in a single academic hand surgery center and to provide follow-up data beyond a year's duration for both treatments in order to help guide future management of the condition.

Methods

Institutional review board approval was obtained for this case–control retrospective study. We reviewed the electronic medical records at a single academic hand surgical center from January 2009 through January 2013, identifying consecutive patients who underwent either fasciectomy or collagenase injection by three fellowship-trained hand surgeons who had previously participated in the CORD-2 trial. Patients were eligible for collagenase injection or fasciectomy if there was a palpable Dupuytren's cord causing a fixed flexion deformity of the MP or PIP joint. Exclusion criteria for both groups were age <18 years, pregnant or breastfeeding women, and arthroplasty or arthrodesis of the treated joint. Collagenase or fasciectomy was chosen at the discretion of the treating surgeon in consultation with the patient. All surgeries were performed by the same three hand surgeons and these same surgeons saw the patients at the follow-up visits. Adverse events and amount of joint contracture were recorded at each follow-up visit. A standardized data collection form was utilized by all three surgeons. Adverse events were defined based on the common adverse events recorded in CORD trials and fasciectomy trials [6, 8, 14, 16].

Procedures

Collagenase

Collagenase (0.58 mg CCH) was administered by injection based on the protocols of the CORD-I trial [8]. We chose to inject Dupuytren's cords crossing the PIP joint using a lateral approach in an attempt to minimize risk of flexor tendon rupture. Manipulation of the treated joint and cord rupture was performed between 24 and 48 h post collagenase injection under local digital anesthesia (3 ml of 1 % mepivacaine without epinephrine). If a skin tear occurred during cord rupture, patients were seen at least weekly for serial wound examinations. Patients who had manipulation and cord rupture without skin tear were seen at 1 month follow-up. Following manipulation, patients used an overnight hand-based extension splint for a minimum of 3 months post-injection.

Fasciectomy

Subtotal fasciectomy was performed using either a Bruner-type incision or a longitudinal incision with Z-plasties. Operations were performed under regional anesthesia and tourniquet control. Fasciectomies combined with other procedures, specifically PIP joint arthrodesis and PIP joint arthroplasty, were excluded from analysis due to their inherent effect on joint range of motion. Following fasciectomy, patients were seen within the first postoperative week for examination and transitioned to hand-based extension splints with initiation of motion (unless concomitant skin graft performed). Sutures were removed at approximately 2 weeks postoperatively. Patients used an overnight hand-based extension splint for a minimum of 3 months postoperatively.

Following cord rupture and fasciectomy, patients underwent supervised hand therapy and independent home exercise programs. In addition to active flexion and extension exercises, patients utilized reverse blocking splints routinely to maximize central extensor force at the PIP and minimize recurrent PIP joint contracture. Static-progressive or dynamic splints were not used. Joint goniometry measurements in both treatment groups were performed by the treating surgeons according to the method used in the initial CORD trials [7, 8]. All surgeries were performed by the same three hand surgeons.

Data Analysis

The primary outcome measure in this study was resolution of joint contracture to 0–5° deficit of full extension. The secondary outcome measure was magnitude of residual flexion contracture. The criteria for additional intervention included: failure to meet primary endpoint or contracture recurrence of >20°. At each follow-up, adverse events following collagenase treatment were recorded based on those studied and identified by Hurst et al., and postoperative complications were delineated based on prior clinical reports [6, 8, 14, 16]. All statistical analysis was performed with the R statistical programming language [19]. Data was analyzed using the two-sample t tests for continuous data and chi-square test for categorical data. A significant P value was set at <0.05.

Results

Between January 2009 and January 2013, a total of 142 patients were identified from the electronic medical record, having undergone collagenase injection ($n=81$) or fasciectomy ($n=61$) as treatment for Dupuytren's disease. Fourteen of the fasciectomy patients excluded from the analysis as they underwent additional procedures during the fasciectomy (PIP arthrodesis ($n=8$) and PIP arthroplasty ($n=6$)). There were 20/117 (17.1 %) of patients who reported a family history of Dupuytren's disease and 58/117 (49.6 %) presented with bilateral disease.

Follow-up data beyond 1-year duration was available for 117 of the 128 (91 %) remaining patients: 44 patients (94 joints) who had undergone fasciectomy and 73 patients (100 joints) who had received collagenase injection were included for the analysis of clinical outcomes. Patient characteristics were similar for both groups (Table 1).

Twenty-four (33 %) patients in the collagenase treatment group had previous fasciectomy, only 3 (4 %) of the collagenase-treated joints were post-fasciectomy. Twelve (27 %) patients undergoing fasciectomy had prior

Dupuytren's surgery, only 4 (9 %) of these patients had revision fasciectomy in the same digit. Two (5 %) of the fasciectomy patients had concomitant skin grafting at the time of surgery to aid with skin closure. Twenty-five patients had collagenase injections for 2 joints and 1 patient had injections for 3 joints.

Four patients treated with collagenase went on to have subsequent fasciectomy of the same joint at a mean of 7 months following index treatment with enzymatic fasciotomy (3 in MCP and 3 in PIP joints). These patients elected surgery following failure of initial injection ($n=3$) or recurrence ($n=1$) in lieu of a repeat collagenase injection. Three of the 4 patients were included in the fasciectomy data set as they achieved greater than 1 year postoperative follow-up.

Eight of the 100 joints (8 %) treated by collagenase (3 MP and 5 PIP joints) underwent more than one injection into the same cord, giving a total number of 108 collagenase injections. The average joint contracture for these 8 patients prior to treatment was 58.6°. Five of the 8 joints did not achieve the primary endpoint and received a second injection at the thirty day follow-up. The other 3 joints had a gradual recurrence over a 3 month period and received a second injection. No patients in the surgical cohort underwent revision fasciectomy or subsequent treatment with collagenase at latest follow-up.

Collagenase vs. Fasciectomy

The mean length of follow-up for the collagenase group was 14.2 months from the time of the first injection (range 12–31 months). The mean length of follow-up for the fasciectomy group was 16.3 months (range 12–34 months). Outcomes following collagenase and fasciectomy are summarized in Tables 2 and 3. In the collagenase group, 51/100 joints met the primary endpoint at early follow-up. Twenty-five out of those 51 joints met the primary endpoint at latest follow-up. At latest follow-up, 4 out of the 49 joints who failed to meet the primary endpoint at early follow-up responded to the second injection and met the primary endpoint. At latest follow-up, significantly more joints treated with fasciectomy met the primary outcome measure of resolution of joint contracture to 0–5° (60 vs 29 %, $P=0.0001$). Individual analysis of MP and PIP joints demonstrated that MP joints responded better than the PIP joints in response to both collagenase and fasciectomy.

Sub-analysis of affected joints based on severity of initial contracture demonstrated that MP and PIP joints with contractures <45° responded better than more severely contracted joints (>45°). With regard to the secondary outcome measures, the mean residual joint contracture was less in the fasciectomy group compared to joints treated with collagenase at latest follow-up (28.4 vs 11.8°).

Table 1 Baseline characteristics of the patients

Variable	Collagenase group (n=73)	Fasciectomy group (n=44)	All patients (n=117)	P value
Total joints treated	100	94	194	
MP	56	53	109	
PIP	44	41	85	
Age, years	64	65	64	0.81
Male sex, no. (%)	61 (83.5 %)	33 (75 %)	94 (80.3 %)	0.34
Total number of joint contractures in affected hand	2.3	2.7	2.4	0.69
Range	1–7	1–8	1–8	
Mean initial joint contracture	52.3° (15–90)	47.2° (5–95)	49.6° (5–95)	0.14
MP	50.2°	45.9°	47.9°	0.13
MP 0–45°	32.2°	29.7°	30.7°	
MP >45°	64.8°	57.2°	61.9°	
PIP	55.9°	49.7°	52.6°	0.15
PIP 0–45°	39.7°	36.1°	37.5°	
PIP >45°	63.5°	56.1°	60.5°	

Adverse Events

Collagenase

Over 70 % of patients experienced mild adverse effects, as defined by the CORD trials [7, 8], following collagenase injection, including local edema, ecchymosis, and pain. Skin tears occurred following 19/108 cord manipulations (18 %). No wound infections were noted following the skin tears, and all skin tears healed with local wound care. Axilla lymphadenopathy was noted following 5/108 injections (5 %). There were no flexor tendon ruptures following collagenase injection.

Fasciectomy

Minor postoperative complications included finger stiffness, paraesthesia, and delayed wound healing, which all resolved without additional surgical intervention. Major adverse events included 1 case of digital neurovascular injury (2.2 %) requiring microsurgical primary repair. There were 2 cases of deep wound infection (4.5 %) requiring irrigation, debridement, and oral antibiotics.

Discussion

This retrospective case–control study demonstrates that patients treated with fasciectomy are more likely to have more complete maintenance of correction of Dupuytren's

Table 2 Primary treatment outcomes

	Collagenase n=100	Fasciectomy n=94	P value
Joints which met primary endpoint at early follow-up (contracture 0–5°)			
All joints (MP + PIP)	51/100 (51 %)	66/94 (70 %)	0.0097
MP	39/56 (70 %)	42/53 (79 %)	0.3536
MP 0–45°	18/25 (72 %)	19/22 (86 %)	0.399
MP >45°	21/31 (68 %)	23/31 (74 %)	0.7796
PIP	12/44 (27 %)	24/41 (59 %)	0.0070
PIP 0–45°	7/14 (50 %)	15/17 (88 %)	0.05
PIP >45°	5/29 (17 %)	9/24 (38 %)	0.17
Joints which met primary endpoint at >1 year (contracture 0–5°)			
All joints (MP + PIP)	29/100 (29 %)	56/94 (60 %)	0.0001
MP	26/56 (46 %)	36/53 (68 %)	0.038
MP 0–45°	14/25 (56 %)	16/22 (73 %)	0.375
MP >45°	12/31 (39 %)	20/31 (65 %)	0.05
PIP	3/44 (7 %)	20/41 (49 %)	0.0001
PIP 0–45°	2/14 (14 %)	13/17 (76 %)	0.002
PIP >45°	1/29 (3 %)	7/24 (29 %)	0.0266

Table 3 Secondary outcomes

Secondary outcome measure: mean contracture at >1 year

	Collagenase	Fasciectomy	P value
All joints (MP + PIP)	28.4°	11.8°	0.001
MP	21.1°	9.8°	0.021
PIP	37.5°	16.7°	0.001
MP 0–45°	19.7°	7.6°	0.018
MP >45°	22.3°	10.9°	0.02
PIP 0–45°	34.2°	15.1°	0.001
PIP >45°	39.6°	18.2°	0.001

contracture after 1 year when compared to those treated with collagenase (60 vs 29 %). Fasciectomy results in a significantly greater correction of digital contractures when compared to collagenase (28.4 vs 11.8°). Both fasciectomy and collagenase were demonstrated to be more effective for the treatment of MP joint contracture compared to PIP joint contracture, which is consistent with the previous studies [7, 8].

The use of collagenase in clinical practice continues to expand since the FDA approval in February 2010, as more patients seek a nonsurgical alternative for the treatment of Dupuytren's disease and as longer-term data is now becoming available to surgeons for collagenase-treated joints. Naam et al. [14] recently presented a smaller retrospective series comparing collagenase with fasciectomy and found contracture outcomes comparable at 2-year follow-up. Collagenase was recently retrospectively compared with percutaneous needle fasciotomy, and both treatments yielded comparable outcomes at 3-month follow-up [15].

McMahon et al. [11] showed that collagenase-treated joints had a tendency toward contracture recurrence overtime (24 and 39 % of MP and PIP joints, respectively, met the criteria for contracture recurrence). At 3-year follow-up, Peimer et al. [16] found that 27 and 56 % of MP and PIP joints, respectively, had recurrence of contracture following collagenase treatments. Recurrence following collagenase is not surprising as collagenase disrupts the collagen cord (i.e., enzymatic fasciotomy) but does not remove the disease process. While disease recurrence also occurs following surgical fasciectomy, we surmise that the more complete excision of gross cord tissue may result in slower contracture recurrence and may account for the improved results at 1-year follow-up seen in our study.

Although fasciectomy yielded significantly greater contracture correction at 1-year follow-up, collagenase remains a viable nonoperative alternative for the management of Dupuytren's disease. While immediate local reactions at the injection site are common, collagenase is generally well-tolerated with a favorable safety profile [16–18]. Return to work or recreational activity is possible much earlier following collagenase injection [14] as would be expected with a less invasive procedure.

No patients in this study experienced flexor tendon rupture following collagenase injection. We attempted to minimize any risk of tendon rupture by using a lateral approach to cord injection wherever possible. Where possible, we manipulated the affected digit at 48 h post-injection rather than 24 h post-injection as was initially described in the CORD-I study. Manipulation with local anesthesia at 48 h post-injection has been successfully used by others [10]. Skin tears following collagenase injection and manipulation are common but usually self-limiting. Our incidence of skin tears (18 %) was higher than that of the previous studies including the CORD-I trial. All 19 skin tears from our study healed with conservative measures. The higher incidence may relate to the use of local anesthesia, enabling stronger manipulation of the digit following injection.

The majority of our patients treated with collagenase received only one injection per treated joint (91 %, 1.08 mean injections per treated joint). The original CORD-I study had a mean number of 1.7 injections per treated joint. However, trends in practice identified by Peimer et al. [16, 18] suggest that most joints are receiving only one collagenase injection rather than multiple injections per joint to achieve satisfactory outcome.

The cost effectiveness of collagenase in clinical practice will depend on a number of factors, including the number of injections required per treated joint, number of follow-up appointments required, amount of hand therapy utilized, and recurrence of contracture resulting in further intervention. A recent study from the UK showed that current use of collagenase is possibly three times more cost-effective than surgical fasciectomy [12]. Additional studies are needed to extrapolate the impact in the US. Naam et al. [14] highlighted that return to work is significantly faster following collagenase treatment as compared to fasciectomy.

This study has the inherent limitations of a retrospective case–control series. Patients were not randomized to treatment groups, and measurements were made by the treating surgeon. Additionally, this study was not designed to specifically assess the effect of splint and hand therapy on outcomes. Recent series have attempted to elucidate the role and impact of nighttime extension splinting and formal hand therapy protocols in the early (1–3 months) post-injection and post-surgical setting [5, 23]. Long-term data will increase our understanding of incidence and magnitude of contracture recurrence. Prospective randomized trials with blinded evaluators of clinical outcomes following multiple treatment modalities will help to further elucidate optimal treatment algorithms for patients with Dupuytren's disease. Additionally, the assessment of patient–based outcomes following the available treatment options should be studied further [28].

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