Early outcomes of a sequential series of 144 patients with Dupuytren's contracture treated by collagenase injection using an increased dose, multi-cord technique

J R Verheyden

Abstract

Collagenase clostridium histolyticum is the first and only United States Food and Drug Association approved nonsurgical treatment for patients with a palpable Dupuytren's contracture cord. However, the Food and Drug Association has only approved injection of 0.58 mg of this enzyme into one palpable Dupuytren's contracture cord at a time. This review reports on the early outcome of 144 patients treated with the entire bottle of enzyme, approximately 0.78 mg, along with use of a novel slow intracord multi-cord technique. Use of 0.78 mg of enzyme, with the slow intracord multi-cord technique is safe and allows one to inject multiple Dupuytren's contracture cords at one setting. Correction at metacarpophalangeal and proximal interphalangeal joints, taken individually, are comparable with the Collagenase Option for the Reduction of Dupuytren's studies at 43° and 33°, respectively, however due to the multi-cord injection, we achieved 94° average immediate and 76° average final combined metacarpophalangeal and proximal interphalangeal contracture releases per bottle of enzyme. Implementation of the slow intracord multi-cord technique has the potential to improve current treatment for Dupuytren's contracture with resultant significant healthcare savings.

Keywords

Dupuytren's contracture (DC), collagenase (CCH), slow intracord multi-cord technique, intracord

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Introduction

Historically, treatment for Dupuytren's contracture (DC) consisted of open fasciectomy, open fasciotomy, or needle aponeurotomy, frequently followed by hand therapy (Coert et al., 2006; Denkler, 2005; Leclercq, 2000; Sennwald, 1990; Stewart et al., 2013; van Rijssen and Werker, 2006; van Rijssen et al., 2006). Unfortunately, this treatment is associated with significant potential complications (Bulstrode et al., 2005; Denkler, 2010; Foucher et al., 2003; Jabaley, 1999; Loos et al., 2007; Mavrohenis et al., 2009; McFarlane and Jamieson, 1966; Sennwalk, 1990). In February 2010, the Food and Drug Administration (FDA) approved injectable collagenase clostridium histolyticum (CCH) (Xiaflex; Auxilium Pharmaceuticals, Inc, Malvern, PA) as the first and only nonsurgical treatment for adult patients with DC with a palpable cord.

The FDA approved the injection of 0.58 mg of CCH into a single DC cord. This injection can be repeated once a month, up to three times, to achieve a contracture release to within 0°–5° of normal. In the Collagenase Option for the Reduction of Dupuytren's (CORD) I and II studies (Gilpin et al., 2010; Hurst et al., 2009), a mean 1.7 injections, were required to achieve a reduction in contracture to within 0°–5° of normal. A bottle of this enzyme costs approximately $3300. Estimated total Medicare surgical costs for DC treatment range from $3500 for palm only disease, to $4300 for two finger proximal interphalangeal (PIP)

The Center for Orthopedic and Neurosurgical Care & Research, Bend, OR, USA

Corresponding author:
J. R. Verheyden, The Center for Orthopedic and Neurosurgical Care & Research, 2200 NE Neff Road, Bend, OR 97701, USA.
Email: jverheyden@thecenteroregon.com

involvement (AMA 2013 CPT/Relative Value Search). Total surgical costs were calculated as the sum of procedure, anaesthesia, facility, and occupational/physical therapy costs. Self pay and private insurance total surgical costs can greatly exceed Medicare amounts.

Previous clinical, toxicology, and immunology studies suggested safety with complete CCH bottle injection (Badalamente et al., 2002; Edkins et al., 2012). Safety with injection greater than 0.58 mg CCH also supported with preliminary unpublished and exploratory published multi-cord studies, injecting two concurrent cords, each with 0.58 mg of CCH (Coleman et al., 2012).

In an effort to save healthcare dollars and improve efficacy, I routinely inject the entire bottle of enzyme using a novel slow intracord multi-cord (SIMple) technique. I hypothesized significant improvement in efficacy, significant reduction in overall healthcare costs, and no increase in patient morbidity.

On 28 February 2011, the European Medicines Agency approved CCH (Xiapex; Swedish Orphan Biovitrum AB; Stockholm, Sweden) for treatment of DC in 28 European Union member countries, including Sweden and Norway, with the same 0.58 mg dosage instructions.

Material and methods

Patients

After obtaining regional institutional review board approval, I retrospectively reviewed every patient that I injected with CCH from May 2010 to November 2012. A total of 144 patients (119 men, 25 women) were injected. Every patient was instructed pre-procedure that this technique was off label, not FDA approved, and the potential serious side effects with use of CCH were outlined and highlighted.

Clinical evaluation

All patients had complete medical records including preinjection and postinjection measurements. Contracture measurements were made using a standard technique with finger goniometer, direct observation, and table-top testing preinjection, after manipulation, and at subsequent visits. Serious adverse events were monitored and screened.

Injection technique

CCH was reconstituted using the manufacturers recommended technique for metacarpophalangeal (MCP) contractures with 0.39 ml of sterile diluent.

The reconstituted vial was gently inverted with care taken to remove every drop of enzyme. With the addition of 0.39 ml of diluent, I routinely retrieved 0.34 ml reconstituted enzyme, representing 0.78 mg of CCH. The FDA approved injection technique allows 0.58 mg of enzyme. Additional enzyme is present in the bottle as it is common in the pharmaceutical business to include more product than needed to account for potential waste (Auxilium – personal communication, February 2010).

For every patient, except the first, the entire bottle was used. This represents 0.2 mg additional CCH, or a 34% increase. The CCH dose was divided, depending on clinical severity, to maximize efficacy of each injection. On average, 2.5 separate DC cords were injected, per patient, per CCH bottle.

For the purpose of this article, to facilitate resultant analysis and to directly compare these results with previously published CCH injection results, pretendinous cords were defined as cords in the palm, proximal to the finger flexion crease. Spiral cords were defined from the finger flexion crease to the proximal interphalangeal (PIP) flexion crease, and retrovascular cords from the PIP flexion crease distally. Injections into pretendinous Y cords were considered single pretendinous injections. Even though there is significant variability among cords located in the proximal phalangeal area, all cords in this region were defined as spiral cords. All cord types were injected. The author did not refuse to inject any cord type.

After approximately the tenth patient, the author serendipitously discovered the SIMple technique. The SIMple technique insures direct CCH injection into the DC cord in an effort to maximize CCH efficacy. The author included his first 10 patients in the retrospective review to most accurately reflect the results of the author's first 144 patients and to provide other hand surgeons, who are considering this technique with its associated learning curve, an idea of expected results.

With the SIMple technique, the needle is inserted into the centre of the DC cord and firm pressure is applied to the plunger of the syringe with one hand. The opposite hand stabilizes the patient's hand and associated cord that is being injected. Given the long injection process, the index finger of the opposite hand stabilizes and applies counterforce to the hub of the needle to prevent inadvertent penetration through the cord. Constant pressure is applied to the syringe plunger, injecting the CCH. With this SIMple technique, no apparent enzyme is frequently injected for several minutes. Depending on the apparent density of the collagen bundle, resistance on the injection plunger usually suddenly

disappears, and one can easily inject the CCH into the cord, after approximately 1–5 minutes. The needle is then routinely partly withdrawn and redirected one to two times at the same location with the same technique. Usually, significant less time is required for injection at each redirected location. This process is repeated for every cord injected. With this technique, complete injection of the entire bottle of enzyme takes anywhere from several to approximately 15 minutes.

For spiral cords, I routinely inject at the PIP joint and mid-proximal phalangeal level. This technique is not recommended by the manufacturer, due to fear of tendon rupture. For these areas, the needle is injected into the spiral cord from dorsal to volar, injecting away from the flexor tendons. Again, the SIMple technique is utilized. For small cords, placement of the needle into the cord is sometimes tricky and feels similar to threading a vein during venipuncture. Retrovascular cords at the middle phalangeal level and distal inter phalangeal (DIP) joint area are injected using a similar technique.

At all times, if no resistance is appreciated at initiation of attempted injection, the needle is redirected and 'rethreaded' into the DC cord. Confirmation of placement into the cord is achieved with solid knowledge of anatomy, careful technique, and firm resistance with the attempted injection. Care is taken to avoid injecting CCH into the soft tissue adjacent to the cord. This injection technique was employed with all cord types, even with very thin or flat cords. On occasion, patients had acute pain during injection, possibly secondary to placement of the needle adjacent to the neurovascular bundle. However, local anaesthetic was given at time of enzyme injection for only two or three patients, and this was only done for repeat injections at the patient's request.

After injection, a soft dressing is applied. The patient returns the next day for manipulation. Local field block was performed for all patients, except one, using a combination of 1% lidocaine and 0.5% marcaine. After 10–15 minutes, the affected cords are manipulated, with the wrist and MCP flexed for spiral and retrovascular cords, and with wrist flexion for pretendinous cords. After manipulation, a soft tissue dressing is applied, except for severe PIP contractures and for patients who developed skin lacerations.

For PIP contractures greater than 60°, a dorsal padded finger splint is applied every night for 2–3 weeks. For patients who develop skin lacerations, occlusive petrolatum gauze, along with soft dressing and plaster splint is applied, holding the affected digits in maximal extension. Patients remove this dressing the next day and start twice daily soaks in warm water with magnesium sulphate salts. They continue their night-time finger splints as directed above.

After injection, patients avoid heavy lifting, gripping, or squeezing for one week. Patients routinely return at 7–14 days. Patients who develop skin lacerations routinely return for a wound check approximately 5–6 days after injection. Patients follow up 1 month after injection and subsequently as needed.

The author excluded patients with thumb, first web space, and retrovascular cord injections, and patients with <20° MCP or PIP contractures from statistical analysis in an effort to directly compare results with previously published reports using a similar cohort of patients (Gilpin et al., 2010; Hurst et al., 2009).

Results

A total of 521 separate DC cords were injected, of these there were 302 pretendinous and 193 spiral cords; 28 thumb, 7 first web space, and 10 retrovascular cords were injected.

The CCH injection results were stratified by the degree of preinjection contracture at the MCP and/or PIP joints (Table 1). Results were stratified in this fashion, and both included and excluded patients with greater than 80° PIP contractures to directly compare results with CORD I and II.

The results for isolated pretendinous and spiral cord injections were analysed (Tables 2 and 3). Patients who only had one bottle of CCH injected per hand were also analysed, to most accurately reflect results for a typical new DC patient who presents to the office for injection. This information is helpful to educate new patients about expected contracture release results with CCH injections (Tables 4 and 5).

Every patient developed swelling, ecchymosis, and tenderness at the injection site. Swelling and tenderness typically resolved by 2 weeks postinjection. Approximately 40% of patients developed axillary swelling, tenderness, and lymphadenopathy. The presence or absence of this finding was not always documented. This typically resolved 1 day postinjection. 35 skin lacerations, defined as skin splitting or tearing at time of manipulation, were noted. Of these, 10 skin lacerations occurred in patients with >80° PIP contractures. All skin lacerations, even those with exposed tendon sheaths, healed by secondary intention. No infections were noted. Five patients developed recurrent DC, defined as >20° contracture for a cord that was injected. All patients underwent repeat

Table 1. CCH injection results stratified by degree of preinjection contracture. All thumb CCH injections excluded.

MCP and/or PIP contracture	Greater than or equal to 20°	Greater than or equal to 20° and less than or equal to 80°	Greater than 80°	Greater than or equal to 20° and less than or equal to 80° Only one bottle of CCH injected per hand	Greater than or equal to 20° Only one bottle of CCH injected per hand
Number of cords injected per bottle of CCH	2.5 cords	2.4 cords	2.7 cords	2.5 cords	2.5 cords
Results at time of extension procedure					
Patients	112	95	17	81	95
Bottles of CCH injected	156	135	21	97	112
Total degrees MCP and PIP correction/bottle	94°	85°	154°	85°	93°
MCP degrees correction/bottle	49°	48°	56°	50°	50°
PIP degrees correction/bottle	45°	37°	98°	35°	43°
Final results					
Patients	81	69	12	55	64
Bottles of CCH injected	119	103	16	66	76
Total degrees MCP and PIP correction/bottle	76°	66°	138°	68°	79°
MCP degrees correction/bottle	43°	40°	64°	43°	46°
PIP degrees correction/bottle	33°	26°	74°	25°	33°
Average follow-up days	60	59	65	43	42

CCH: collagenase clostridium histolyticum; MCP: metacarpophalangeal; PIP: proximal interphalangeal.

Table 2. Results for pretendinous cords injected with CCH; thumb injections excluded.

MCP contracture	Greater than or equal to 20°	Greater than or equal to 20° and less than or equal to 80°	Greater than or equal to 20° Only one bottle of CCH injected per hand
Pretendinous cords injected	142 cords	127 cords	104 cords
CCH injected per pretendinous cord	0.38 mg	0.38 mg	0.39 mg
Average preinjection MCP contracture	49°	43°	47°
Average MCP contracture correction improvement achieved at extension procedure	48°	42°	47°
Average final MCP contracture correction improvement	44°	39°	45°
Percentage pretendinous cords achieving complete correction at extension procedure	99%	98%	100%
Pretendinous cords injected with final measures	118 cords	106 cords	80 cords
Percentage of pretendinous cords achieving complete correction - Final	78%	81%	83%
Average follow up	55 days	55 days	35 days

CCH: collagenase clostridium histolyticum; MCP: metacarpophalangeal.

injection of those cords. Less than 5 patients went to occupational therapy after injections and these were all multiple finger DC patients. Except for these 5 patients, nearly all patients had supple full finger range of motion, as allowed by their residual DC, 2 weeks post injection.

Table 3. Results for spiral cords injected with CCH; thumb injections excluded.

PIP contracture	Greater than or equal to 20°	Greater than or equal to 20° and less than or equal to 80°	Greater than or equal to 20° Only one bottle of CCH injected per hand
Spiral cords injected	130 cords	103 cords	83 cords
CCH injected per spiral cord	0.31 mg	0.3 mg	0.29 mg
Average preinjection PIP contracture	58°	50°	57°
Average PIP contracture correction improvement achieved at extension procedure	51°	44°	52°
Average final PIP contracture correction improvement	41°	38°	45°
Percentage spiral cords achieving complete correction at time of extension procedure	80%	82%	87%
Spiral cords injected with final measures	102 cords	81 cords	57 cords
Percentage of spiral cords achieving complete correction – final	48% # 49/102	53%	58%
Average follow up	53 days	55 days	38 days

CCH: collagenase clostridium histolyticum; PIP: proximal interphalangeal.

Table 4. Results for pretendinous cords injected with CCH.

Pretendinous cord injections	SIMple technique Only one bottle CCH per hand	CORD I	CORD II	
Cords injected with final measures	80 cords	129 cords	20 cords	
CCH injected per cord	0.39 mg	0.99 mg	0.99 mg	
Average final MCP contracture correction improvement	45°	41°	40° All	
				78%
Percentage of MCP joints achieving complete correction	83% # 66/80	77% 99/129	65% 13/20	178/229
Average follow up	35 days	30 days	30 days	

CORD I and II – average of 1.7 injections/patient ×0.58 mg CCH/injection = 0.99 mg CCH.
CCH: collagenase clostridium histolyticum; CORD: Collagenase Option for the Reduction of Dupuytren's; MCP: metacarpophalangeal.

Table 5. Results for spiral cords injected with CCH.

Spiral cord injections	SIMple technique Only one bottle CCH per hand	CORD I	CORD II	
Cords injected with final measures	57 cords	70 cords	25 cords	
CCH injected per cord	0.29 mg	0.99 mg	0.99 mg	
Average final PIP contracture correction improvement	45°	29°	32° All	
				45%
Percentage of PIP joints achieving complete correction	58% # 33/57	40% 28/70	28% 7/25	68/152
Average follow up	38 days	30 days	30 days	

CORD I and II – average of 1.7 injections/patient ×0.58 mg CCH/injection = 0.99 mg CCH.
CCH: collagenase clostridium histolyticum; CORD: Collagenase Option for the Reduction of Dupuytren's; PIP: proximal interphalangeal.

Discussion

This article is clinically significant as it represents the entire CCH clinical experience of a single practitioner, utilizing a non-FDA approved injection technique, and represents 1% of all CCH injections performed in the United States, from inception of CCH clinical trials to completion of this retrospective review.

The results are compared with previously published studies (Gilpin et al., 2010; Hurst et al., 2009). CORD I demonstrated 41° mean improvement in range of motion (ROM) at the MCP when pretendinous cords were injected and a 29° mean improvement in ROM at the PIP when spiral cords were injected. The CORD II study demonstrated a 40° mean improvement in ROM at the MCP when pretendinous cords were injected and a 32° mean improvement in ROM at the PIP when spiral cords were injected. These results were achieved with a mean of 1.7 injections per DC cord. Using a similar patient cohort, this study demonstrated an immediate 49° average MCP and 45° average PIP contracture correction improvements per bottle of enzyme, along with a final 43° average MCP and 33° average PIP contracture correction improvement at an average follow-up of 60 days. This 94° average immediate and 76° average final combined MCP and PIP contracture releases per bottle of enzyme demonstrates a significant improvement from the isolated MCP or PIP release results noted with the FDA-approved technique in CORD I and II.

Looking at isolated injections into single cords, a mean of 0.38 mg of CCH was injected per pretendinous cord and 0.31 mg of CCH was injected per spiral cord with comparable or better results than found in the CORD I and II studies where a mean of 0.99 mg of CCH was injected per isolated cord. On average, the author injected 2.5 separate DC cords per CCH bottle. Frequently, patients with severe three and four finger DC had complete correction with only one bottle of CCH.

Improved results, compared with CORD I and II, are partly attributed to routine use of local anaesthetic for manipulation, allowing for more forceful, but painless manipulation. A retrospective review (Denkler K et al., 2011; ASSH E-poster #21) demonstrated improved success with local anaesthetic prior to attempted cord manipulation, with 63% of injections into single cords achieving complete immediate release, compared with 39% of patients achieving similar complete release in CORD I, 30 days after first injection.

With use of the first CCH bottle, 100% complete immediate correction was achieved for contracted pretendinous cords with MCP contracture ≥20°, using only a mean 0.39 mg CCH. An 87% complete immediate correction rate was achieved for contracted spiral cords with PIP contracture ≥20° using only a mean 0.28 mg CCH. These results were maintained. A total of 83% of patients maintained complete MCP correction at a 35 day average and 58% of patients maintained complete PIP correction at a 38 day average.

Frequently, new patient's present and ask what the expected results would be with CCH for their DC. Results for only one bottle of CCH injected per hand were analysed to most accurately reflect the expected results for a new DC patient who presents to the office. These results were compared with CORD I and II results. Using the SIMple technique, significantly less CCH was required to release both spiral and pretendinous cords, with improved final DC corrections and a higher percentage of complete MCP and PIP corrections. With this technique, multiple cords can be injected at one visit, with one bottle of CCH, resulting in improved patient convenience and reduced overall healthcare costs (Tables 4 and 5).

The CCH preparation consists of two distinct collagenases, AUX-1 and AUX-II, in an approximate 1:1 ratio that cleaves collagen strands at different sites (Badalamente and Hurst, 2007; French et al., 1987; Starkweather et al., 1996). The author believes improved results are related to the SIMple technique. Micro amounts of AUX I and AUX II enzyme are released into the collagen cord with initial injection. These enzymes work immediately, breaking down collagen. After one to several minutes, depending on the density of the DC cord, enough collagen strands are disrupted, dramatically increasing permeability of the cord. This loss of resistance, with constant pressure on the needle plunger, is very reproducible. The author believes that relatively only a few collagen strands have to be disrupted for this loss of resistance and increased permeability to be noticed.

The injected enzyme then runs along and inside the cord, dissolving the cord from inside-out over the next several hours. In contrast, with an injection adjacent to the cord, the CCH dissolves the cord from outside-in. In this scenario, some of the enzyme molecules are effectively washed away. Others are broken down by the bodies' endogenous Alpha 2 macroglobulin enzymes that act against its own collagenolytic matrix metalloproteinases. Further, with injection adjacent to the cord, there is greater potential for spread of the enzyme to nearby flexor tendons or pulleys. The SIMple technique allows one to use less CCH at a location to dissolve a cord. This technique, however, does take significant time. By using the entire bottle of CCH with this technique, one can inject multiple cords with improved efficacy and

potentially fewer side effects as the enzyme is contained within the cord as opposed to being in the soft tissue adjacent.

Compared with a standard 0.58 mg injection, there was no apparent additional morbidity with injection of the entire bottle of CCH. Further, with good knowledge of anatomy, and careful technique, one can safely inject spiral and retrovascular cords with good results. The SIMple technique is important whenever an attempt is made to inject more than 3–4 mm distal to the MCP joint flexion crease. The intracord injection minimizes potential spread of the enzyme to nearby flexor tendons, lessening potential for tendon disruption.

A total of 100% of patients injected developed swelling, ecchymosis, and tenderness at their injection sites. This is in contrast to previous studies and verbal discussions with other injecting physicians where a small percentage of injected patients are nonresponder patients, i.e. no swelling, ecchymosis, or tenderness at their injection sites and no apparent cord disruption with the finger extension manoeuvre.

No patients developed tendon ruptures, anaphylaxis, or other serious adverse events. The incidence of skin lacerations and blood blisters was higher than found during CORD I and CORD II (Gilpin et al., 2010; Hurst et al., 2009), likely related to increase enzyme dosage used, and manipulation performed, under local anaesthesia, allowing for more forceful manipulation. These potential risks, including immunologic sensitization, were discussed with every patient pre-injection. No immunologic evaluations were performed. Over the course of the review, one patient received nine complete CCH bottles. The author is not aware of any other patient who has received this dose of CCH.

Five patients developed recurrent DC, defined as greater than 20°, at a mean of 11.5 months after injection (range 2–28 months). This retrospective review was not designed to evaluate long term recurrence.

Injection of CCH into the thumb is an FDA off-label technique. The injection results were less reliable and favourable with thumb and first web space cord injections. This could be related to patient demographics and small sample size. The author had several young patients in this subset, with bilateral five digit DC and multiple diathesis risk factors. First web space cords softened after injections. Involvement of the thumb and first web space reflects more severe DC. The author cautions patients with significant thumb and first web space involvement that results appear worse with injection into these areas, yet other authors (Bendon and Giele, 2012) have reported good outcomes after thumb injection.

The author notes decreased results with severe PIP contractures and Boutonniere deformities, secondary to attenuation and stretching of the extensor mechanism. Frequently, complete passive correction of the PIP contracture is achieved with a mild to moderate residual Boutonniere deformity. The author cautions patients with severe PIP contractures to expect skin lacerations during manipulation.

Weaknesses of this study are the retrospective nature with an unblinded and potentially biased author. Widespread adoption of this SIMple technique will require other researchers and clinicians to verify and support these findings.

This technique demonstrates improved patient convenience by allowing multiple cords to be injected at the same time, resulting in significant overall healthcare savings. The FDA-approved technique only allows 0.58 mg CCH to be injected into one cord at a time. If the results of this technique are verified and the use of this method becomes commonplace, the potential healthcare savings are enormous compared with the typical surgeon, surgicentre, anaesthesia, and occupational therapy charges associated with open fasciectomy. Highlighting these results, less than five patients needed occupational therapy after injection, and most had five finger DC.

This study demonstrates improved efficacy with the SIMple technique, allowing one to inject multiple DC cords at one setting, with no apparent additional morbidity with use of the entire bottle of CCH. A hurdle to widespread implementation is the significant increased time required to perform this SIMple injection, compared with injecting single cords. Unfortunately, current reimbursement methods reward additional injections performed, as opposed to improved results. Implementation of the SIMple CCH technique has the potential to improve current treatment for DC with resultant significant healthcare savings.

Conflict of interests

The author is a speaker and consultant for Auxilium.

Ethical approval

After obtaining regional institutional review board approval, I retrospectively reviewed every patient that I injected with collagenase from May 2010 to November 2012. A total of 144 patients (119 men, 25 women) were injected. Every patient was instructed preprocedure that this technique was off label, not FDA approved, and the potential serious

side effects with use of collagenase were outlined and highlighted.

Funding

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