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Collagenase clostridium histolyticum in Dupuytren's contracture: a systematic review

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Abstract

Introduction: In the last few years, the use of collagenase clostridium histolyticum for management of Dupuytren's contracture has increased. The procedure of enzymatic fasciectomy has become popular because it is non-invasive, safe and fast to perform.

Sources of data: A systematic search was performed on Medline (PubMed), Web of Science and Scopus databases using the combined keywords 'Dupuytren collagenase' and 'Dupuytren clostridium histolyticum'. Forty-three studies were identified. The quality of the studies was assessed using the Coleman Methodological Score.

Areas of agreement: The use of collagenase clostridium histolyticum provides better outcomes in patients with mild-moderate joint contracture, with lower complications and side effects than open fasciectomy. Manipulation can be performed 2–7 days after the injection. The use of collagenase is cost-effective.

Areas of controversy: Most of the studies did not report patient-related outcomes. The role of dynamic splint has to be investigated with randomized clinical trials.

Growing points: The shorter recovery time and the low incidence of serious or major adverse effects are the main advantages of this new technology.

Areas timely for developing research: There is a need to perform studies with longer follow-up because the recurrence rate seems to increase with

time. Further investigations are necessary to assess whether it is safe and effective to inject two or more cords at the same time.

Key words: Dupuytren, collagenase, non-operative, clostridium histolyticum, contracture

Introduction

Dupuytren's disease (DD) is a common connective disorder of the palmar fascia of the hand, which evolves to progressive contracture in flexion of the fingers, severely impairing function and quality of life.[1] The overall prevalence of DD is 0.2%, up to 50% in some subgroups of patients at high risk.[2,3] Age and race may be predisposing; it is four to six times more frequent in males than females[4]; women develop it later. A genetic predisposition has also been recognized.[5] High alcohol consumption, smoking, diabetes, epilepsy, hypercholesterolemia and exposure to vibrations are all risk factors.[6] Usually, the first appearance is a nodule in the palm of the hand, which usually progresses to form cords.

Open fasciectomy, needle fasciotomy and enzyme fasciectomy have all been successfully performed. The first application of enzymes in patients with DD was in 1965[7]: it was a mixture of trypsin and hyaluronidase; lidocaine[8] was introduced later. When the role of immature Type III collagen[9] was clarified, enzyme fasciectomy using collagenase became advantageous because, differently from other enzymes, it is collagen specific. It was investigated first *in vitro* in 1996, using the Clostridial collagenase[10]; the toxicity was studied later in *in vivo* studies.[11] The first open label study on patients with DD was published in 2000.[12] Then, several clinical trials have been undertaken in the USA, Europe and Australia. The Food and Drug Administration approved the collagenase clostridium histolyticum for the management of DD in 2010. This is a comprehensive review of studies published on management of patients with DD using enzyme fasciectomy with collagenase which aims to investigate whether it provides better outcomes compared to other techniques, with lower serious or major side effects and recurrence rates. The costs–benefits of its use have been investigated; the methodological quality of the available studies was also assessed.

Materials and methods

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] The keywords 'Dupuytren collagenase' and 'Dupuytren clostridium histolyticum' were used for the search, with no limits for year of publication. Medline (PubMed), Web of Science and Scopus were accessed on October 12, 2015. Articles in English, Spanish, Italian and French were identified, all published in peer-reviewed journals. Biomechanical studies, studies on animals or cad, avers, technical notes, letter to the editor and instructional courses were excluded. Two authors (A.D.B. and F.S.) independently assessed the abstract of each publication. When the article could not be included or excluded based on the abstract, a full-text version of the article was downloaded. If the abstract was not available, the article was excluded from the study. In addition, the reference list of each selected article was searched by hand to identify additional studies missed at the electronic search.

The two investigators assessed each study according to the Coleman Methodological Score (CMS),[14] a score ranging from 0 to 100. A score of 100 was the best study design. Both investigators performed the CMS assessment twice, with an interval of 10 days, and they discussed the scores until consensus was reached when more than a two-point difference was present. Data on demographic features, operative readings, diagnostic methods, follow-up periods, type and rates of complications, return to work activity, recurrence and outcome measures were recorded.

Results

A total of 182 studies were identified at the first search. Of the 75 studies selected on the basis of the abstract, 22 were excluded after the full text had been read; 43 publications relevant to the topic were included (Fig. 1). All the studies were published between 2000 and 2015; some studies include patients who are included in other studies. The total number of patients was 6795: 81% (5195) were male and 19% (1127) female. Gender data were not available in 12 studies.[15–26] The average age of the patients at the treatment time was 64 years; the mean follow-up was 15 months, ranging from 1 to 96 months.[15]

Quality assessment

All the Coleman scores are given in Table 1. Articles analyzing the cost analysis without any clinical information were excluded from the assessment with CMS. A score >85 is considered excellent, good from 70 to 84, moderate from 50–69 and poor when <50. The mean CMS was 65.6 (range 39–90). Four studies were graded as excellent, 11 studies as good (Table 1).

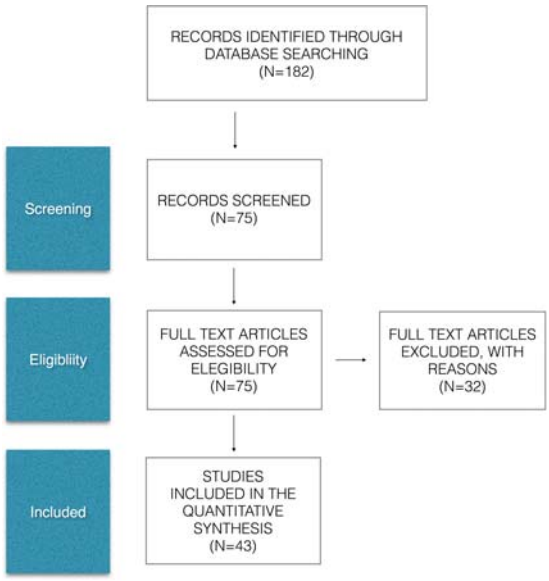

Fig. 1 PRISMA flow diagram.

Description of subject selection process

The study CORD I,[29] a Phase 3 clinical trial based on previous studies by Badalamente *et al.*,[12,27,28] followed strict selection criteria: healthy patients, older than 18 years, with one cord, metacarpophalangeal joint (MP) contracture between 20° and 100°, and proximal interphalangeal joint (PIP) contracture between 20° and 80°. Postmenopausal women or women who had used contraceptive therapy were also included. Exclusion criteria were breast feeding, bleeding disorder, recent stroke, the use of tetracycline, primary arthroplasty, anticoagulant therapy taken within 7 days of the injection, allergy to collagenase and chronic muscular or neuromuscular disorders. Later, 12 studies followed the same entry protocol.[17,24,30,32,34,35,38,39,46,49,52,53]

Coleman *et al.*[25,33] and Gaston[51] extended the indications to collagenase for patients with at least three joints involved; two injections were administered at the same time.

Skirven *et al.*[37]included only patients with severe PIP contracture >40 S.

Rehabilitation protocol

In the first rehabilitation protocol described by Badalamente *et al.*,[12] the patients were examined the day after the injection. At that stage, passive extension was allowed as patients tolerated up to the rupture of the cord, without any local anesthetic. Later, the protocol was modified by the same group of investigators[29] using a static splint in extension over night for 4 months. Many studies followed the same protocol, exception for four studies. Skirven *et al.*[37] used a custom-made orthosis in extension to extend gradually the contracted PIP joints. Mickleson *et al.*,[40] Manning *et al.*[47] and Kaplan *et al.*[48] performed manipulation 1, 4 and 7 days after application of collagenase, showing no differences in terms of efficacy and complications.

Objective outcome

Eighteen studies considered the clinical satisfaction of the patients and a residual contracture <5° as primary end points (Table 2).

Table 1 General features of the studies

Authors	Number of patients	Follow-up (m)	Type of study	CMS
Badalamente *et al.*[12]	35	20	Case series	69
Badalamente *et al.*[27]	80	48	Prospective, randomized, double-blind, placebo-controlled	90
Badalamente *et al.*[28]	35	24	Prospective, randomized, double-blind, placebo-controlled	79
Hurst *et al.*[29]	306	3	Prospective, randomized, double-blind, placebo-controlled	84
Gilpin *et al.*[30]	66	12	Prospective, randomized, double-blind, placebo-controlled	82
Watt *et al.*[15]	8	96	Case series	62
Chen *et al.*[31]	50		Cost analysis	
Witthaut *et al.*[32]	299	1	Prospective, randomized, double-blind, placebo-controlled	76
Bendon *et al.*[16]	4		Case series	42
Rozen *et al.*[17]	12	12	Case series	54
Coleman *et al.*[33]	12	1	Case series	57
Peimer *et al.*[34]	463		Retrospective case control	55
Sanjuan-Cerverò *et al.*[18]	91		Retrospective case control	65
Hayton *et al.*[35]	616		Retrospective case control	60
Martin Ferrero *et al.*[19]	35		Prospective case series	47
Nydick *et al.*[36]	59	6	Retrospective case control	67
De Salas-Cansado *et al.*[20]	123		Cost analysis	
Skirven *et al.*[37]	21	1	Case series	59
Witthaut *et al.*[38]	587	9	Retrospective analysis	73
Peimer *et al.*[39]	643	36	Retrospective analysis	63
Baltzer *et al.*[21]			Cost analysis	
Mickelson *et al.*[40]	43	1	Prospective, randomized	79
Naam[41]	61	24	Retrospective case control	58
Mc Mahon *et al.*[42]	48	15	Retrospective case series	70
Povisen *et al.*[22]	20		Case control	42
Povisen *et al.*[23]	20		Case control	39
Sood *et al.*[43]	16	12	Retrospective case series	50
Mehta *et al.*[44]	40		Cost analysis	
Mc Grouther *et al.*[24]	58	12	Case series	87
Coleman *et al.*[25]	60	2	Case series	71
Alberton *et al.*[45]	40	6	Case series	53
Raven *et al.*[46]	271	1	Randomized controlled double blind	86
Manning *et al.*[47]	45	2,5	Case series	61
Atroshi *et al.*[26]	32		Cost analysis	
Kaplan *et al.*[48]	37	3	Randomized controlled double blind	84
Zhou *et al.*[49]	132	3	Retrospective matched patients	70
Atroshi *et al.*[50]	164	1	Case series	57
Gaston *et al.*[51]	715	2	Case series	67
Badalamente *et al.*[52]	506	1	Prospective, randomized, double-blind, placebo-controlled	80
Peimer *et al.*[53]	644	60	Retrospective analysis	85
Verheyden et al.[54]	144	1	Case series	61
Muppavarapu *et al.*[55]	117	15	Retrospective case control	60
Tay *et al.*[56]	37	24	Retrospective case control	49

Gilpin *et al.*[30] reported the worst percentage of clinical success for both MP (13/20; 65%) and PIP (7/25; 28%); Badalamente *et al.*[27] reported the best result for MP (18/18; 100%) and in 2007 for PIP (9/9; 100%). Several studies (Table II and [13,16,19,22,23,33,35,37,41–43,49,50,54–56]) reported secondary end points, described as clinical improvement, but these results are difficult to compare because different variables such as range of motion (ROM) changes and decreased contracture were considered. Some studies[15,17,39,53] did not report objective outcomes. Cost analysis studies[18,20,21,26,31,44] did not report clinical outcomes.

Subjective outcomes

The patient satisfaction was evaluated in nine studies,[15,25,30,33,36,38,41,42,56] all reporting >80% of good satisfaction. In a study,[36] there were no differences in terms of satisfaction between patients who had undergone collagenase and needle fasciotomy.

The Disability of Arm, Shoulder and Hand (DASH) score[57] was administered in one study.[41] After 3 months, patients who had undergone collagenase fared better than those who had undergone open fasciectomy, with no statistical differences at 1 year and 2 years.

The quick DASH was used in one study.[42] The Michigan Hand Questionnaire (MHQ)[58] was used in two studies. Kaplan *et al.*[48] did not find any difference between the two groups (patients who received mobilization at Day 1 vs mobilization Day 2); Zhou *et al.*[49] found larger improvement in MHQ in the collagenase group compared to the fasciectomy group.

Table 2 Clinical success (residual contracture <5°, up to three injections)

Authors	MP joint	PIP joint
Badalamente *et al.*[12]	30/34 MP (88%)	7/9 PIP (77%)
Badalamente *et al.*[27]	18/18 (100%)	6/7 (85%)
Badalamente *et al.*[28]	12/14 (86%)	9/9 (100%)
Hurst *et al.*[29]	102/133 (76.7%)	28/70 (40%)
Gilpin *et al.*[30]	13/20 (65%)	7/25 (28%)
Witthaut *et al.*[32]	MP + PIP 126/197 (64%)	
Peimer *et al.*[34]	MP + PIP 310/467 (67%)	
Nydick *et al.*[36]	14/22 (64%)	5/12 (42%)
Witthaut *et al.*[38]	369/531 (70%)	128/348 (37%)
Mickelson *et al.*[40]	10/11 (91%)	4/10 (40%)
Mc Grouther *et al.*[24]	MP + PIP 53/65 (82%)	
Coleman *et al.*[25]	57/75 (76%)	15/45 (33%)
Alberton *et al.*[45]	MP + PIP 30/40 (75%)	
Raven *et al.*[46]	112/167 (67%)	44/104 (42%)
Manning *et al.*[47]	35/38 (92%)	
Kaplan *et al.*[48]	34/37 (91%)	
Gaston *et al.*[51]	213/325 (66%)	62/211 (29%)
Badalamente *et al.*[52]		219/644 (34%)

Complications

Five studies did not report adverse effects because they were not clinical studies.[20,21,26,31,44] In seven studies,[15,16,18,22,23,32,39] adverse effects were not reported. In all the remaining studies, adverse effects were widely reported. All the studies reported high rates of minor/mild adverse effects. Hayton *et al.*[35] reported minor adverse effects in 98% of the patients (604/616), specifically, peripheral edema in 81% (500), pain at the site of injection in 39% (239), hemorrhage at the site of injection in 38% (231), tenderness in 29% (170), swelling at the site of injection in 28% (170), contusion in 65% (402), limb pain in 43% (263), pruritus in 15% (94), ecchymosis in 14% (87), skin lacerations in 13% (79), blood blister in 11% (70), lymphadenopathy in 11% (67). Serious adverse effects occurred in eight studies (Table 3).

Recurrence

Twelve studies reported on recurrences rate (Table 4), varying from 0%[29,30,36,41] to 75%.[15] In all the studies, the recurrence was considered a decrease in passive extension >20°. Nevertheless, surgery is not recommended when the contracture is <30°.

Table 3. Major complications

Authors	Tendon rupture	Complex regional pain syndrome	Pulley rupture	Sensory abnormality	Deep tissue adhesion	Anapylactic reaction	Hyperestesia	Hemorrhage post-procedural	Deep vein thrombosis
Hurst *et al.*[29]	2/306 (0.6%)	1/306 (0.3%)							
Gilpin *et al.*[30]			1/66 (1.5%)	1/66 (1.5%)					
Rozen *et al.*[17]					2/12 (16%)				
Sanjuan Cervero *et al.*[18]							1/43 (2%)		
Mc Mahon *et al.*[42]	1/64 (1.5%)								
Coleman *et al.*[25]	1/60 (1.6%)		1/60 (1.6%)						
Gaston *et al.*[51]	1/715 (0.1%)					1/715 (0.1%)		1/715 (0.1%)	1/715 (0.1%)
Badalamente *et al.*[52]	2/506 (0.3%)	1/506 (0.2%)							

Cost analysis

Six studies[18,20,21,26,31,44] reported the costs of the application of collagenase. All the authors agreed that the use of collagenase is cost-effective, with savings between 29%[18] and 70%[44] compared to traditional surgery. According to Chen *et al.*,[31] collagenase is cost-effective only if the drug costs <945 dollars. A Canadian study[21] reported that the use of collagenase would be convenient if costs are significantly lower than the current price in USA. All the studies compared only the direct costs without including the costs of low productivity or sick leave. Naam[41] highlighted that the return to work was significantly faster after collagenase compared to open fasciectomy (1.9 days vs 37.4 days).

Discussion

The use of collagenase to manage DD has increased in the last 5 years. Even though the average CMS is moderate, most studies are of good to excellent methodological quality (Table 1). On the contrary, the relatively short follow-up limits the possibility to inform on the recurrence rate in the long term.

In this systematic review, the primary end point was the clinical success considered as a residual contracture <5° at 1 month after the last injection (Table 2). Nevertheless, the various studies report great variability in clinical success rate, especially when referring to the different joints of the hand. Specifically, the mean percentage of ROM of the metacarpophalangeal joint was 79.4% whereas that of the proximal interphalangeal joint was 48.9%. Hurst[29] and Gilpin[30] reported that joint with contracture <50° for the MCP and <40°for the PIP responded better than more severely contracted joints. The secondary end points were difficult to compare given their heterogeneity.

After manipulation, in almost all the studies, with exception for the three studies by Badalamente *et al.*,[12,27,28] patients were advised to wear a splint overnight for 4 months in order to achieve the maximal extension of the finger. Skirven *et al.*[37] used for severe PIP contracture (>40°; mean 56°) a custom-made dorsal orthosis allowing gradual

Table 4. Recurrences

Authors	Follow-up (months)	Total number of recurrences
Badalamene *et al.*[12]	20	3/35 (8.5%)
Badalamene *et al.*[28]	24	5/35 (14%)
Hurst *et al.*[29]	3	0/306 (0%)
Watt *et al.*[15]	88	6/8 (75%)
Gilpin *et al.*[30]	12	0/66 (0%)
Witthaut *et al.*[38]	9	19/497 (4%)
Peimer *et al.*[39]	36	217/623 (35%)
Nydick *et al.*[36]	6	0/59 (0%)
Naam[41]	24	0/61 (0%)
Mc Mahon *et al.*[42]	15	13/48 (28%)
Alberton *et al.*[45]	6	2/40 (3.8%)
Peimer *et al.*[53]	60	291/623 (47%)

progressive extension of the PIP joint to correct the residual flexion contracture. One week after manipulation, a cylinder orthosis in maximal extension was placed on the PIP joint for 4–6 weeks. In this short-term study,[37] clinical success (residual contracture <5°) was observed in 55% of the patients after one injection. Three studies[40,47,48] showed no statistical differences in patients undergoing collagenase and manipulation after 1, 4 or 7 days, without different occurrence of lesions to the skin and spontaneous ruptures in patients manipulated after 4 days, compared to those manipulated after 1 or 2 days.[48] Therefore, manipulation can be performed based on the needs of the patient.

All the studies[15,25,30,33,36,38,41,42,56] reported good satisfaction in >80% of the patients. Given that only some studies[41,42,48,49] used subjective outcome tools (DASH and MHQ), we now point out that future studies should concentrate on patient-related outcomes.

Major complications have been reported after fasciectomy in ~15% of patients, including injuries to the digital nerve (5.5%) and digital artery (2%), infection (2.4%) and complex regional pain syndrome (5.5%).[59] A recent review[60] comparing the occurrence of major adverse effects after application of collagenase vs fasciectomy showed lower rates of nerve injury (0% vs 3.8%), neurapraxia (4.4% vs 9.4%), complex regional pain syndrome (0.1% vs 4.5%) and arterial injury (0% vs 5.5%) in patients undergoing collagenase; the occurrence of tendon injury was similar (0.3% vs 0.1%). Our systematic review reported similar findings (Table 3). In addition, an anaphylactic reaction and a case of deep vein thrombosis evolving in pulmonary embolism have also been reported.[51] King and Belcher[61] reported two cases of cold intolerance after collagenase injection.

In all the studies (Table 4), a recurrence was defined as an increased contracture >20°.[29] The wide discrepancy of recurrence rates may be related to the follow-up, with higher recurrences in longer follow-up studies. The CORDLESS[39,53] was a long-term study that examined patients enrolled in three previous studies[29,30,32] at 3 and 5 years, showing a recurrence rate of 35% at 3 years and 47% at 5 years. Most of the recurrences (219/623; 75%) occurred in the first 3 years after treatment. In a *post hoc* analysis, Peimer advises to change the criteria of recurrence as a contracture >30° as a contracture of 20° does not need surgery. Using this threshold, the recurrence rate at 5 years was 32% (198/623).[53] The study with the longest follow-up (8 years) showed a recurrence rate of 75%,[15] with an average contracture of the MP joint of 22°. Van Rijssen *et al.*,[62] using a worsening of 30° as threshold, found a recurrence rate of 85% at 5 years after needle fasciotomy, and 21% after limited fasciectomy. Atroshi *et al.*[50] and Verheyden *et al.*[54] used a higher dose than that recommended, injected in different portions of the cord to treat multiple sites of contracture in a single session, showing higher efficacy without increased occurrence of major adverse effects.

Even though Coleman *et al.*[33] demonstrated good results after management of two cords on the same hand, these findings need to be supported by studies with larger sample size.

All the cost analysis studies[18,20,21,26,31,44] agree that collagenase treatment is cost-effective. Furthermore, all the patients treated with collagnease required less medical and physiotherapic cares. All the studies highlight to maintain low the price of the enzyme. According to Naam,[41] the time to return to work or daily activity was shorter in the collagenase group compared to the fasciectomy group (average 1.9 days vs 37.4 days).

This systematic review has several limitations. First, many studies report longer follow-ups of previous studies and some studies utilize the same cohort of patients. Also, although we included studies from several European languages, investigations in non-European languages may have been missed.

Surgical fasciectomy or collagenase injections do not provide a definitive management for patients with DD. Serious adverse events associated with the use of collagenase clostridium histolyticum are uncommon and less frequent compared to the rates of major complications which occur after surgery. In conclusion, the injections of collagenase clostridium histolyticum are satisfying for the patients, and should be encouraged. In cases of recurrence, the injections may be safely repeated.

Conflict of interest statement

The authors have no potential conflicts of interest.

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