ARTIGO DE REVISÃO | REVIEW ARTICLE
The Role of Clostridium Histolyticum in Dupuytren's Disease

The Role of Collagenase *Clostridium histolyticum* in Dupuytren's Disease: A Systematic Review

O Papel da Colagenase Clostridium histolyticum na Doença de Dupuytren: Uma Revisão Sistemática

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Abstract

Introduction: *Dupuytren's disease (DD) is a benign and progressive fibroproliferative disease that involves the palmar fascia, where collagenous cords form from the overlay of nodular fibrotic tissue. Clostridium histolyticum collagenase (CHC) is a minimally invasive option for the treatment of advanced DD. CHC allows collagen lysis, leading to the rupture of fibrous cords. This review aims to reflect on the existing scientific evidence about the role of CHC in the treatment of DD.*

Methods: *The study presented is a systematic review. Authors followed PRISMA reporting guidelines. The search was performed using the following databases: PubMed, ClinicalTrials.gov and Cochrane Central Registry of Controlled Trials (CENTRAL). As inclusion criteria, randomized and non-randomized clinical trials and observational studies were considered. As an exclusion criterion, all studies not written in English were excluded. The primary outcome was efficacy, through reduced contracture or increased range of motion. Safety/adverse effects, degree of contracture recurrence and patient satisfaction with the application of this technique were considered secondary outcomes. All relevant articles were systematically reviewed by 2 reviewers.*

Results: *The search resulted in 30 studies, 15 of which were selected by 2 independent reviewers. CHC therapy was shown to be superior in efficacy when compared to placebo and similar results when compared to surgical options. Regarding secondary outcomes, CHC therapy proved to be a safe treatment with a high patient satisfaction, with low recurrence rates and similar recurrence rates after surgical treatments with 5 years of follow-up.*

Conclusion: *CHC has proven to be an effective and safe therapy in DD patients, as well as a non-invasive alternative to surgery.*

Keywords: *Clostridium histolyticum; Dupuytren Contracture; Microbial Collagenase*

Resumo

Introdução: A doença de Dupuytren (DD) é uma doença fibroproliferativa benigna e progressiva que envolve a fáscia palmar, onde são formados cordões de colagénio a partir da sobreposição de tecido fibrótico nodular. A infiltração da colagenase *Clostridium histolyticum* (CCH) é uma opção minimamente invasiva para o tratamento da DD avançada. A CCH permite a lise do colagénio, despoletando a rotura dos cordões fibrosos. Esta revisão visa refletir sobre a evidência científica existente acerca do papel da CCH no tratamento da DD.

Métodos: O estudo apresentado é uma revisão sistemática. Os autores seguiram as *guidelines* PRISMA. A pesquisa foi realizada nas seguintes bases de dados: *PubMed*, *ClinicalTrials.gov* e *Cochrane Central Registry of Controlled Trials* (CENTRAL). Como critérios de inclusão, foram considerados ensaios clínicos randomizados e não randomizados e estudos observacionais. Como critério de exclusão, todos os estudos não escritos em inglês foram excluídos. O *outcome* primário foi a eficácia, traduzida por redução da contratura em flexão ou aumento da amplitude de movimento. Segurança/efeitos adversos, grau de recorrência da contratura e satisfação do doente com a aplicação desta técnica foram considerados *outcomes* secundários. Todos os artigos relevantes foram sistematicamente revistos por 2 elementos.

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Resultados: Da pesquisa resultaram 30 estudos, 15 dos quais foram selecionados por 2 revisores independentes. A terapia com CCH mostrou ser superior em eficácia quando comparada ao placebo e apresentou resultados semelhantes quando comparada às opções cirúrgicas. Em relação aos *outcomes* secundários, a terapia com CCH provou ser um tratamento seguro com elevado grau de satisfação do doente, com baixas taxas de recorrência e taxas de recorrência semelhantes após tratamentos cirúrgicos com 5 anos de *follow-up*.
Conclusão: A CCH provou ser uma terapia eficaz e segura em pacientes com DD, bem como uma alternativa não invasiva à cirurgia.
Palavras – chave: Clostridium histolyticum; Colagenase Microbiana; Contratura de Dupuytren.

Introduction

Dupuytren´s disease (DD) is a benign and progressive fibroproliferative disease which affects the palmar fascia, where collagenous cords form from the superposition of nodular fibrotic tissue.[1,2] It is a multifactorial pathology, influenced by genetic and environmental factors that affects around 3%-6% of the general population, being more frequent in males and northern-europeans.[2,3] The age of onset is variable and it may be associated with other fibroproliferative diseases, such as Peyronie´s disease and plantar fibromatosis.[2] This condition typically evolves with progressive deformation of the affected hand, resulting in flexion and contracture of the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints, causing a considerable functional impairment.[1,3,4]

Although there is no curative therapy for DD, corrective surgical intervention remains the standard of care. There are several invasive procedures approved for the treatment of the disease and palmar fasciectomy (PF) is currently considered the gold standard, as it is associated with better long term clinical outcomes.[1,2] However, this procedure presents some disadvantages, with risks associated to the surgical aggression and a long recovery period after the intervention.[2] Furthermore, recurrence of the disease is frequent and surgical reintervention tend to result in more long-term complications compared to first-time procedures.[1] Alternatively, there are available minimal invasive procedures, such as percutaneous needle fasciotomy (PNF), which have fewer complications, but a higher recurrence rate compared to surgical procedures.[2]

The *Clostridium histolyticum* collagenase (CHC) was the first non-surgical treatment approved in the USA and in European Union for the treatment of DD, with evidence supporting the benefits of this option in the contractures associated with the disease.[2,4] This biological therapy of enzymatic nature consists in direct collagenase injection on the palmar cords of the affected hand, promoting the degradation of the fibrotic tissue which had been formed due to excessive collagen production.[3] After collagenase administration, finger extension exercises must follow, starting 24 hours after the procedure in order to facilitate the complete destruction of the cords and full recovery of the hand's normal function.[3,5]

Although some comparative studies between the two possible types of treatment of DD have been conducted, there is some difficulty in comparing the efficacy and safety of PF and CHC in the treatment of DD, as the long-term outcomes vary with the type of population studied, the associated comorbidities, the number of affected joints and how therapy efficacy and disease recurrency are defined.[3]

According to the currently available literature, the use of CHC seems to contribute to the reduction of the joint contracture typically seen in DD, without the risks involved with the conventional surgical procedures.[6] This systematic review was developed with the goal of comparing different outcomes between conventional surgical procedures and CHC in the treatment of DD regarding treatment´s efficacy, safety and disease´s recurrence.

Methods

Studies' eligibility: The selected articles were those that focused on the efficacy of CHC in improving the functionality of patients with DD in comparison to placebo, other therapeutic interventions or without comparison to other interventions. The main outcome was the level of efficacy of CHC's application, measured through the contracture's improvement or the increase of the joint's range of motion. The secondary outcomes were safety/adverse effects, the degree of recurrence of the contracture and patient´s satisfaction. Only clinical randomized trials, non-randomized trials and observational studies with available results were included in this review. Articles written in different languages than English were excluded.

Studies' identification: Our research was conducted in PubMed, ClinicalTrials.gov and CENTRAL databases. All articles published until October of 2022 were considered. The research terms used in our query were "*Clostridium histolyticum*" (MeSH term) and "Dupuytren Contracture" (MeSH term). All references of the selected articles were reviewed to guarantee maximum coverage. The last research in the databases was performed on the 7th of October of 2022.

Studies' selection: Two reviewers performed an independent and duplicate review of every potentially eligible abstract obtained by the research method. One article was added by backward citation.

Data extraction: Data was extracted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers were responsible for the selection and extraction of pre-specified data from every study. Blinding of the reviewers was not performed. In case of disagreement, a third reviewer was responsible for the analysis of the study in question and a team discussion was made in order to achieve a common decision about the extracted data. Every included study was classified according to their risk of bias. Randomized Controlled Clinical trials were evaluated with Cochrane Risk-of-Bias Tool for Randomized Clinical Trials (RoB2) and non-randomized trials were evaluated with NewCastle Ottawa Scale (NOS). Tables 1 and 2 present the details of the quality evaluation process for randomized clinical trials and observational studies, respectively.

As a systematic review, no approval by the ethic's commission was required.

Table 1 - Bias risk for Randomized Clinical Trials, according to Cochrane Risk-of-Bias Tool for Randomized Clinical Trials (RoB2). "+" – Low bias risk; "?"– Moderate bias risk; "-" – High bias risk.

Study	Gilpin *et al.*	McGrouther *et al.*	Withaut *et al*.	Badalamente *et al.*	Bainbridge *et al.*	CORD I Study	Costas *et al.*	Bystrom *et al.*
Randomization Process	+	+	+	?	+	+	+	+
Deviation from the intended intervention	+	?	?	+	?	?	+	+
Outcome measure	+	+	+	+	+	+	+	+
Missing data	?	?	?	+	+	+	?	?
Reported Outcomes	+	+	+	+	+	+	+	+

Table 2 - Bias risk for Non Randomized Trials, according to NewCastle Ottawa Scale (NOS). Good quality: 3 or 4 stars in "Selection" or 1 or 2 stars in "Comparison" and 2 or 3 stars in "Outcome". Moderate quality: 2 stars in domain "Selection" and 1 or 2 stars in "Comparison" and 2 or 3 stars in "Outcome". Poor quality: 0 or 1 stars in "Selection" and 0 stars in "Comparison" and 0 or 1 stars in "Outcome".

Study	Pess *et al.*	Gaston *et al.*	Hurst *et al*.	Bear *et al.*	Peimer *et al.*	Gruber *et al.*
Selection	***	***	***	***	***	*
Comparison	**	**	*	**	**	*
Outcome	**	***	**	**	***	**

Results

The investigation strategy identified 30 references, 16 of which were potentially selectable studies after title and abstracts' analysis. Of those, two studies were excluded after full text analysis (one of them did not fulfill the intended outcomes and the other one was not about DD). After analyzing every study reference, one study was added by backward citation. A total of 15 studies were included and reviewed. Figure 1 details the evidence acquisition process.

Every included study was published until the 7th of October of 2022. Five of those studies are post-hoc analysis of clinical trials, five are randomized controlled clinical trials, three are non-randomized clinical trials, one is an observational prospective trial and one is an observational retrospective trial. The follow-up period varied between 30 days and 5 years. The number of participants varied between 35 and 1082 individuals. Table 3 presents each included study characteristics.

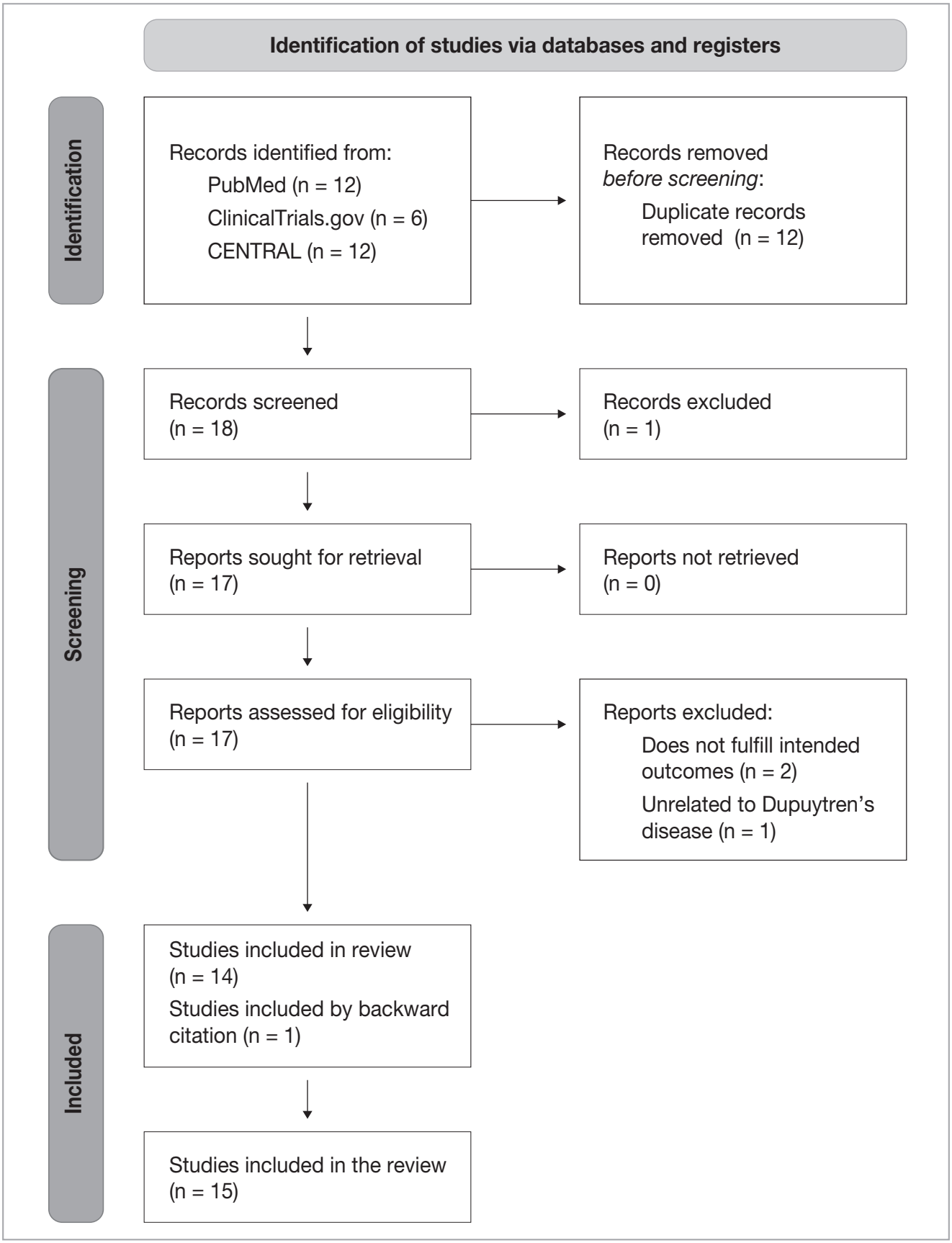

Figure 1 - Flow-chart of evidence acquisition.

Table 3 - Design and characteristics of the included studies.

First Author	Publication Year	Study Design	Interventions	n (%)	Follow-up
Pess *et al.*	2018	Post hoc analysis	CHC	527 (100)	31 days
McGrouther *et al.*	2014	Post hoc analysis	CHC	58 (100)	12 months
Witthaut *et al.*	2011	Post hoc analysis	CHC vs Placebo	204 (66) /104 (34)	90 days
Gilpin *et al.*	2010	RCT	CHC vs Placebo	45 (68) / 21 (32)	12 months
Badalamente *et al*.	2015	Post hoc analysis	CHC	506 (100)	90 days
Gaston *et al.*	2015	Non randomized clinical trial	CHC	715 (100)	60 days
CORD I Study	2009	RCT	CHC vs Placebo	204 (66) / 104 (34)	90 days
Costas *et al.*	2017	RCT	CHC vs Placebo	58 (77) / 17 (23)	8 weeks
Bainbridge *et al.*	2012	Post hoc analysis	CHC and previous surgery vs CHC without previous surgery	422 (39) / 660 (61)	30 days
Hurst *et al.*	2010	Non randomized clinical trial	CHC vs Placebo	23 (66) / 12 (34)	30 days
Abe *et al.*	2019	RCT	CHC vs PNF	36 (51) / 34 (49)	3 years
Bear *et al.*	2017	Non randomized clinical trial	CHC	52 (100)	12 months
Peimer *et al.*	2015	Observational Prospective study	CHC	644 (100)	5 years
Gruber *et al.*	2021	Observational Retrospective study	CHC vs PF	111 (70) / 48 (30)	5 years
Bystrom *et al.*	2022	RCT	CHC vs PNF	78 (50) / 78 (50)	5 years

RCT – randomized clinical trials; CHC – *Clostridium histolyticum* collagenase; PNF – percutaneous needle fasciotomy; PF – palmar fasciectomy

The studied interventions included – I) analysis of injection with CHC without comparison to other interventions; II) injection with CHC in patients previously injected with CHC; III) injection with CHC *versus* injection with placebo; IV) injection with CHC in a fibrous chord with previous surgical intervention *versus* injection with CHC in a fibrous chord without previous surgical intervention; V) injection with CHC *versus* PNF; VI) injection with CHC *versus* PF.

The instruments used to evaluate the outcomes were different across several studies. The efficacy of the intervention was evaluated through range of motion or the degree to which the contracture improved. As for disease´s recurrence, side effects and personal satisfaction, those were reported in different ways in the included studies.

I – Effect of injection with CHC without comparison with other interventions

Pess *et al* conducted a post-hoc analysis of the clinical trial NCT01674634 that included two populations with DD with a total of 181 and 346 participants. All participants received two concurrent CHC injections (0.58 mg/injection) for two joint contractures (MP and/or PIP). The mean (SD) improvement in total fixed contraction contracture (FFC) 31 days post-CHC treatment in 181 patients was: 71.1% for Tubiana I, 77.0% for Tubiana II, 72% for Tubiana III and 66.4% for Tubiana IV. Treatment of MCP and PIP in the same finger resulted in a mean improvement of 82.5% and 66.4%, respectively.[1]

McGrouther *et al* conducted a post-hoc analysis of two phase III clinical trials – CORD I and CORD II (NCT00528606 e NCT00533273) – which included 58 subjects with moderately severe DD. All participants were given an injection with CHC (0.58 mg/injection). Forty-nine patients received treatment for one joint and 9 patients received treatment for two joints. Of 65 evaluated joints, 82% met the primary endpoint of clinical success (reduction in

contracture to ≤ 5º of full extension 30 days after the last injection). Reported adverse events were mild to moderate in intensity; none resulted in discontinuation. Recurrence at 12 months was observed in 3.8% of the joints. 66% of the participants reported that were "very satisfied", 27% "quite satisfied", 4% "neither satisfied nor dissatisfied" and 0% "very dissatisfied" with the treatment.[2]

Badalamente *et al* performed a combined review of four phase III clinical trials – CORD I/II and JOINT I/II – in which 506 subjects participated and were submitted to CHC injection (0.58 mg/injection), in a total of 644 PIP joints that were treated. A total of 60% of the participants received one injection, 24% two injections, 16% three injections and 1% four injections. Clinical success (0º to 5º of full extension) occurred in 27% of PIP joints after one injection and 34% after the last injection. Clinical improvement occurred in 49% after one injection and in 58% after the last injection. 16% that received three injections did not reach clinical success. Adverse events occurring in more than 10% of the patients were peripheral edema (58%), contusion (38%), injection site hemorrhage (23%), injection site pain (21%), injection site swelling (16%), and tenderness (13%). Two tendon ruptures occurred, but no further ruptures were registered after a modified injection technique was adopted.[5]

Gaston *et al* conducted a clinical trial which consisted in the administration of two injections with CHC (0.58 mg/injection) in one or two joints of 715 patients with DD. At day 31, mean total FFC (sum of 2 treated joints) decreased 74%, from 98º to 27º. Mean total ROM increased from 90º to 156º. The incidence of clinical success was 65% in MCP joints and 29% in PIP joints. Most treatment-related adverse events were mild to moderate, resolving without intervention; the most common events were swelling of tread extremity, contusion, and pain. The incidence of skin laceration was 22%. Two concurrent injections of CHC to 2 affected joints in the same hand were generally well tolerated. Greater than 90% of patients reported being very satisfied or quite satisfied with the treatment.[6]

Peimer *et al* directed a prospective trial, CORDLESS, with a five year follow-up that included 644 subjects. Enrolled patients were evaluated annually for contracture and safety at 2, 3, 4 and 5 years after the first injection (0.58 mg) of CHC. At year 5, 47% of successfully treated joints had recurrence (≥20º worsening) - 39% of MCP joints and 66% of PIP joints. Most recurrences occurred prior to 3 years after treatment. CHC was not part of CORDLESS. However, during follow-up period 66 patients received treatment of CHC. Among these patients, 28 experienced adverse events after injection - the most common were peripheral edema and contusion. Most adverse events were mild to moderate and skin atrophy was considered treatment-related by investigators.[7]

II – Effect of the injection with CHC in patients previously injected with CHC

Bear *et al* conducted a clinical trial with 52 individuals, in which the cord affecting the recurrent joint (increased more than 20º with palpable cord) was treated with up to 3 injections of CHC (0.58 mg per injection). A total of 57% of the joints achieved contracture of 5º or less. Overall, 86% of patients had a 20º or greater increase in ROM. At least 1 adverse event was reported by 46 of 52 patients (89%). Four patients reported 6 serious adverse events. No systemic hypersensitivity reactions or tendon injuries were reported.[8]

III – Effect of the injection with CHC vs placebo injection

Witthaut *et al* performed a post-hoc analysis of the CORD I study, which had 308 participants, with 204 of them being injected with CHC (0.58 mg/injection) and 104 with placebo (10 mM TRIS per 60 mM sucrose in reconstituted in diluent). The mean increase in ROM was 36.7º in the CHC-treated joints ($p<0.001$) and 4º in the placebo-treated joints. The mean increase in ROM exceeded the clinically important difference (CID) in CHC group but not in placebo group; the difference between CHC group and placebo group in the mean increase in ROM also exceeded the CID. More CHC treated patients than placebo treated patients achieved "normal" status (81% vs 25%; $p<0.0001$). More collagenase than placebo treated patients reported being "very/quite satisfied" (87% *vs* 32%, $p<0.001$).[4]

Gilpin *et al* conducted a randomized clinical trial (CORD II), with 66 patients with DD, 45 of which were given CHC (0.58 mg/injection) and 21 of which were given placebo (lyophilized TRIS and sucrose only in sterile diluent). Statistically significantly more cords injected with collagenase than placebo met the primary endpoint (44.4% *vs* 4.8%; $p<0.001$). The mean percentage decrease in degree of joint contracture from baseline to 30 days after last injection was 70.5%±29.2% in CHC group and 13.6%±26.1% in placebo group ($p<0.001$). The mean increase in ROM was significantly greater in the collagenase (35.4º±17.8º) than in the placebo group (7.6º±14.9º; $p<0.001$). Most adverse events were related to the injection or finger extension procedure. No tendon ruptures or systemic allergic reactions were reported. One patient had a flexion pulley rupture, and one patient underwent routine fasciectomy to address cord proliferation and sensation abnormality. No joint met the criteria for recurrence of contracture by the end of the 12-months study. More patients were satisfied with collagenase ($p<0.001$).[3]

Hurst *et al* conducted a randomized clinical trial (CORD I) in which 308 individuals participated. Two hundred four of them were given CHC (0.58 mg/injection) and 104 were given placebo (10mM TRIS per 60 mM sucrose reconstituted in diluent). More cords that were injected with collagenase than cords injected with placebo met the

primary endpoint [reduction in primary joint contracture to 0 to 5 degrees of full extension 30 days after the last injection] (64.0% *vs* 6.8%; $p<0.001$) as well all secondary endpoints ($p<0.0002$). Overall, the ROM in the joints was significantly improved after injection CHC a compared with placebo (from 43.9º to 80.7º *vs* from 45.3º to 49.5º; $p<0.001$). The most reported adverse events were localized swelling, pain, bruising, pruritus, and transient regional lymph-node enlargement and tenderness. Three treatment-related serious adverse events were reported: 2 tendon ruptures and 1 complex regional pain syndrome (CPRS). No significant changes in flexion or grip strength, no systemic allergic reactions, an no nerve injuries were observed.[9]

Costas *et al* executed a randomized clinical trial with 75 participants, with 58 receiving different doses of CHC (0.25 mg; 0.40 mg; 0.60 mg) and 17 receiving placebo (TRIS-HCL and sucrose). Percentage changes in area were significantly greater with 0.40 mg and CHC 0.60 mg, but not CHC 0.25 mg, *versus* placebo at post-treatment week 8. Mean change in nodular consistency and hardness were significantly improved in CHC *versus* placebo at weeks 4 and 8. The most common adverse events in CHC groups were contusion, extremity pain, and localized swelling. There were no trends for increased adverse events occurrence with increasing CHC dose, except for injection-site bruising and localized swelling. Most patients were "very satisfied" or "quite satisfied" with CHC 0.40 mg and 0.60 mg.[10]

Hurst *et al* directed a phase III clinical trial with 35 patients, in which 23 of them were given up to three injections of CHC and 12 of them were given up to three injections of placebo. A total of 100% of the interventional group reported non-serious adverse events and 80% of the control group reported non-serious adverse events.[11]

IV – Effect of the injection with CHC in a fibrous chord with previous surgical intervention vs injection with CHC in a fibrous chord without previous surgical intervention

Bainbridge *et al* conducted an analysis of data collected from 12 clinical trials that used CHC. This analysis included 1082 individuals, 442 of which received CHC in previous DC hand surgery [CHC in operated hand (206); CHC in non-operated hand (196) and CHC in unknown hand (20)] e 660 received CHC and no previous DC hand surgery. After treatment with CHC, fibrous flexion contractures at MCP joints was reduced by 75% in previously operated hands and by 80% for non-operated hands. Improvements in ROM were 32º in both groups. For PIP joints, the reductions in FFC for the operated and non-operated hands were 52% and 50%, respectively; improvements in ROM were 24º and 26º, respectively. Some adverse events rates were significantly higher in the operated vs non-operated hand groups but were not clinically relevant.[12]

V - Injection with CHC vs percutaneous needle fasciotomy (PNF)

Abe *et al* executed a randomized clinical trial with 70 participants. 36 received CHC (0.58 mg/injection) - 0.25 mL of injected volume to MCP joint and 0.20 mL of injected volume to PIP joint and 34 were submitted to PNF. At day 30, a measurable improvement was obtained in all treated joints. A successful correction was obtained in 100% of MCP joints in both groups, and in 89% and 100% of the stage I PIP joints in the CHC group and PNF group, respectively. Successful corrections were obtained in only 50% in injection group and in 67% in PNF group of the stage II PIP joints. In the injection group, adverse events were reported for all patients, such as edema, lymphangitis, blister, contusion, and/or skin rupture. In the fasciotomy group, complications were reported for 15% of patients, such as complications of nerve damage, edema, and/or skin rupture. There were no statistically significantly differences between the injection group and the fasciotomy group in any stage for recurrence.[13]

Byström *et al* directed a prospective randomized controlled clinical trial with 156 patients. Seventy-eight patients received CHC injection and 78 patients were treated with PNF. The 5-year outcomes for NF are similar to those for collagenase in terms of sustained correction, recurrence, presence of Dupuytren cords, and patient-reported outcomes for the treatment of MCP joint contractures.[14]

VI - Injection with CHC *versus* palmar fasciectomy (PF)

Gruber *et al* conducted a retrospective analysis with 159 patients. One hundred and eleven patients received CHC treatment and 48 received PF. After propensity score matching, there were 44 patients in each group with similar disease and demographic characteristics. Rates of reintervention and perceived recurrence were significantly higher in the CHC group than the surgery group at a minimum of 5 years following treatment.[1]

Discussion

The therapeutic options available to approach DD have been expanding throughout last decades and injection with CHC is a recently explored alternative. It is important to measure the efficacy of this intervention in comparison to other ones, while also considering the levels of recurrence of the disease with this treatment, its side effects and patients' satisfaction.

There are some methodological differences between the studies included in this review. Sample's size and sample´s characteristics were variable, and one can assume that not all samples were representative of the population to whom the application of CHC is intended. The number and location

of the joints treated as well as the number of CHC's administrations, the follow-up period and the reported side effects were other factors that diverged between studies. Such differences may limit the internal, and therefore, external validity of the review, as well as the generalization of the obtained results to the overall population.

Five articles that evaluated CHC's efficacy in the treatment of DD without comparison to placebo or any other intervention were included. The absence of a comparison factor can condition the study of causality between CHC´s administration and DD improvement.

Five studies compared CHC with placebo administration and all of them revealed therapeutic advantage of the collagenase in the treatment of DD, which seems to suggest that it is beneficial in the management of the disease.

The comparison between the therapeutic effect of CHC and PNF was performed by Abe *et al*, reporting a similar effect as well as a similar recurrence rate of the disease without any statistically significant differences.

Only one study included in this review compared CHC and PF – Gruber *et al*. This study suggested necessity of reintervention and disease recurrence is significantly higher with CHC treatment.

Overall, treatment with CHC seems to improve DD contractures, has similar recurrence rates with more invasive treatment techniques and ensures high patient satisfaction. CHC appears to be a secure intervention for DD treatment and its most common side effects have minimal impact and include peripheral edema, contusion, injection site hemorrhage, injection site pain, swelling and tenderness.

Conclusion

This systematic review intended to reflect on the role that CHC may have to play in DD's treatment. The results of the included studies seem to demonstrate a superiority of the treatment with CHC in comparison to placebo. In comparison to PNF and PF, the benefits seem to be similar between the two approaches, although only one of the included articles focused on each one of these specific comparisons. More clinical randomized trials should be performed, if possible, with larger samples, longer follow-up periods and greater homogeneity between the intervention protocols used, in order to obtain scientific evidence with stronger validity regarding this subject.

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