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HANDSURGERY

Collagenase clostridium histolyticum injection versus limited fasciectomy for the treatment of Dupuytren's disease: a systematic review and meta-analysis of comparative studies

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Abstract

Introduction The aim of the present study is to systematically review the literature on well-selected comparative studies for meta-analysis on outcome differences between collagenase clostridium histolyticum (CCH) injection and limited fasciectomy (LF) for Dupuytren's disease.

Materials and methods PubMed/Medline, Embase, and the Cochrane Library were searched for comparative studies assessing differences in outcomes of CCH and LF. Effect estimates were pooled across studies using random effects models and presented as weighted mean difference (MD) and odds ratio (OR) with corresponding 95% confidence interval (CI).

Results A total of 11 studies encompassing 1′051 patients was included (619 patients in the CCH and 432 in the LF group). The residual contracture at a minimal average follow-up of three months was higher in the CCH group than in the LF group (27.8 vs. 16.2°, MD 11.6°, 95% CI [8.7, 14.5°], $p < 0.001$). The recurrence rate was significantly higher in the CCH group (25.8 vs. 9.3%, OR 5.2, 95% CI [1.5, 18.8], $p = 0.01$) while the rate of severe complications was significantly higher in the LF group (0.3 vs. 7.3%, OR 0.12, 95% CI [0.03, 0.42], $p = 0.001$).

Conclusions Evidence of the present study confirms that CCH injection has a higher rate of disease recurrence whereas LF carries a higher risk for severe complications. It's imperative that the trade-off between these aspects is considered, keeping in mind that CCH injections may be repeated in case of disease recurrence without increasing procedure related risks, especially in complex cases.

Keywords Dupuytren's disease · Collagenase injection · Limited fasciectomy · Meta-analysis

Introduction

Dupuytren's disease is a benign, fibroproliferative condition that involves excessive collagen deposition in the palmar fascia of the hand potentially resulting in contractures of the digits [1]. The aetiology of the disease is not yet fully understood. Differentiation of fibroblasts into myofibroblasts with contractile properties and excessive type III instead of type I collagen deposition within a less organized cross-linked extracellular matrix occurs. This pathogenesis seems to be related to heredity as an autosomal dominant pattern with varying penetrance has been suggested [2, 3]. Further identified associations with Dupuytren's disease are diabetes mellitus, liver disease and epilepsy [4]. The prevalence in caucasians is estimated at 12% in patients aged 55 years and 29% in those aged 75 years while men are much more often affected than women [5]. Around half of the diagnosed patients undergo treatment [6].

Over time, various treatment options have become established. Surgery is the mainstay treatment, with limited fasciectomy (LF) involving removal of the contracture cords is most commonly performed nowadays [7]. Injectable collagenase clostridium histolyticum (CCH) was introduced into clinical practice after showing promising efficacy results compared with placebo in 2009 [8]. The effect of CCH is based on the lysis of collagen, which leads to the disruption of the contracture cords. A recent systematic review stated that CCH injection is a safe, effective treatment to improve hand function in Dupuytren's contracture with only

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minimal risks for major complications [9]. For many years, it has become a standard of treatment in the armamentarium of hand surgeons alongside LF. Because CCH injection is no longer available in Europe since the withdrawal of Xiapex® from the market in March 2020, an increasing number of patients are again being treated by LF ever since. To emphasise the relevance and support efforts to reintroduce this treatment option, comparative outcome analysis of CCH injection and LF are very topical. Several different studies indicate a comparable success rate of CCH injection and LF, while it seems that CCH injection has a higher recurrence rate but fewer severe complications. These claims have been strengthened by two recently published network meta-analyses. Cooper et al. included three comparative trials, while the remaining studies were retrospective case series evaluating only one of both treatment methods [10]. Obed and co-workers included studies assessing three different treatment strategies (CCH injection, LF and needle fasciotomy) without considering comparative studies investigating outcome differences between CCH injection and LF [11]. Both studies report limited comparability of patients in the different treatment groups, raising concerns about the reliability and interpretability of the reported results in regarding true outcome differences between CCH injection and LF.

In light of this, the aim of the present study was to conduct a comprehensive systematic literature review and pool the results of exclusively comparative studies in a meta-analysis that provides the highest available evidence to date regarding outcome differences between CCH and LF.

Material and methods

This systematic review and meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [12, 13]. No ethical approval was required for this study.

Search strategy and selection criteria

The PubMed/Medline, Embase, and the Cochrane Library databases were searched for studies comparing CCH injection to LF as treatment method for Dupuytren's disease. The search syntax is demonstrated in Fig. 1. Two reviewers (RL, DNM) screened title and abstract for eligibility independently. Both randomised clinical trials and observational studies were considered for inclusion.

Data collection was performed according to the principles laid out by the Cochrane Collaboration [14]. Keywords selection was based on the PICO model [15]. Accordingly, the search terms used described the study population and intervention comparing different outcomes: (Dupuytren OR Dupuytren's disease OR Dupuytren's contracture) AND (clostridium histolyticum OR collagenase OR xiapex OR xiaflex) AND (surgery OR fasciectomy OR aponeurectomy). Both reviewers independently performed full-text screening. Inclusion criteria were comparison of CCH injection to LF and reporting on outcomes of interest (residual contracture at a minimal average follow-up of three months, recurrence, and severe complication rates). Exclusion criteria were inclusion of less than ten cases, languages other than English, French, Italian or German, no availability of full-text, letters, study protocols, and published abstracts from scientific meetings. Disagreements on eligibility of full-text articles were resolved by consensus or by discussion with a third reviewer (EV). An extensive cross-check of the references from the original studies was performed to identify potential additional articles.

Data extraction

Two reviewers (RL, DNM) independently performed data extraction. The following baseline characteristics were extracted from the included studies; first author, year of publication, study design, level of evidence, number of included patients, follow-up duration, number of fingers involved, age, gender, history of diabetes, smoking, alcohol use, and mean preoperative contracture of MP and PIP joints.

Quality assessment

Two reviewers (RL, DNM) independently assessed the methodological quality of the included studies using the Methodological Index for Non-Randomised Studies (MINORS) [16]. Disagreements were resolved by consensus.

Study outcome

The primary outcome was the residual contracture at a minimal average follow-up of three months. Residual contracture was defined as the combined extension deficit in metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints.

Secondary outcomes included recurrence rate and the safety of the procedure. Disease recurrence was defined differently in several studies. It was characterized as a deterioration of the total passive extension deficit by 20 degrees compared to the immediate post-intervention situation in three studies [17–19], and by 30 degrees in one study [20]. Two included studies defined disease recurrence by patient perception or the need for reintervention [21, 22].

Procedure safety was judged by the rate of severe complications including infection, delayed wound healing, iatrogenic nerve, vascular or tendon injury.

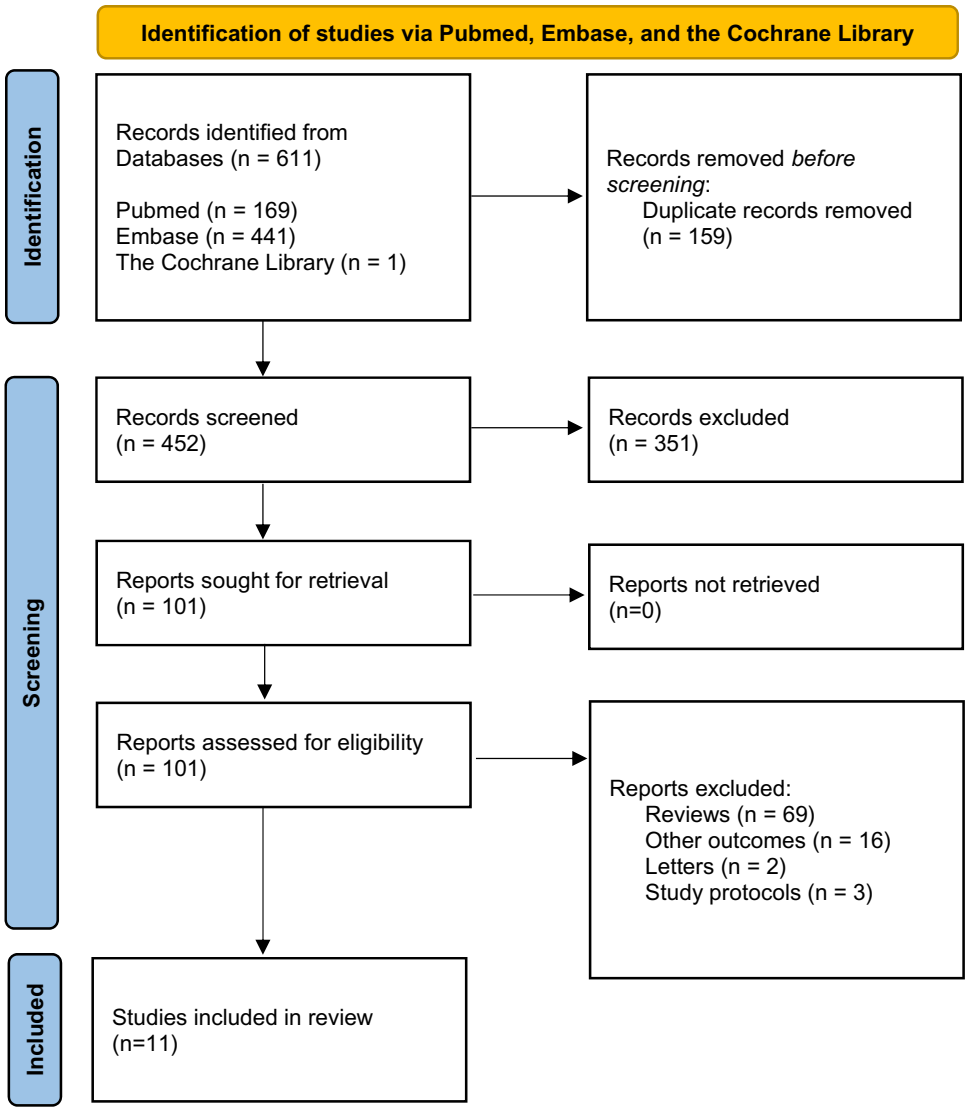

Fig. 1 PRISMA 2020 flow diagram of the database search. From [12]

Statistical analysis

Information about continuous variables was presented as means with standard deviation (SD), or information was converted to mean and SD using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [14]. Dichotomous variables were presented as counts and percentages. Effects of treatment options on continuous outcomes were pooled using the (random effects) inverse variance weighting method and presented as mean difference (MD) with a corresponding 95% confidence interval (CI). Effects of treatment options on binary outcomes were pooled using the (random effects) Mantel–Haenszel method and presented as odds ratio (OR) with a corresponding 95% CI.

Heterogeneity between studies was assessed by visual inspection of forest plots (overlapping of 95% CI) and by the I^2 statistic for heterogeneity. A p value below 0.05 was considered as statistically significant. Review Manager (RevMan, version 5.3.5) was used for all statistical analyses.

Results

Search

Figure 1 presents the flowchart of the literature search and study selection. A total of 11 observational comparative studies was included, one prospective and ten retrospective studies [17–27].

Study and patient characteristics

The 11 studies encompassed 1051 patients; 619 underwent CCH injection and 432 patients were treated by LF. All

baseline characteristics were equally distributed between the treatment groups and included age (mean 66.1 [SD 9.2] years in the CCH group versus 65.0 [SD 9.2] years in the LF group), mean number of rays involved per patient (1.4 versus 1.4), male distribution (83% versus 72%), diabetes mellitus (13% versus 11%), smoking (15% versus 17%) and alcohol use (40% versus 30%). In terms of preoperative contracture levels, no statistical difference was found between the CCH injection and surgery groups in either the MP or PIP joints. However, the weighted mean of preoperative joint contractures was slightly higher in the CCH group for both MP and PIP joints: 36.5° in CCH patients versus 34.4° in LF patients at the MP joint (MD 2.1°, 95% CI [− 20.7, 24.9°] and 44.1° versus 37.4° (MD 6.7, 95% CI [− 18.2, 31.6]) at the PIP joint. Study and patient characteristics are shown in Table 1.

Quality assessment

The details and distribution of the MINORS scores are described in Table 2. The mean MINORS score was 15.7 points (range 13–22 points).

Study outcomes

Regarding the primary outcome, four studies reported on residual contracture of the treated rays at a minimal average follow-up of three months [17, 18, 20, 25]. The residual contracture was significantly higher in the CCH group than in the LF group (27.8 vs. 16.2°, MD 11.6, 95% CI [8.7, 14.5°], $p < 0.001$, Fig. 2). Secondary outcomes included recurrence rate and the rate of severe complications such as infections, delayed wound healing, neurovascular and tendon injuries. The recurrence rate was reported in six studies and was significantly higher in the CCH group (25.8 vs. 9.3%, OR 5.2, 95% CI [1.5, 18.8], $p = 0.01$, Fig. 3). Severe complications were reported in four studies and occurred at a significantly higher rate in the LF group (0.3 vs. 7.3%, OR 0.12, 95% CI [0.03, 0.42], $p = 0.001$, Fig. 4). The I^2 statistic for heterogeneity was low in the comparison of residual contracture and severe complication rate ranging from 0 to 11% (Figs. 2 and 4). Heterogeneity was notably higher in the comparison of the estimated recurrence rates with a I^2 statistic of 80% (Fig. 3). The recently published study by Eckerdal and coworkers was the only one to demonstrate a higher recurrence rate in the LF group, thus providing the main contribution to the heterogeneity of effect estimates in this outcome [23].

Discussion

This study represents a systematic review and meta-analysis of eleven comparative observational studies comparing outcomes of CCH injection with LF in patients with Dupuytren's disease. Evidence of this study suggests that CCH has higher risks for residual contracture at a minimal average follow-up of three months and disease recurrence while LF carries a higher risk for severe complications such as infection, delayed wound healing, neurovascular and tendon injuries.

Comparison to previous literature

To date there are no meta-analyses assessing outcome differences of CCH versus LF based on exclusively comparative studies. The aforementioned systematic review published in 2020 analyzed 17 studies of which three were comparative studies whereas 14 trials focussed on only one of both treatment methods [10]. Results of the mentioned study suggest similar contracture improvement in both techniques. They also found a higher recurrence rate and a lower risk for severe complications for patients undergoing CCH compared to LF. The absolute risks of disease recurrence and severe complications were notably lower than in the results presented here, except for the rate of severe complications in the LF group (disease recurrence: CCH 6.8% vs. 29.9%, LF 2.3% vs. 7.9%, severe complications: CCH 0.1% vs. 0%, LF 16.8% vs. 7.5%). However, comparative analysis was methodologically not possible and thus not performed in the mentioned systematic review. Furthermore, effect estimates regarding improvement of joint contracture showed marked heterogeneity possibly reflecting important variability in the baseline patient characteristics of the included studies. The second aforementioned systematic review compared three different treatment options (CCH injection, LF and needle fasciotomy) in a network meta-analysis [11]. Comparative studies investigating outcome differences between CCH injection and LF were not included. The comparison of these two treatment options was based on a generalized pairwise modelling framework. This methodology has known drawbacks such as the assumption of independence of pairwise comparisons and absence of unobserved confounders. Taking these aspects into account, we saw the need to conduct a meta-analysis pooling data of exclusively comparative studies.

Interpretation of results

Residual contracture and the risk for disease recurrence seem to be the main disadvantages of CCH injection compared to LF. The definition of Dupuytren's disease recurrence has historically been subjective to controversial discussions and has shown to be time dependent. In 2016, 21 experts from 10 countries found a consensus over the definition of Dupuytren's disease recurrence using the Delphi method: more than 20 degrees of contracture recurrence in any treated joint at one year post-treatment compared to six

Table 1 Study and patient baseline characteristics of the included studies

Author and year	Country	Study design	Level of evidence	Study period	Number of patients, n		Follow-up duration (range)	Number of fingers involved, mean		Mean age, y (SD)	
					CCH	LF		CCH	LF	CCH	LF
Yamamoto 2022 [20]	Japan	Pro	III	2018–2019	52	26	3.5 months	2.2	2.2	71 (8.9)	70 (7.6)
Eckerdal 2022 [23]	Sweden	Retro	IV	2018–2020	112	46	> 5 years	1.6	1.4	69 (8)	65 (10)
Gruber 2021 [22]	USA	Retro	IV	2010–2013	44	44	> 5 years	1.0	1.0	68 (7.2)	70 (8.8)
Leafblad 2019 [21]	USA	Retro	IV	2005–2016	153	116	Median 2 years	1.4	1.5	65.8 (10.2)	63.7 (9.8)
Sefton 2018 [27]	Australia	Retro	IV	NR	21	18	> 6 months	NR	NR	NR	NR
Leclère 2018 [18]	Switzerland	Retro	IV	2012–2013	38	14	2 years	1.3	1.3	64.7 (9.7)	61.9 (12.2)
Neuwirth 2016 [26]	Austria	Retro	IV	2012–2014	17	18	NR	1.2	1.1	64.9 (8)	59.6 (11.5)
Zhou 2015 [25]	The Netherlands	Retro	IV	NR	66	66	Mean 11 weeks (6–12 weeks)	1.5	1.5	61 (10)	63 (8)
Tay 2015 [24]	Malaysia	Retro	IV	2002–2005	18	19	> 2 years	NR	NR	65.1 (10.4)	66.2 (7.1)
Muppavarapu 2014 [19]	USA	Retro	IV	2009–2013	73	44	> 1 year	NR	NR	64 (NR)	65 (NR)
Naam 2013 [17]	USA	Retro	IV	NR	25	21	> 2 years	1.0	1.4	65 (NR)	67 (NR)
				Total	**619**	**432**		**1.4**	**1.4**	**66.1 (9.2)**	**65.0 (9.2)**

Author and year	Males, n (%)		Diabetes, n (%)		Smoker, n (%)		Alcohol use, n (%)		Mean preop ED at MCP (SD)		Mean preop ED at PIP (SD)	
	CCH	LF	CCH	LF	CCH	LF	CCH	LF	CCH	LF	CCH	LF
Yamamoto 2022 [20]	50 (96)	25 (96)	12 (23)	11 (42)	15 (29)	4 (15)	40 (77)	21 (81)	39.9 (20.5)	36.5 (21.9)	37.2 (23.6)	46.9 (27.8)
Eckerdal 2022 [23]	100 (89)	38 (83)	11 (10)	5 (11)	17 (15)	11 (24)	NR	NR	NR	NR	NR	NR
Gruber 2021 [22]	31 (70)	31 (70)	2 (4.6)	3 (6.8)	5 (11)	6 (14)	NR	NR	NR	NR	NR	NR
Leafblad 2019 [21]	115 (75)	92 (79)	25 (16)	12 (10)	23 (15)	19 (16)	41 (46)	21 (36)	30.1 (26)	33.6 (26.5)	47.0 (28.5)	33.2 (30.8)
Sefton 2018 [27]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Leclère 2018 [18]	33 (87)	11 (79)	NR	NR	NR	NR	NR	NR	43.7 (20.4)	30.4 (21.2)	51.3 (21.3)	30.0 (20.9)

Table 1 (continued)

Author and year	Males, n (%)		Diabetes, n (%)		Smoker, n (%)		Alcohol use, n (%)		Mean preop ED at MCP (SD)		Mean preop ED at PIP (SD)	
	CCH	LF	CCH	LF	CCH	LF	CCH	LF	CCH	LF	CCH	LF
Neuwirth 2016 [26]	17 (85)	18 (90)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhou 2015 [25]	54 (82)	50 (76)	4 (6)	3 (5)	5 (8)	10 (15)	NR	NR	26 (25)	23 (25)	27 (26)	33 (25)
Tay 2015 [24]	13 (72)	15 (79)	NR	NR	NR	NR	NR	NR	38.9 (16.8)	44.8 (19.0)	59.4 (17.6)	50.7 (17.1)
Muppa-varapu 2014 [19]	61 (84)	33 (75)	NR	NR	NR	NR	NR	NR	50.2 (NR)	45.9 (NR)	55.9 (NR)	49.7 (NR)
Naam 2013 [17]	23 (92)	13 (62)	NR	NR	NR	NR	NR	NR	43.5 (NR)	41.4 (NR)	30.0 (NR)	29.9 (NR)
	497 (83)	**296 (72)**	**54 (13)**	**34 (11)**	**65 (15)**	**50 (17)**	**81 (40)**	**42 (30)**	**36.5 (23.8)**	**34.4 (24.7)**	**44.1 (25.8)**	**37.4 (27.2)**

Table 2 Methodological quality of included studies using the Methodological index for non-randomised studies (MINORS)

	Yamamoto 2022 [20]	Eckerdal 2022 [23]	Gruber 2021 [22]	Leafblad 2019 [21]	Sefton 2018 [27]	Leclère 2018 [18]	Neuwirth 2016 [26]	Zhou 2015 [25]	Tay 2015 [24]	Muppavarapu 2014 [19]	Naam 2013 [17]
Clearly stated aim	2	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	0	2	0	0	0	0	0	0	0	2	0
Prospective data collection	2	1	0	0	0	0	0	1	1	0	0
Appropriate endpoints	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of endpoints	0	2	1	0	0	0	2	2	0	0	0
Appropriate follow-up (> 6 months)	0	2	2	2	2	2	0	0	2	2	2
Loss to follow-up < 10%	0	1	0	0	0	2	0	0	0	2	0
Prospective calculation study size	2	2	2	0	0	0	0	0	0	0	0
Adequate control group	2	2	2	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	1	2	2	2	1	2	2
Adequate statistical analysis	2	2	2	2	2	2	2	2	2	2	2
Total score	**16**	**22**	**17**	**14**	**13**	**16**	**14**	**15**	**14**	**18**	**14**

Explanations: 2 points = total agreement, 1 point = partial agreement, 0 points = not reported or no agreement

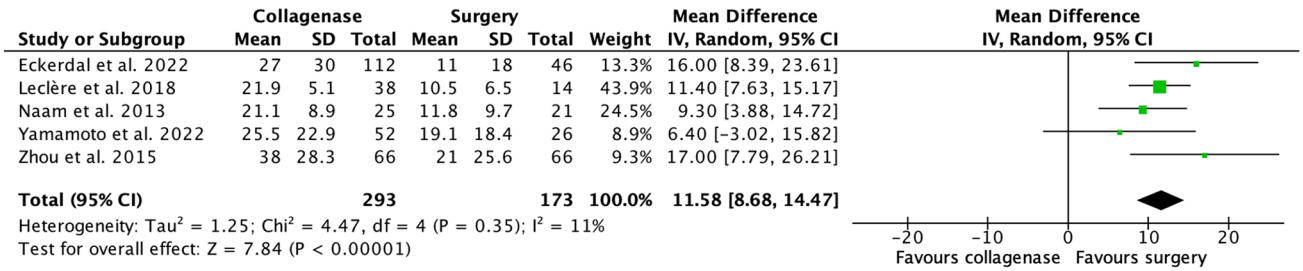

Fig. 2 Forest plot depicting effect estimates regarding mean degrees of residual contracture at a minimal average follow-up of 3 months

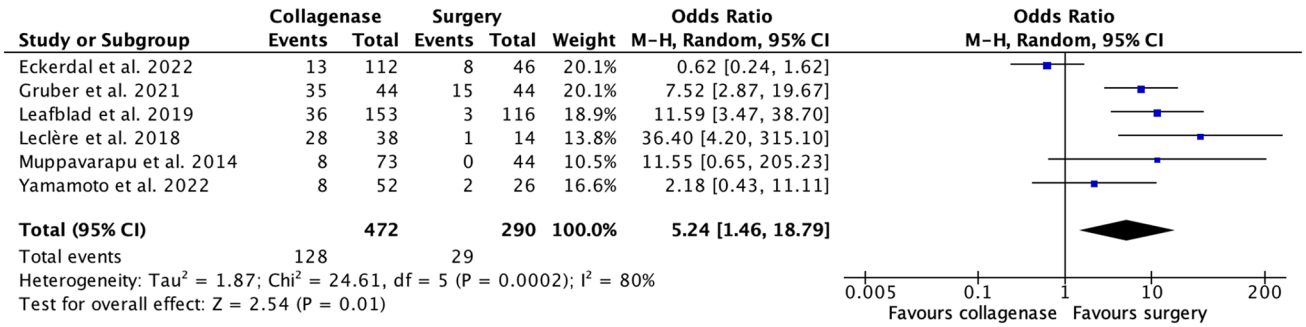

Fig. 3 Forest plot depicting effect estimates regarding the recurrence rate

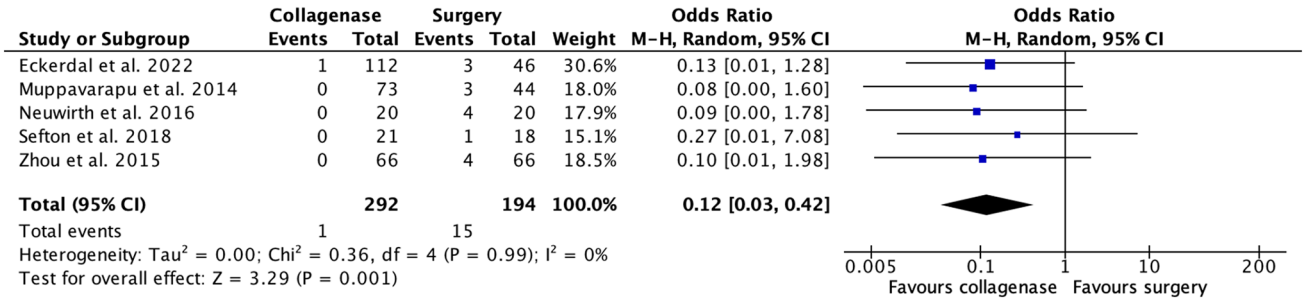

Fig. 4 Forest plot depicting effect estimates regarding the rate of severe complications

weeks post-treatment was determined as definition of disease recurrence [28]. Up until now, the literature lacks large scale cohort studies assessing recurrence rates after CCH injection according to the Delphi consensus. A literature review of 2011 found recurrence rates ranging from 10 to 31% after CCH injection, although the definition of disease recurrence and follow-up periods varied widely across studies [29]. Scherman et al. defined recurrence as > 30° compared with 3 months after treatment which was found in 33% of 93 treated patients at a 3-year follow-up [30]. The authors of the CORDLESS study (Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study) defined recurrence as > 20° compared with one month after the intervention which led to a recurrence rate of 47% in 623 patients at 5 years post-treatment [31]. These latter values are closely in line with the results reported in the present meta-analysis, however, the definition of disease recurrence also substantially varied across studies included in this study.

Disease recurrence after LF occurred in 9.3% in our study, which lies within the wide range of 0–31% published in literature [10, 29]. A very recently published study that used the Delphi definition reported a recurrence rate of 3.5% in a retrospective cohort of 142 patients undergoing LF [32]. This result suggests that the recurrence rate after LF in our study is somewhat overestimated, probably again due to the heterogeneity of recurrence definition. The same authors promoted residual contracture as a helpful alternative outcome parameter treatment of Dupuytren's contractures.

We therefore assume that the degree of residual contracture reported in the included studies with comparable baseline situations allows a more accurate comparison of the treatment effect in this meta-analysis. However, even though the degree of residual contracture and the recurrence rate was significantly higher in the CCH group, there are multiple reports in the literature showing that the number of medical and hand therapy visits after CCH is significantly lower than after LF [33–35]. Besides the fact that this increases the cost benefit in favour of CCH treatment, it also speaks for a faster recovery and reintegration into everyday life. This is in line with the findings of Zhou and colleagues, who found a significantly higher satisfaction in patients who underwent CCH injection than in patients after LF [25].

The incidence of severe complications differed significantly between the two treatment groups in the present meta-analysis. Following LF, the rate of severe complications was as high as 7.3%. This result is in line with a structured literature review of 48 studies looking at the safety of LF which revealed an incidence of 8.9% [36]. Severe complications hardly ever occur after CCH injection which has been consistently confirmed in literature [37]. This finding confirms that CCH injection is significantly safer than LF for the treatment of Dupuytren's disease. In addition to procedure safety, there are considerations with regard to disease pattern, subjective experience and socioeconomic factors. The studies included in the present meta-analysis focussed on patients with limited numbers of ray involvement as 1.4 digits were treated per patient on average in both groups. There are no studies assessing this aspect but, in our opinion, more diffuse patterns of the disease are probably more efficiently and more safely treated by CCH injection whereas surgery in these patients often is more complex. Furthermore, in case of disease persistence or recurrence, CCH injections can be repeated without increasing procedure-related risks. Several studies have focussed on patients who underwent both procedures in the course of their life and found that these patients preferred CCH injection over LF [38–40]. Their preferences were largely attributed to convenience and shorter down-time [40]. From a socioeconomic point of view, multiple studies compared the healthcare-related costs of both treatment methods and consistently found significantly higher costs of LF compared to CCH, despite the high medication costs associated with CCH [33–35, 41–44]. In addition, a very recently published large-scale retrospective cohort study suggests that CCH treatment results in lower opioid and nonsteroidal anti-inflammatory drug use compared with LF [45]. All these aspects must be taken into account when choosing between CCH and LF for the treatment of Dupuytren's contractures. In view of the results obtained in this study and in our experience, we consider the treatment with CCH to be a very safe, patient-friendly, and socioeconomically valuable option. In our opinion, these strengths outweigh the higher degree of residual contracture and recurrence rate especially for patients with a more complex and diffuse disease pattern involving multiple digits. Particularly in times of reduced availability of CCH in Europe, since the withdrawal of the market authorisation in March 2020, the value of this treatment option becomes more evident.

Limitations

Several limitations must be considered. As previously described, there was high heterogeneity in the definition of recurrence in the pooled analysis for the secondary outcome "recurrence rate" thus limiting its value. Baseline characteristics for the primary outcome were equally distributed between both intervention groups and the I^2 statistic for heterogeneity was low in two of three outcomes. Therefore, these results seem robust. However, any residual confounding by none-measured baseline characteristics such as surgery and measurement techniques cannot be ruled out.

All studies available for analysis were observational studies. There is increasing evidence that pooled estimates of observational studies do not differ from those obtained from randomised clinical trials [46]. However, we are looking forward to the results of a large-scale multicenter, prospective, randomized trial comparing CCH injection to LF of which the study protocol was published in 2021 [47].

Conclusion

In summary, the present meta-analysis suggests with the so far highest quality of evidence available that CCH injection has a higher degree of residual contracture and recurrence rate whereas LF carries a higher risk for severe complications. Several studies in literature report that the number of postinterventional medical and hand therapy visits, as well as the analgetic drug use are lower and patient satisfaction is higher after CCH treatment. It's imperative that the trade-off between these aspects is considered, keeping in mind that CCH injections may be repeated in case of disease persistence or recurrence without increasing procedure related risks, especially in a diffuse disease pattern.

Author contributions All listed authors have made substantial contributions to this article. The design and conception of the work, analysis, and interpretation of data was carried out by RL and DNM. RL wrote the first draft of the manuscript. Critical revision for important intellectual content as well as final approval of the version to be published was done by DS, RI and EV. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy

or integrity of any part of the work are appropriately investigated and resolved.

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Data availability The data used for this study were generated, processed, analyzed and stored on a specific form designed for this study. No registration within a recognized repository was performed. The data are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interest.

Ethical approval Not applicable.

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