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Cost-Utility Analysis of Collagenase *Clostridium Histolyticum* versus Fasciectomy for Dupuytren´S Contracture

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Abstract **Original Research Article**

Objective: The main aim of this cohort study was to determine which option is more cost-effectiveness for treatment of Dupuytren´s contracture (DC); partial fasciectomy (FSC) or a single administration of collagenase *Clostridium Histolyticum* (CCH), with a six months follow-up thereafter. ***Material and Methods:*** The cohort study prospective compared FSC patients (n= 48) and CCH patients (n= 43). Incremental cost-utility ratios (ICUR) was calculated based on a case-control study (CCH vs. FSC) and extrapolated to a life-time horizon, adjusted by age and sex. We performed a deterministic, probabilistic (bootstrapping method) and structural sensitivity analysis to validate our results. ***Results:*** The effectiveness observed in patients who underwent FSC was 87.5% and 67.4% for those who received a CCH infiltration, with similar complications (18%). The average cost per patient in the CCH group was of 1168.19€ (CI95%: 1131.63 to 1204.74€) and 1420.19€ (CI95%: 1411.41 to 1428.97€) for FSC group. The most influential variable is the acquisition cost of CCH. If threshold decision is 20000 or 30000€/QALY, the probability to choose CCH versus FSC at finish follow-up is over 50%. ***Conclusions:*** We conclude that one CCH injection is a cost-effectiveness alternative in the treatment of DC in comparison to FSC.

Keywords: Cost effectiveness, cost utility, Dupuytren´s contracture, fasciectomy, clostridium histolyticum collagenase.

INTRODUCTION

Dupuytren's contracture (DC) involves pathologic myofibroblast forming cords due to deposition of collagen into the digitopalmar fascia, which can result in fixed flexion deformity of the affected finger impairing normal hand function. Depending on the degree of contracture, the patient´s daily activities may become significantly affected as well as their quality of life, a point where they often seek treatment [1].

Most common surgical treatment is usually carried out in the main operating room (OP) under general or regional anaesthesia, the operating time being, on average, about one hour [2, 3]. Nonetheless, OP times can be substantially longer in patients with severe contractures in multiple fingers. After surgery, many patients need therapy and splints to keep up the extension of the affected fingers. Although surgery is often effective in reducing the contracture, postoperative complications are common, and patients often develop contracture recurrence [4].

An alternative nonsurgical treatment for DC is collagenase *Clostridium Histolyticum* (CCH), which is injected directly into the cord to weaken it by enzymatic degradation, allowing the treating physician to manipulate and break the cord [5]. It demonstrates favourable clinical results following administration, with good or excellent rates of improvement in 70-90% of cases at short-term follow-up [6, 7]. The safety profile of DC treatment is well-defined, both for the CCH and fasciectomy (FSC) [8, 9]. Since its marketing authorization, its use as an alternative for DC has demonstrated the advantage of this non-invasive treatment over surgical treatments [10].

Many studies have estimated the costs of FSC or administration of CCH, in different health levels or countries, and with differences between them [10, 11]. However, few studies have evaluated the effectiveness of the CCH compared to surgery [12, 13]. The main aim of this cohort study was to find which option is more cost-effectiveness partial FSC versus single administration of CCH in DC patients.

MATERIAL AND METHODS

General model overview

Incremental cost-utility ratios (ICUR) was calculated based on a prospective, non-randomize case-control study (FSC vs CCH) and extrapolated to a 20-year time horizon, adjusted by age and sex [14]. The economic model distinguished between two periods of time based on the data available in the case-control study. In the short term, costs and effects were estimated for each patient during the follow-up period based on the current data from the case-control study. Thus, clinical complications (nerve injury, chronic regional pain syndrome or others) and use of resources (length of stay, physiotherapy, drugs,...) were identified for each patient. The long term was based on the recurrence and clinical complications, mainly. The study was conducted from the perspective of the Spanish National Health System; therefore, it included only direct medical costs of Hospital de Denia Marina Salud (Spain). As recommended by the main Spanish economic evaluation guidelines, a discount rate of 3% was applied, both for costs and for effects [15].

CCH was identified as cost-effectiveness when it was less costly and more effectiveness than the alternative evaluated (i.e. dominant strategy), or when the ICUR versus the alternative fell below the threshold of willingness to pay per QALY gained assumed in Spain, i.e. €30000/QALY gained[16].

To readily interpret negative ICUR, the net monetary benefit (NMB) was calculated based on the difference between, on the one hand, costs and effects and, on the other hand, willingness to pay per QALY [16].

$$NMB = \Delta QALYs * Threshold - \Delta Costs$$

A positive NMB indicated that CCH was cost-effective against partial FSC.

Study design

The control group (FSC) and a case group (CCH) were included consecutively from November 2015 to November 2017 with at least a follow-up of 6 months. Treatments were decided according to physician's criteria based on inclusion/exclusion criteria. Surgeons were familiar with and used the recommendations of the European guidelines [6,7] on prescribing each treatment although patient's assignment to FSC or CCH was mainly based on their own experience and judgement. The study included 91 patients with DC who were over 18 years old, single finger affected (Table 1). Exclusion criteria were breast-feeding or pregnancy, a bleeding disorder, a recent stroke, previous treatment of the primary joint within 90 days before the beginning of the study, CCH treatment or treatment with any investigational drug within 30 days before the beginning of the study, the use of a tetracycline derivative within 14 days before the beginning of the study, the use of an anticoagulant within seven days before the beginning of the study, an allergy to CCH, and a chronic muscular, neurologic, or neuromuscular disorder affecting the hands.

Single infiltration of CCH on each affected finger was compared to FSC. For the evaluation of CCH treated patients, the results of the affected articulation and compensatory extension of the adjacent joint in the same finger were considered, to balance both techniques studied [13]. The Regional Ethics Committee approved this study. All patients provided written informed consent.

Efficacy

Clinical success for both interventions was defined as 0-5º or complete (0º) extension, measured as lack of degrees of extension, 30 days after either procedure [5]. In those cases where global clinical success was not achieved, a satisfactory result was described as a 66% (or more) reduction of the initial contracture six months after the intervention.

Recurrence was defined as 20º or greater worsening (compared to day 30 after the last injection) with a palpable cord or any medical/surgical intervention to correct new/worsening contracture [17]. For partial FSC group, recurrence rate was 47% (range: 12-73%) in a 5-year period [18]. For CCH group, cumulative recurrence rates were 20% for year two, 35% for year three, 42% for year four, and 47% for year five.[17] Life expectancy was estimated from the Spanish general mortality tables, adjusted by age and sex (National Institute of Statistics, 2017).

Quality of life

Health outcomes were expressed based on QALYs, defined as a combination of survival and quality of life (utility) associated with each state of health. Utilities are essential since they show individual's preferences for different outcomes. Utility is expressed as a value, where 1 represents an ideal health state and 0 represents death.

Due to, utilities were not performed in the case-control study neither in electronic medical records, we used the only study with utilities of FSC and CCH based on standard gamble research [13]. The utilities were assigned to successful or failed with/out complications (nerve injury, chronic regional pain syndrome or others) from 0.994 for CCH and 0.991 for FSC (success without complication) to 0.964 for CCH

0.967 for FSC (failed with chronic regional pain syndrome) (Table 2).

Costs

The healthcare resources evaluated were mainly limited to drugs, visits (surgeon, anaesthesiologist and physiotherapy), drug administration, surgeon procedure (operating theatre, hospital stay, major ambulatory or minor surgery) and complications [10], considering that they are directly associated with disease (Table 2). The costs were obtained from the Analytic Accountancy Department and from the Hospital de Denia Marina Salud Pharmacy Service. All healthcare staff expenditure was considered and all costs were referenced to € at 2017. Costs of previous years were updated using the consumer price index (National Institute of Statics, 2017).

SENSITIVITY ANALYSIS

Because the cost-effectiveness analysis uses multiple sources to model probabilities of outcomes, there is inherent uncertainty. To account for this uncertainty, we performed a sensitivity analysis to highlight the variables with the greatest impact on the result [14]. Several sensitivity analyses were carried out. In one-way sensitivity analyses, key inputs (recurrence, acquisition and complications) were varied one at a time to simulate the impact on the incremental cost-effectiveness ratio. We have performed a scenario and structural sensitivity analysis,[19] modifying at the same time three utilities. When we equal the utilities values of the complications we do the simplest model, so we can check how it varies from the reference model used.

Finally, we employed probabilistic sensitivity analyses on the base-case model at the last stage of the study and at life-time horizon, adjusting this time interval to the mean age and life expectancy of our patients. We performed a bootstrapping simulation with 1,000 samples from the results obtained in our patients [20].

Statistical analysis (case-control study)

We used the Student T-test to compare the average values; alternatively, when required, we used the Mann-Whitney U test. Nominal data are shown as numbers and percentages. Error alfa were 5% to be considered statistically significant. We presented our results with confidence interval 95%, particularly for ICUR [14, 20].

RESULTS

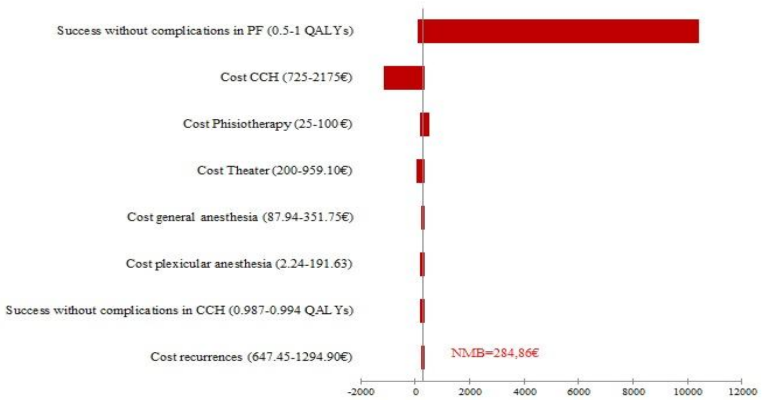
The effectiveness observed in the patients who underwent FSC was 87.5% (42 out of 48), and 67.4% (29 out of 43) for those who received a single CCH infiltration at one month follow-up. Both groups presented similar (major and minor) complications: 18.8% and 18.6% in the FSC and CCH group, respectively. Similar results were maintained at six months follow-up [10] (Table 3).

When quality of life was applied, it was seen that FSC was 0.9892 QALYs and CCH was 0.9900, at six-months (Table 4). At life time, FSC showed non-significant less QALYs than CCH (6.368 vs 6.423), probably due to the low sample size.

The average cost per patient in the CCH group was 1168.19€ (CI95%: 1131.63 to 1204.74€), 62.1% of which was due to the acquisition price of the drug (Table 4). In the FSC group, the surgery procedure was the highest cost incurred in all patients, accounting for a 40.2% of 1420.19€ (CI95%: 1411.41 to 1428.97€), followed by anaesthesia (16.0%) and physiotherapy (14.0%). The ICUR at six months was negative (Table 4) so CCH injection was the dominant strategy (more effectiveness and less costly) against partial FSC. The NMB of CCH was 284.86€ at six months. Consequently, CCH turned out to be the best option short and long-term in our study.

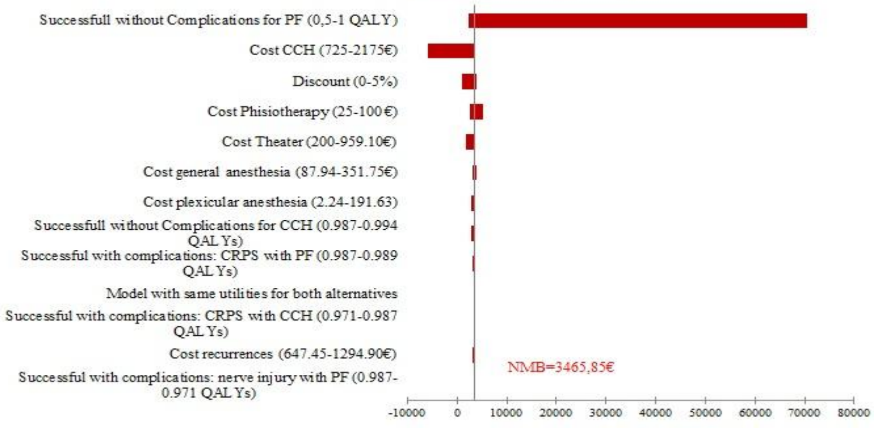
The unvaried sensitivity analysis performed is shown in Figure 1 and Figure 2 with a Tornado diagram. It shows that the most influential variable is the acquisition cost of CCH.

Figure 1. Tornado diagram at six months follow-up*.



* Deterministic sensibility analysis of main parameters tested, their values vary in an explicit range for each variable shown in parentheses.

Figure 2. Tornado diagram after horizon time 20 years*.



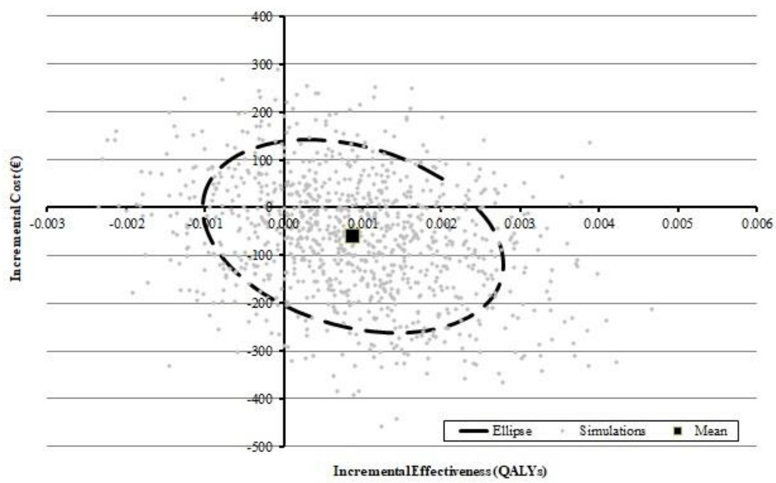
* Deterministic sensibility analysis of main parameters tested, their values vary in an explicit range for each variable shown in parentheses.

The change of using one to three vials is reflected in a substantial variation, at the last follow-up with an ICUR= 1354251.14 €/QALY and NMB= -1165.14€, then FSC could be a dominant option. If we used two vials to treat each finger, FSC could be a dominant option with an ICUR= 530242.32€/QALY. These results show that the CCH treatment is only cost-effectiveness if we use just one vial of CCH. Other variables that may influence decision-making to a lesser extent include the following cost of a physiotherapy session, cost of the OP and success without complications in FSC.

When we analyse the scenarios, modifying the utilities of the final health status, we get a variation in favour of the CCH of 49.12%: 22662.20 (ICUR= -46137.40€/QALY) at final follow-up. The life-time horizon would be obtained through a simpler model such as the Chen´s[13] with an ICUR= -11835.35€/QALY, which represents a variation 895.65 higher in favour of the CCH. Therefore, the model that incorporates more complications to each alternative, does not favour CCH in comparison to FSC.

Cost-effectiveness scatter plot of 1000 bootstrap replicates for incremental cost and incremental effectiveness are shown in Figure 3. The ellipse is depicting 95% of observations. For each simulation run (like dots), parameters were simultaneously and randomly sampled.

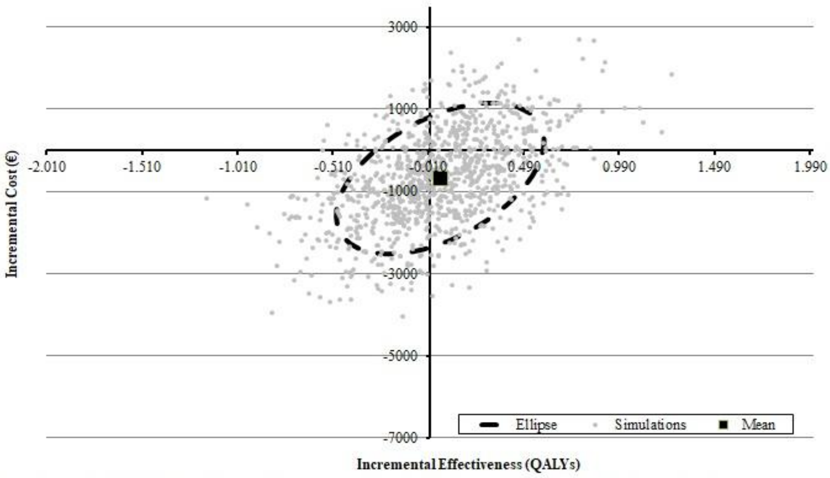
Figure 3. Cost-effectiveness plane after simulation*. Finish Follow-up.



*Cost-effectiveness scatterplot of 10 000 bootstrap replicates for incremental cost and incremental effectiveness. The circle is depicting 95% of observations. For each simulation run (represented as a dot), parameters were simultaneously and randomly sampled from the probability, cost, and outcome distributions for each strategy, to account for uncertainty in the base case parameter estimates. The mayority of simulation´s result fell in quadrant II (lower right) or the lower in quadrant I (upper right) of the cost-effectiveness plain: where the CCH strategy was both more costly and more effective than FSC, so the CCH strategy is dominant. €, euros; CCH, collagenase *Clostridium histolyticum*; FSC, fasciectomy; QALYs, quality-adjusted life years.

Probabilistic sensitivity analysis showed ICUR= -8864.10€/QALY after 20-year time horizon, being CCH the main or most cost-effective option, except in 9% of the simulations performed (Figure 4).

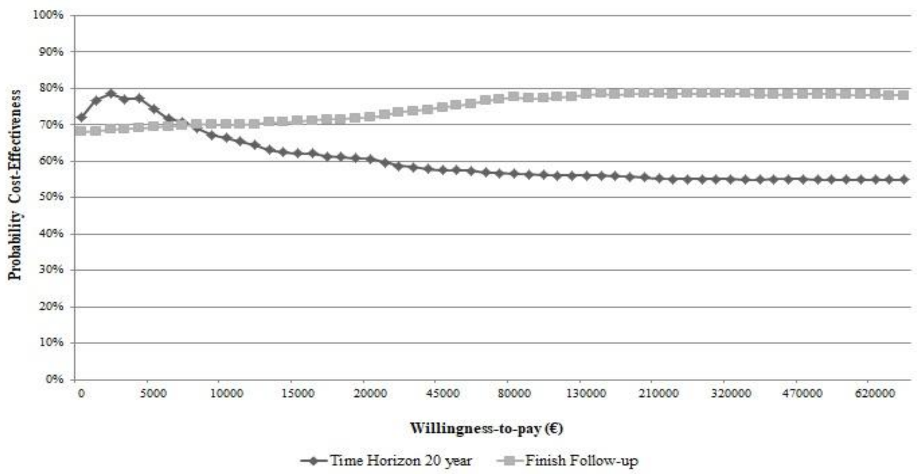
Figure 4. Cost-effectiveness plane after simulation*. Time Horizon 20 year.



*Cost-effectiveness scatterplot of 10 000 bootstrap replicates for incremental cost and incremental effectiveness. The circle is depicting 95% of observations. For each simulation run (represented as a dot), parameters were simultaneously and randomly sampled from the probability, cost, and outcome distributions for each strategy, to account for uncertainty in the base case parameter estimates. The mavority of simulation´s result fell in quadrant II (lower right) or the lower in quadrant I (upper right) of the cost-effectiveness plain: where the CCH strategy was both more costly and more effective than FSC, so the CCH strategy is dominant €, euros; CCH, collagenase *Clostridium histolyticum*; FSC, fasciectomy; QALYs, quality-adjusted life years.

For different willingness-to-pay values, the cost-effectiveness acceptability curve (Figure 5) shows the probability that CCH strategy is cost-effectiveness compared to FSC. If threshold decision is 20000 or 30000€/QALY, the probability to choose CCH versus partial FSC at finish follow-up is over 50%.

Figure 5. Cost-effectiveness acceptability curve*.



*For different willingness-to-pay values, the cost-effectiveness acceptability curve shows the probability that the CCH strategy is cost-effective compared with FSC. The willingness-to-pay can be interpreted as the maximum amount one would be willing to pay for a gain of one quality-adjusted year of life. €, euros; QALY, quality-adjusted life years; CCH, collagenase *Clostridium histolyticum*; FSC, fasciectomy.

Table-1: Demographic and characteristics of Dupuytren´s contracture patients

Variable	Fasciectomy (n: 48)	Collagenase (n: 43)	p value
Sex, Male N (%)	39 (81.3)	38 (88.4)	0.347
Age, Mean years (SD)	66.4 (9.2)	65.6 (9.7)	0.693
Hand (right/left)	26/22	24/19	0.875
Metacarpophalangeal joint, in degrees (SD)	33.5 (27.3)	37.1 (29.5)	0.550
Proximal interphalangeal joint, in degrees (SD)	43.2 (23.7)	39.1 (29.8)	0.465
Levels of Tubiana, N (%)			p= 0.20448775†
I	8 (16.7)	10 (23.3)	
II	23 (47.9)	21 (48.8)	
III	17 (35.4)	8 (18.6)	
IV	0 (0)	4 (9.3)	

SD: standard deviation. CI; Confidence Interval

†OR: odds ratio. Mantel-Hanzel test for trend: z=0.2882 (p=0.77316). The first category is a reference in all variables.

Table-2: Cost and utilities

RESOURCES	Value (€ 2017)		SOURCE
Surgeon visit: First visit	59.44		Hospital de Denia Marina Salud Pharmacy Service
Surgeon visit: Next visits	42.69		
Pre-operative visit	70.08		
Anaesthesiologist visits	62.61		
Physiotherapy session	50.00		
Operating theatre & Materials	959.10		
Hospital stay (days)	283.77		
Mayor Ambulatory surgery (days)	128.71		
Minor surgery procedure	81.99		
Treatment room	54.55		
Administration cost (personal)	22.38		
Collagenase (unit)	725.00		
Recurrence	1294.90		
UTILITIES / PROBABILITIES	**Fasciectomy**	**Collagenase**	Chen NC *et al*. 2011
Successful without complications	0.991 / 0.771	0.994 / 0.628	
Successful with complications: nerve injury	0.989 / 0.021	--	
Successful with complications: CRPS*	0.971 / 0.000	0.971 / 0.000	
Successful with complications: Others	0.987 / 0.083	0.987 / 0.047	
Failed without complications	0.987 / 0.042	0.987 / 0.186	
Failed with complications: nerve injury	0.985 / 0.021	--	
Failed with complications: CRPS	0.967 / 0.042	0.964 / 0.023	
Failed with complications: Others	0.983 / 0.021	0.980 / 0.116	

*CRPS: chronic regional pain syndrome

Table-3: Clinic results

JOINT	Fasciectomy	Collagenase	p value*
Metacarpophalangeal, in degrees mean (SD)			
1. A month from the intervention	6.80 (8.33)	6.70 (18.03)	0.982
Differences with initial	26.50 (21.23)	30.40 (26.87)	0.447
2. After six months from interventions	7.60 (8.94)	7.20 (14.01)	0.885
Differences with initial	25.70 (21.00)	29.90 (26.61)	0.401
Proximal interphalangeal, in degrees (SD)			
3. A month from the intervention	11.70 (11.33)	16.90 (22.60)	0.162
Differences with initial	31.00 (18.32)	22.10 (28.67)	0.080
4. After six months from interventions	12.60 (11.40)	17.30 (22.53)	0.211
Differences with initial	30.20 (18.07)	21.80 (28.51)	0.098

*Test T Student

Table-4: Results cost-effectiveness analysis per patient (6 months and life-time)

DC treatment	**Cost (€)**		**Effectiveness (QALYs)**		**Efficiency**	
	Value	Dif	Value	Dif	**ICUR (€/QALYs)**	NMB
6 months						
Fasciectomy	1420.19	-	0.9892	-		
Collagenase	1161.72	-258.47	0.9900	0.0009	-293766.49	284.86 €
Life-time (20 years)						
Fasciectomy	9445.47	-	6.3680	-		
Collagenase	7628.44	-1817.03	6.4230	0.0550	-33066.04	3465.58 €

ICUR: Incremental Cost-utility Ratio, QALY: Quality Adjusted life year, NMB: Net Monetary Benefit

DISCUSSION

A recent study conducted that compared the cost-effectiveness of FSC, needle aponeurotomy and CCH from a societal perspective, concluded that needle aponeurotomy was the preferred strategy for managing contractures affecting a single finger [12]. In our study, we didn't compare needle fasciotomy for several reasons. First, it is not often performed in our hospital. Second, even though needle fasciotomy is by far the cheapest treatment, recurrence rates vary from 50-85% after 5 years [21]. Education and physiotherapy costs must be added to the advantages of a minimally aggressive procedure. In one analysis which was conducted, an extra review of the recurrence rates according to the technique used for the treatment of DC, concluded that needle fasciotomy had a recurrence rate of 60%, FSC 30% and CCH infiltration only 15% for a complete treatment of three injections in the short and medium term [13]. Recurrence rates are very different between series. A literature review provides recurrence rates between 15 and 46% for surgery, 0 to 75% for CCH, 12 to 65% for needle fasciotomy, 12% for dermofasciectomy, and 23% for skeletal traction, with great variability regarding the time of evolution and no consensus about the definition of recurrence [21]. These results match the Peimer *et al*. [8] study, in which recurrence rates were 47% for both treatments, CCH and FSC, with 5 years follow-up.

We obtained favourable results to CCH if we used one vial per finger. In all pivotal randomised clinical trials CCH infiltration was compared to placebo [5, 6]. The effectiveness obtained in our study is considerably lower than the one in clinical trials (67.4% vs 80%), due to the fact that a clinical practice setting (with systematically on injection per patient) was used and possibly because it gathers the learning curve of a new technology. One study obtained 91% efficacy for CCH but it would allow the administration of three vials per joint (median of 1.4 vials per affected joint) [5]. When we analyse the data by dividing it into subgroups, patients who received a CCH injection obtained an efficacy of 70%, comparable to our patients' sample. These results were confirmed subsequently with bigger sample sizes and an increased effectively follow-up[6,7].

A cost study comparing CCH to FSC reflects that CCH was less expensive in comparison to FSC, very similar to those in other studies [10]. The total average cost per treatment of FSC in three tertiary public hospitals in Spain was 2250€ [11]. This cost varied according to the Hospital and its admission plan, like general anaesthesia, minor surgery, plastic surgeon, orthopaedic surgeons and so on. The cost results from these Hospitals were like the ones presented in our study. Another study was conducted that considered the FSC cost in the UK and the average established costs were 2885£ (3579€) for ambulatory patients and 3534£ (4384€) for admitted patients in 2011 [22]. More recently, the average cost of an open partial FSC pathway was 7115.34£ (9087.36€) and the cost of a CCH pathway was 2110.62£ (2695.58€) [3]. Treatment of DC with one CCH injection costs 33% less than FSC with equal efficacy at 6 weeks in Sweden [2]. Costs of CCH also vary from different countries where the product is marketed: from 725€ in Spain to 3300$ in USA, which varies considerably [10,13]. All these have a higher cost because of differences in Health Systems which makes direct comparisons less representative.

The cost-utility results of our cohort were very similar to previous studies based on decision analysis models. These models concluded that injectable CCH will only be feasible in our public funded Healthcare System if the cost is significantly less than the current United States or Canada pricing [12,13]. Our deterministic sensitivity analysis shows that the CCH cost is the driver that produces more variation on the ICUR and it also shows that two CCH injections (1450€) would lead to an ICUR= 755209.21€/QALY, a higher threshold than any admitted elsewhere (30000€/QALY).

We have not compiled the indirect costs as other studies [13], which followed a social perspective, per pharmacoeconomic studies guidelines [14]. The use of indirect and negligible costs in this disease is controversial. It is not completely clear the importance of lost working hours, as it is more prevalent in elderly patients and many of them are retired [23]. Taking into consideration indirect costs clearly favours the CCH option as it produces less time off work due to a faster recovery by being less aggressive than FSC. For example, in Finland healthcare system, payer´s preferences depends on rapid recovery, thinking in the price of the total process (treatment and recovery); from the patient point of view CCH has more advantages too, because its rapid recovery time, non-invasive and lower risk of complications [24].

In our study, we used reference utilities obtained in the USA for each final health status in both interventions [13]. Utilities of interventions for DC were of high universality, but it is possible that it does not show exactly the preferences for our patients. In contrast to the other studies on the failure scenarios for each intervention, we subtracted the complications referred as disutilities [12]. Therefore, we performed a scenario sensibility analysis to check if our model could change in comparison from a standard model, providing a similar ICUR and contributing to our findings' robustness. A more accurate and realistic approach would be to use utilities depending on the dominant hand, finger, joints and degrees of DC severity [25]. However, there is insufficient data available to be able to carry out a cost-effectiveness study with this point of view, being a route of investigation once these utilities are obtained.

Regarding the limitations on our study, comparison between both techniques, CCH and FSC, is difficult because both variability in the results measurement, as Rodrigues *et al*.[26] mentions in his study, as the target are different for both treatments. CCH is focused on one articulation treatment meanwhile FSC treats the whole finger ineffectively. This limitation has been minimized in our study treating, a homogeneous group. Comparing surgery with CCH infiltration is complicated due to the difficulty in measuring the effectiveness of these interventions, remaining on many occasions defined by patient subjectivity, constituting other of the limitations of our study.

Another limitation is the number of patients in both groups. A bigger sample would be convenient to get a more reliable ICUR between CCH and FSC. To solve this problem, we have performed a bootstrapping simulation of 1000 samples coming from our sample, not only at last follow-up but also long-term [14]. Other studies have been simulated through a 15 years period to observe the costs and results [12]. We have considered a 20-year time horizon as other studies which would ensure the data collection of effects and costs adjusted by age and sex throughout the entire life of our cohort sample [13].

A recent study by Sefton *et al.*[27] in the Australian Health System, endorse our results and conclude that CCH treatment of DC represents a significant reduction in cost relative to fasciectomy, with 64% savings, length of follow up and number of visits.

CONCLUSION

In summary, we conclude that one infiltration of CCH of each finger affected is a cost-effectiveness alternative in the short and medium term, to treat DC in comparison to partial FSC, considering patients´ life expectancy.

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Declaration of conflicting interests

The authors declare that have no conflicts of interest with regard to the content of this article.

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