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Clinical Paper

The use of Collagenase Clostridium Histolyticum in the management of Dupuytren's contracture- outcomes of a pilot study in a District General Hospital setting

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ABSTRACT

Introduction: Collagenase Clostridium Histolyticum (CCH) is a recognised treatment option for adult patients presenting with Dupuytren's contracture (DC).

Patients and Methods: Twenty male patients with established DC were treated using CCH. The average metacarpophalangeal (MCP) joint and proximal interphalangeal joint (PIP) contractures pre-treatment were 52^0 (range, 0 – 75^0) and 35^0 (range, 0 – 84^0) respectively. The average DASH score pre-treatment was 24.2 points (range, 0 – 68.2 points). Patients were reviewed at 1month, 3months and at an average of 23 months (17 to 27 months).

Results: MCP joint contractures significantly improved compared to pre-treatment and the improvement was maintained at latest follow up. PIP joint contractures did significantly improve but to a lesser degree and there was no significant improvement compared to pre-treatment beyond 3months. A trend for MCP and PIP joint contracture recurrence was observed at latest follow up but did not reach statistical significance. DASH scores significantly improved from pre-treatment and the improvement was maintained at latest follow up. At 3months, the average patient satisfaction score was 9.5 (range, 6 – 10), which decreased to 8.6 (range, 6 – 10) at latest follow up. We estimated a potential cost saving of approximately £70,000 by treating 20 patients using CCH compared to inpatient operative fasciectomy.

Conclusion: CCH is a useful option in the management of DC in appropriately selected patients. Cost-effectiveness in the treatment of DC should be carefully considered.

Keywords: Dupuytren's contracture, Collagenase Clostridium Histolyticum, fasciectomy

INTRODUCTION

Dupuytren's disease (DD) is characterized by an imbalance of collagen synthesis over degradation[1–3] leading to the development of nodules and cords within the palmar fascia. With progressive cord formation flexion contractures of the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joints may occur resulting in impaired hand function.[2, 4] The prevalence of DD has been reported to vary between 0.2 and 56% and rises with increasing age.[5, 6] DD is found most frequently in white males.[7] The precise aetiology of DD is unknown although it has been suggested that several genetic and environmental risk factors are involved each contributing to disease susceptibility.[8] There is no cure for DD and because the condition can be progressive, recurrence after treatment is often considered inevitable over a patient's lifetime. [9]

Histologically, DD is composed primarily of types I and III collagen. Collagenase Clostridium Histolyticum (CCH) [Xiapex; Swedish Orphan Biovitrium AB; Stockholm, Sweden] is an approved enzymatic treatment for adult patients with DD with a palpable cord. CCH consists of two distinct collagenases (clostridial type I collagenase [AUX-I] and clostridial type II collagenase [AUX-II]). Types I and III collagen are substrates for both collagenases. These enzymes have been shown *in vitro* to cleave collagen strands at complementary terminal and internal sites into peptide fragments that are rapidly degraded.[10] Enzymatic degradation results in cord rupture and improvement of the digital contracture.

The primary aim of this pilot study was to evaluate the clinical outcome of CCH in the management of adult patients presenting with DC to a District General Hospital and to determine if the outcomes were comparable to those reported in the literature. We also performed an estimated cost saving

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analysis by comparing the cost of treatment using CCH to the potential cost of treating the study group surgically utilising operative fasciectomy in our unit.

PATIENTS AND METHODS

Local approval was obtained for a pilot study to treat 20 patients with DC using CCH. Patients were identified as suitable candidates by the senior author (NWT). Patients were included if they: were of either sex, aged ≥ 18 years, had a palpable cord on clinical examination with a fixed flexion deformity of $\geq 20^0$ and $\leq 100^0$ for MCP joints and $\geq 20^0$ and $\leq 90^0$ for PIP joints in at least one finger other than the thumb. Exclusion criteria included patients with recurrent disease, any other prior treatment or operation on the finger to be treated, any other condition limiting motion in the finger to be treated, any contra-indications to CCH and any chronic neuromuscular disease compromising hand function. All patients received an information booklet and provided written informed consent.

Baseline data recorded included: age, gender, hand dominance, hand involvement, affected digit (s), disease duration, smoking status, alcohol habit, family history and the presence of associated fibromatoses (e.g. Garrod's pads, Ledderhose disease or Peyronie's disease). In patients with a digital contracture involving both the MCP and PIP joints in all cases this was due to a single cord crossing the MCP and PIP joints of the same finger. Digital angles of the finger planned for treatment were measured to the nearest degree using a hand-held goniometer. A pre-treatment Disabilities of the Arm, Shoulder and Hand (DASH) score was recorded.[11] Based on his experience, the senior author also estimated the surgical time in minutes (not inclusive of anaesthetic or recovery time) that would have been needed to treat the contracture by operative fasciectomy.

The senior author (NWT) performed all of the CCH injections in the outpatient clinic. Local anaesthetic (LA) was not administered prior to the CCH injection to avoid inadvertent intra-neural injection. The CCH injection was administered in accordance with the manufacturers instructions (0.58mg per injection). Only one digit or joint contracture was treated per visit. For those patients with a combined MCP and PIP joint contracture, the MCP joint contracture was corrected first. Immediately following the injection the patient was asked to rate the degree of pain experienced using a visual analogue scale (0 = no pain; 10 = worst possible pain). All patients were observed for 30 minutes after the procedure in case of an allergic reaction.

Patients re-attended the clinic 48 hours post-injection. The injection site was checked. Under aseptic conditions a nerve block was performed using 10mls 1% lignocaine to anaesthetise the finger for manipulation. The affected finger was manipulated until the maximum amount of correction could be achieved. The digital angle measurements for the manipulated finger were repeated. Any skin tears that occurred were dressed and a thermoplastic splint applied with the manipulated digit in maximal extension.

Patients attended for hand therapy as per protocol. They were advised to use a night splint for 3months. Digital angle measurements and a DASH score were obtained at 1month and 3months following the manipulation procedure and at latest follow up (average, 23 months; range, 17-27 months). A patient satisfaction score for the treatment was obtained using a simple scoring system at 3months and at latest follow up (0 = very dissatisfied; 10 = very satisfied). The patients were not routinely reviewed at the senior authors clinic.

Statistical analysis was performed using the one-way Analysis of Variance (ANOVA) method utilising a statistics software package (SPSS, Version 22) to determine if the changes noted in the MCP and PIP joint contractures and the DASH score were statistically significant. Tukey's test was performed to determine any significant differences between time frames. For all analyses, a p value <0.05 was considered statistically significant.

RESULTS

Twenty patients were enrolled into the study. The baseline characteristics of the patients are summarised in Table 1. Twenty-two CCH injections were administered. Two patients had 2 injections (one patient had two different cords injected in the same digit and the other patient had two injections into the same cord in the same digit). The second injection was performed in both cases approximately 4weeks from the initial injection.

The mean pain score following the CCH injection was 3.5 (range, 1 – 10). All patients had a minor local reaction at the injection site most commonly bruising and swelling. There were no instances of a systemic reaction. Following the finger manipulation procedure, 9 patients sustained a skin tear of variable size (ranging approximately from 1 to 5mm) all of which healed satisfactorily. One patient on warfarin therapy had a significant bleed, which stopped with the application of a pressure dressing. One patient suffered a vasovagal episode after the manipulation procedure.

In one patient, no improvement was obtained following the manipulation procedure. A second CCH injection into the same cord was performed approximately 4weeks later and a second manipulation procedure was attempted which was unsuccessful. The patient refused any further injections and was listed for operative fasciectomy leaving 19 patients within the study group at 1 month. One patient at this stage had an 84^0 PIP joint contracture that was treated by a second separate injection after correction of his MCP joint contracture.

One patient refused to attend for his 3 month assessment stating that he was happy with the outcome and cited no reason to attend. Eighteen patients attended for their 3 month assessment. At latest follow up (average, 23months; range 17 to 27months) one patient was too ill to attend but stated over the telephone that he was happy with the outcome in relation to the treated digit thus leaving 17 patients available

Table 1:

Baseline characteristics of study group

Parameter	N=20
Age	Average: 64.8 years; Range: 38 – 86 years
Gender	20 males
Dominant hand affected	11 patients
Affected digit	Little finger, 10; ring finger, 8; middle finger 2
Isolated or combined contracture	16 combined MCPJ/PIPJ; 3 isolated MCPJ; 1 isolated PIPJ
Duration of disease	Average: 6 years; Range: 1 – 20 years
Smoking	1 patient
Alcohol intake	14 social; 3 alcohol-dependent; 3 abstinence
Family History	11 patients
Estimated fasciectomy time	Average 64 minutes; Range: 45 – 120 minutes)
Associated fibromatoses	1 patient (plantar and penile disease)

for review. The digital angle measurements and DASH score for each time point are summarised in Table 2. At 3months, the average patient satisfaction score was 9.5 (range, 6 – 10), which decreased to 8.6 (range, 6 – 10) at latest follow up.

Statistical analysis demonstrated that MCP joint contractures significantly improved ($p<0.0001$). A between group analysis demonstrated that MCP joint contractures improved significantly from baseline at each time point ($p<0.01$) however there was no significant difference between each stage. A trend, which was not statistically significant, for MCP joint contracture recurrence was observed at most recent follow up, however the MCP joint contracture still remained significantly better compared to baseline.

Similarly, PIP joint contractures significantly improved but to a lesser degree than MCP joint contractures ($p=0.023$). Only at 3months was there a significant improvement compared to baseline PIP joint contracture ($p<0.05$). There was no significant improvement compared to baseline beyond 3months. Furthermore, there was no significant difference between each stage of assessment. Similar to the MCP joint a trend for PIP joint contracture recurrence was observed at most recent follow up but did not reach statistical significance. DASH scores significantly improved from baseline ($p<0.0001$). Significant improvements from baseline were also noted at each time point ($p<0.01$) however there was no significant difference when comparing the DASH scores at each time point.

In order to simplify the cost analysis we excluded the elements both treatment methods had in common e.g. consumables, hand therapy and Consultant appointments. The senior author does not have access to daycase facilities and hence each patient would have required an inpatient bed and main theatre appointment for their hand surgery. The senior author estimated that the average surgical time per patient would be approximately 1 hour and that each patient would most likely require approximately 2 hours in total of main theatre time (includes anaesthetic, surgical and recovery time). The drug cost was thus compared to the cost of operative fasciectomy. The drug cost of performing 22 CCH injections was approximately £16,000 (plus VAT). Based on information provided by the hospital Finance Department at the time of the study we estimated that the cost of treating the same 20 patients surgically without complication would have been approximately £86,500 (plus VAT) giving a potential cost saving of approximately £70,000.

DISCUSSION

Surgery is the mainstay for the treatment of DC. Procedures include sectioning the cords with a scalpel (fasciotomy), using needles to puncture diseased cords (percutaneous needle fasciotomy-PNF), and more invasive techniques such as removal of the diseased fascia (limited, partial or total fasciectomy); in addition, the lost tissue may be replaced with a full-thickness graft (dermofasciectomy).[12 – 15]

Table 2:

Digital angle measurements and DASH score for each stage (range in parentheses)

Parameter	Pre-CCH	Post-MUA	1 month	3 months	Latest Review
MCP joint	52^0 ($0 – 75^0$)	12^0 ($0 – 65^0$)	7^0 ($0 – 25^0$)	8^0 ($0 – 26^0$)	17^0 ($0 – 53^0$)
PIP joint	35^0 ($0 – 84^0$)	23^0 ($0 – 64^0$)	18^0 ($0 – 84^0$)	16^0 ($0 – 43^0$)	29^0 ($0 – 66^0$)
DASH score	24.2 (0 – 68.2)	–	4.5 (0 – 25)	3.8 (0 – 27.4)	4.5 (0 – 29.5)

Complications associated with surgical treatment occur frequently in patients with DC, especially when the severity of contracture is high.[9, 16 - 17] Overall complication rates after surgery are reported to be between 4% and 39%. The most common complications reported have been problems with wound healing (23%), scar pain from incisions (17%), dysaesthesia or paraesthesia (13%), hypoaesthesia (10%), flare reaction (10%), complex regional pain syndrome (6%), infection (2%), and hematoma (2%). [18 – 19] Complication rates after re-operation are even greater. [19]

CCH has been demonstrated in well-controlled level-1 clinical trials to reduce digital contractures and increase digital range of motion. [18, 20 - 21] Peimer et al. [22] collected data on the real-world effectiveness of CCH during its first year of use following US Food and Drug Administration approval and compared the results with clinical trial efficacy data. Clinical use, including the number of injections per cord and effectiveness outcomes such as, joint contracture and range of motion, were compared with the results from the CORD I and CORD II trials. [18, 20] The authors concluded that despite a lower injection rate, correction of joint contracture and range of motion was similar to the findings from the clinical trials. Furthermore, it has been reported that the incidence of adverse events is numerically lower with CCH versus equivalent complications from fasciectomy and that most CCH-related adverse events are predominantly injection-related and transient. [23]

The baseline characteristics of our study group are comparable to the literature i.e. older males predominantly affected, preponderance for ring and little finger involvement and frequently a positive family history. In keeping with other studies, the number of administered injections in our study was 1.1 per patient and the side-effect profile was similar to that reported in the literature with the CCH injection being well tolerated by the majority of patients. [22 - 24]

In keeping with all the CCH studies to date, we noted that the results of CCH are better at the MCP joint level compared to the PIP joint level. We also observed that individuals with less severe MCP and PIP joint contractures at baseline had a better response to CCH than those with more severe contractures. In the JOINT I and II studies, severely contracted PIP joint cords had lower success rates than both MCP joints and less severely contracted PIP joints. [21] The observation that PIP joints are more resistant to full correction than MCP joints is also consistent with other studies.[25] In a randomized study by van Rijssen et al. [26] fasciectomies or PNF performed on MCP joints were much more successful than those on PIP joints, affirming that severe contractures in PIP joints are associated with a less favorable prognosis. In a comprehensive review, Rayan[1] reported that after excising the offending cord in severe and prolonged PIP joint contractures, residual contracture can be expected, especially when the flexion contracture exceeds 60°. Our finding of greater benefit in joints with milder contracture suggests that CCH could result in better outcomes when joints are treated earlier in the course of the disease. DC can be a progressive disease, and the current evidence suggests that providing treatment to contractures of lower severity is more likely to result in clinical success rather than watching and waiting for contractures to become more severe.

At latest review, approximately 2 years on average from CCH treatment, we noted a trend towards recurrence of the MCP and PIP joint contractures in keeping with the 5-year data reported by Peimer et al. [27] This finding most likely accounts for the slight increase in the average DASH score at latest review. Patient satisfaction, which we feel is an important measure of outcome, however only fell by approximately one point overall suggesting that despite some degree of recurrence patients remain happy with the outcome of their CCH treatment. The overall recurrence rate reported by Peimer et al. is comparable to published recurrence rates after surgical treatments. [27]

Given the increasing financial pressures within the NHS, it is important that the management of DC is cost-effective. PNF is a non-surgical treatment option for DC, which has been popularized in recent years.[28 – 30] PNF can be performed in the outpatient setting under LA using a hypodermic needle. Multiple digits can be treated and the procedure can be performed in patients with significant morbidities. [31] Major risks however include nerve and vessel injury and flexor tendon ruptures. Pess et al. [32] reported their results of PNF in over 1000 patients with DC. They concluded that PNF is a safe procedure with a low complication rate however recurrences were more common in younger patients and the procedure was less effective for PIP joint contractures. Nydick et al. [33] compared PNF and CCH injection in the treatment of DC and in the short term, both PNF and CCH had similar clinical outcomes and patient satisfaction. A recently published prospective, single-blinded randomized study comparing the efficacy of CCH and PNF for MCP joint contracture secondary to DD did not demonstrate any difference between the treatment outcomes after 1 year. [34] The authors also acknowledged that CCH was significantly more expensive than PNF (1280 euros versus 479 euros respectively).

We estimated a potential saving of approximately £70,000 using CCH instead of treating the study group utilising operative fasciectomy. Whilst we appreciate that this is an over-simplified cost analysis, one fact that it does highlight is the significant cost of inpatient treatment for DC. We acknowledge that performing operative fasciectomy in a daycase setting or employing PNF in appropriate cases can reduce the cost of treating DC within the NHS and this is one of the aims within the hand surgery service in our unit. To the best of our knowledge this is the first study to objectively evaluate the use of CCH in the Health and Social Care system in Northern Ireland.

Whilst we acknowledge the limitations of our study in terms of the small patient numbers and relatively short follow up, we have demonstrated CCH to be safe and clinically

effective with a high level of patient satisfaction. CCH is also cost-effective when compared to operative fasciectomy in our unit. Furthermore, we have demonstrated that the same results can be achieved in the DGH setting to those reported in large multi-centre studies. It would be our opinion that this procedure is not a substitute for surgery but should be part of the armamentarium available to a hand surgeon when treating patients with DC.

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