Clostridium histolyticum collagenase in the treatment of Dupuytren's contracture

Dupuytren's disease is a common, costly and recurrent health issue. This review compares* Clostridum histolyticum *collagenase with current operative treatments. Collagenase management is an effective non-surgical alternative associated with lower risks of serious adverse events, but higher incidence of non-serious adverse events.

Dupuytren's disease is a common and costly condition, associated with significant morbidity from both disease progression and its classical treatment. In the UK Dupuytren's disease has an incidence of 32.5/100 000 patients/year, equating to approximately 12 000 operations annually (Dias and Braybrooke, 2006; Gerber et al, 2011). Notwithstanding a shift from inpatient to day-case procedures, the total annual cost of operative treatment in the UK is over £41 million (Gerber et al, 2011). 'The curse of the MacCrimmons' (Elliot, 1988), as the disease was called in the 16th century because of its disabling effects in a particularly musical 16th century Scottish clan, is known to lead to a loss of manual dexterity and work. The domino effect caused by lost earnings and disability suggests that the overall cost to society may be much higher.

First described by Platter of Basel in the 17th century, the condition was initially thought to be caused by tendon contracture. The condition was later correctly characterized by the eminent English surgeons Henry Cline and Astley Cooper of St Thomas' Hospital in London (Cooper, 1823) as a 'condition of the aponeurosis'. Baron Dupuytren's subsequent work extensively furthered understanding of this condition which now bears his name as a sobriquet. Much work has since been directed into the exact aetiology of this progressive, fibro-proliferative disorder. A strong familial component is recognized, and generally accepted to be autosomal dominant with variable penetrance (Townley et al, 2006).

In the absence of an exact environmental cause at which treatment can be directed (Hart and Hooper, 2005), management is largely geared towards the disease's effects. Until recently, surgery was the only effective treatment, and has significant complication rates. Novel, safe and effective non-operative treatment modalities could have significant effects on the management of this condition. *Clostridium histolyticum* collagenase is one such recent innovation in this field. This article reviews established options for treatment of Dupuytren's contracture in view of this novel treatment modality, its licensed applications and future possible uses.

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Current treatment modalities

Surgical procedures

Surgical procedures are the commonest treatment for Dupuytren's contracture. In the UK, the vast majority of procedures involve palmar fasciectomy (Gerber et al, 2011), and can be classified into local, regional or radical approaches (Swartz and Lalonde, 2008). Fasciotomy (aponeurotomy) is an alternative technique, performed by dividing the diseased cord without excision of the diseased tissue. While avoiding complications associated with a more radical approach, diseased tissue is left in situ and is more prone to recurrence (van Rijssen and Werker, 2006). Fasciotomy may be performed in a closed fashion, with the bevelled edge of a large bore needle (Foucher et al, 2003; Cheng et al, 2008), or in an open fashion, with direct cord visualization. A variety of skin management options include transverse, longitudinal incisions, modified by Bruner, 'Z' or 'V-Y' approaches, dermofasciectomy (Brotherston et al, 1994) or an open palm approach (McCash, 1964).

Non-surgical procedures

Several non-operative treatments have been described. There is limited evidence that radiotherapy may be effective in slowing down early disease, without raising any serious safety concerns (National Institute for Health and Clinical Excellence, 2010). Splinting, local steroid injection, topical vitamin A, ultrasound treatment and dimethyl sulfoxide (DMSO) have been described, but their use, including radiotherapy (National Institute for Health and Clinical Excellence, 2010), is limited (National Institute for Clinical Excellence, 2004; Desai and Hentz, 2011). Until recently, there was no clinically viable, non-operative alternative for the management of Dupuytren's disease.

Clostridium histolyticum collagenase: history and mode of action

Fibroblast proliferation is a key feature of early Dupytren's disease, and progression to myofibroblasts may be key in promoting contracture (Bisson et al, 2003). Through

synthesis and secretion of diverse growth factors (Bobinski, 2009), the myofibroblast modulates the metabolism of extracellular molecules, including collagen, elastin and laminin. As the disease progresses cell proliferation subsides while connective tissue assembles, manifesting clinically as a cord.

Enzymatic fasciotomy was first reported by Hueston and co-workers, using proteolytic and anti-inflammatory enzymes including trypsin and hyaluronidase (Hueston, 1971). Since diseased cords are primarily composed of type 1 and type 3 collagen research has focused primarily on the development of collagenase enzyme therapy.

Currently available *Cl. histolyticum* collagenase consists of two subtypes. AUX I and AUX II are both single polypeptide chains cleaving interstitial collagen by hydrolysis which represent clostridial class 1 and class 2 collagenases respectively. The class I collagenase will preferentially hydrolyse near the amino and carboxy termini of triple helical domains to generate large proteolytic fragments. Class II collagenase cleavage sites are located within the interior of the molecule, generate smaller collagen fragments and have higher affinity for small collagen fragments. As a result these two enzymes complementarily produce enzymatic hydrolysis of cord collagen. *Cl. histolyticum* collagenase is currently intended for injection into palpable cords, followed by a finger extension procedure to facilitate cord rupture. Up to three injections and extensions are currently advised, each 4 weeks apart. Owing to the proximity of the disease cord to the flexor tendons, depth of injection is an important consideration and requires experience and expertise.

Efficacy of treatment

Several measures have been used to assess the efficacy of treatment such as summary scores, percentage improvement, change in joint categories and patient satisfaction (Crean et al, 2011), rendering comparison of different studies difficult.

In the CORD II study, 44% of patients met their predefined end point ('reduction in contracture to 0–5° of normal 30 days after the last injection'), returning a highly statistically significant improvement in collagenase-treated patients *vs* controls. After open label treatment, efficacy was similar to that after the double-blind phase: 50.7% of all joints. In contrast, Crean et al (2011) reported the efficacy of fasciectomy and fasciotomy for Dupuytren's contracture in European patients through a structured evidence-based review of 48 peer-reviewed articles. Across these studies, for fasciectomy, the proportions of patients with a 100% correction in contracture angle ranged from 61–97%, while for fasciotomy, the range of fingers that were 100% corrected was 29–73%.

The CORD studies also reported a mean improvement in the correction angle. Hurst et al (2009) reported an improvement from 43.9–80.7° and Gilpin et al (2010) reported an improvement from 47–82.5° in the metacarpophalangeal joint and from 33.6–66° in the proximal interphalangeal joint. This compared favourably to the mean improvement in contracture angle for fasciotomy ranging from 46–88% and in contracture angle for fasciectomy ranging from 58–79% (Crean et al, 2011).

Patient satisfaction is an important methodology used to assess surgical outcome. Although open to reporter bias, this is clinically relevant because Dupuytren's contracture has a negative impact on the patient's quality of life. Using a validated five-point Likert scale, Gilpin et al (2010) reported that both patient and physician rating of improvement were significantly higher with Clostridium collagenase therapy than with placebo. These results concur with those of Watt et al (2010), who reported the results of a 8-year follow-up study post-collagenase injection for Dupuytren's cords. They had an 88% rate of patient satisfaction, although the sample size was small (n=8). These data agree with a large, multicentre questionnaire study in the UK, investigating patient-reported surgical outcomes. Dias and Braybrooke (2006) reported that surgery for Dupuytren's contracture achieved a high initial success rate (75%) but had a high incidence of postoperative patient-reported complication (46%) and recurrence (15%). An evidence-based review by Brandt (2010) favoured collagenase therapy as an effective alternative to surgery in the management of Dupuytren's cords.

Comparison of complication rates

Complications in surgically-treated patients

Comparing complication rates and adverse events offers a different view of established *vs* novel treatments for this disease. This is especially relevant since there is no established, universally accepted efficacy measure for this condition. A structured review of studies on European patients reported that approximately 20% of patients who underwent fasciectomy or fasciotomy experienced an adverse event (Crean et al, 2011), with reported post-fasciectomy complication rates ranging from 17–29% (Watt et al, 2010).

Reported complications in decreasing order of frequency include haematoma and skin necrosis, nerve injury (0–9.6%) and arterial injury (Watt et al, 2010). Other complications include infection, tendon rupture and amputation. However, the rate of nerve injury upon revision surgery almost doubles (Coert et al, 2006).

Complications in patients treated with *Clostridium histolyticum* collagenase

The Collagenase Option for Reduction of Dupuytren's (CORD) I study (Hurst et al, 2009) reported a large Food and Drug Administration phase III, prospective randomized multicentre clinical trial on collagenase treatment. In this trial patients treated with collagenase reported a higher degree of non-serious adverse events

including peripheral oedema (72.5%), contusion (51%), injection site haemorrhage (37%), injection site pain (32%) and upper extremity pain (31%). However, out of 204 patients, only three developed serious adverse reactions (1.4%) – chronic regional pain syndrome (one patient) and tendon rupture (two patients). More recently, another phase III trial, the Collagenase Option for the Reduction of Dupuytren II study (Gilpin et al, 2010), reported treatment-related adverse events in 97% of patients but these were mostly self-limited local reactions. This prospective, randomized, placebo-controlled trial with an open-label phase also reported three tendon ruptures, one case of chronic regional pain syndrome, one case of tendonitis, one pulley rupture and one finger deformity.

Evidence therefore suggests that injection of *Cl. histolyticum* collagenase is likely to reduce the risk of serious adverse events, albeit with increased frequency of minor adverse events. One possible explanation for this elevated risk of minor adverse events may be related to the quality of published data for the different treatment modalities. Both CORD studies constitute high quality, randomized controlled trials with an excellent pick-up rate for local complications, but many studies constitute lower quality evidence, where recall and observational bias are more likely to influence pick-up rates. To date there is no trial comparing *Cl. histolyticum* collagenase to surgical treatment. Only one case of tendon rupture post-collagenase treatment has been reported in the peer-reviewed literature (Zhang et al, 2011).

Comparison of recurrence rates

Studies comparing incision and surgical modality

Recurrence after surgery for Dupuytren's contracture is common (Wilbrand et al, 2003). A recurrence rate of 58% after 3 years has been reported for percutaneous fasciotomy whereas the recurrence rate of limited fasciectomy has been reported to be 41% after 5 years (van Rijssen et al, 2006).

A life-table model of 173 segmental aponeurectomies by Moermans (1996) predicted that 68% of patients would have a recurrence over 10 years. The study also predicted that virtually all patients would show progression of disease affecting both hands within that time (Moermans, 1996). More recently, Crean et al (2011) conducted a structured, evidence-based review of studies on European patients. From pooled data they reported an average recurrence rate of 39% after a fasciectomy and 62% post-fasciotomy at a median time of approximately 4 years. Ullah et al's (2009) prospective randomized trial attempted to determine whether dermofasciectomy and full thickness skin graft (a 'fire break' procedure) was superior to Z-plasty after limited fasciectomy. They reported a 12.2% combined rate of recurrence and no statistical difference between the groups.

Most studies concord that the approach to skin incision and closure also has a bearing on the rates of recurrence. Matton and Beck (1982) compared longitudinal palmar incisions (closed by Z-plasty or directly closed Bruner's incision) to transverse incisions. For these two groups, recurrence rates of 4% and 2% were recorded, but the follow-up period was not specified. The external validity of this study may be limited by the lack of any reported statistical analysis. Citron and Hearnden (2003) prospectively compared open fasciotomy using direct closure of transverse palmar incisions with a Z-plasty closure of a longitudinal palmar incision, and reported recurrence rates of 50% and 15% respectively. However, the rigour of this study is limited because the study groups underwent pseudo-randomization rather than true randomization.

Citron and Nunez's (2005) prospective randomized study reported recurrence rates of 33% for longitudinal incisions and 18% for the Bruner's incision closed with multiple V-Y plasties, but found no statistically significant difference between these two groups, although this study may have suffered from statistical under-powering. Recurrence was defined as any new nodule of disease in the operative field under the flaps. Skoff et al's (2004) prospective comparative limited fasciectomy in two consecutive groups (open palm McCash technique *vs* local advancement flap combined with a hypothenar-based full-thickness skin graft) reported a 50% recurrence rate at 5 years with the former compared to 0% recurrence (average follow up 2.7 years) in the latter. Apart from the notable variation in follow up between the two groups, the criteria for defining recurrence were not reported.

A study by Tonkin et al (1984) followed up patients for an average of 38 months. When comparing fasciectomy without skin excision to dermofasciectomy and skin replacement, despite an overall post-surgery recurrence rate of 46.5%, skin excision and replacement prevented recurrence of Dupuytren's tissue. The function of the hand was assessed with regard to the improvement in flexion contracture, ability to flex the finger to the distal palmar crease, sensibility of the replaced skin, time to return to work and full activity. It was concluded that skin replacement did not jeopardize hand function.

Despite varying in follow-up rates, comparator procedures and end-point definitions, these studies show that the approach to closing the wound may be an independent factor involved in the aetiology of recurrence. Directly closed incisions are associated with higher recurrence rates than those performed in Bruner, multiple Z-plasty or multiple V-Y plasty. Hence, that skin tension triggers myofibroblast activity is a consequent hypothesis meriting future investigation. The literature also suggests that the recurrence rate is higher for fasciotomy rather than fasciectomy, but an inverse ratio also exists to surgical complications. Whether

these effects are statistically significant and whether there is sufficient magnitude of effect is as yet unknown. Trends in the literature also suggest that literature saturation is being approached in terms of single-centre observational studies. Further benefit may now be achieved by moving in the direction of randomized controlled studies addressing number needed to treat and magnitude of effect.

Recurrence post-*Clostridium histolyticum* collagenase injection

Higher quality evidence with excellent recurrence pick-up rates was encountered compared to post-surgery studies. Until recently a potential difficulty with collagenase treatment was the paucity of long-term follow-up data. A randomized double-blind, placebo-controlled trial by Badalamente and Hurst (2007) followed up patients for 2 years. Out of 62 treated joints, they reported recurrence in four proximal interphalangeal joints and one metacarpophalangeal joint (8% recurrence at 2 years), with a minimum disease-free interval of 6 months. Hurst et al (2009) evaluated recurrence of contracture, defined as an increase in joint contracture to 20° or greater in the presence of a palpable cord at any time during the study in joints that attained a reduction in contracture to up to 5° of normal. They reported zero recurrence after 12-month follow up in the 20 successfully treated cords. The CORDLESS study (Kaplan et al, 2011) reported an overall 19.3% nominal 2-year recurrence rate post collagenase treatment from five phase III studies. In this study, recurrence was defined as 'contracture increase by at least 20 degrees with a palpable cord, or if the joint had further medical or surgical treatment'.

Therefore, it may be discerned from the available evidence that collagenase treatment is associated with a disease-free interval of 6–12 months and recurrence rates of 8–20% at 2 years. This compared favourably to studies of post-surgery recurrence rates with similar follow-up timespans. However, it should be noted that 2 years is a relatively short time period to monitor long-term follow up, and long-term cohort follow-up or randomized controlled trials in this regard would be eagerly expected.

Cost of care

Only one study reported the annual UK cost of treatment for Dupuytren's disease. In a retrospective database analysis from the UK NHS, Gerber et al (2011) reported an annual total cost of £41 576 141 in 2010–11 for 12–13 000 admissions, with costs per patient ranging from £2885 for day surgery to £9210 for revision surgery. Similar annual admission rates to an earlier French study were reported (Maravic and Landais, 2005). In the UK, collagenase treatment has been estimated to cost £780 per injection on an outpatient basis. This compares well to the cost of palmar fasciectomy, estimated between £2500 and £5000 per case (Horsley, 2011).

It is anticipated that the suitability of collagenase treatment as an outpatient procedure may help to substantially reduce the cost of treatment.

Future applications

The approval by the Food and Drug Administration of the first *Cl. histolyticum* collagenase for Dupuytren's contracture opens exciting avenues of research. Several trials are underway to evaluate the efficacy of this novel product in the management of Peyronie's disease, and Lederhosen's disease and burn contractures (Thomas and Bayat, 2010). Furthermore collagenase treatment may have an important role in other unrelated avenues such as wound debridement (Karagol et al, 2011) and release of peritoneal adhesions (Aysan et al, 2011).

Conclusions

Dupuytren's contracture is a common, costly, recurrent and progressive disease which leads to significant morbidity and cost of care. Until recently, surgery was the only viable management option. A significant complication rate and risk of serious adverse events is associated with surgical treatment, especially for fasciectomy and revision surgery. The literature suggests that *Cl. histolyticum* collagenase is an effective non-surgical alternative that results in comparable correction rates, and magnitude of effect, to surgery. Literature suggests that this treatment modality is associated with a significantly lower risk of serious adverse events, although occurrence of non-serious adverse reactions is increased. Judicious use of this novel treatment modality may reduce cost of care and the operative caseload, while giving comparable efficacy, recurrence rates and patient satisfaction. **BJHM**

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KEY POINTS

- Dupuytren's disease is a common and costly condition, whose only effective treatment was surgery.
- *Clostridium histolyticum* collagenase presents the first effective non-surgical option for the treatment of this disease.
- Treatment with *Cl. histolyticum* collagenase results in significantly lower rates of serious adverse events, but an increased incidence of non-serious adverse events.
- Two-year recurrence rates (8–20%, 6 months minimum disease-free interval) compare favourably with surgical treatment, but longer-term studies are eagerly awaited.

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