Using collagenase to treat Dupuytren’s disease: a hypothetical cost benefit analysis

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Section: Hand

Abstract

Background: Dupuytren’s disease is a disorder of abnormal collagen production that may manifest in the palmar fascia. Treatment options vary according to clinical circumstances but surgical fasciectomy remains the gold standard. Collagenase, an enzyme produced by clostridium histolyticum (CCH), is a relatively new injection able to cleave collagen strands in vitro. While the drug is not yet available on the Pharmaceutical Benefits Scheme, its side effect profile and risk of recurrence are comparable to fasciectomy in appropriately selected patients. In this study, we aimed to demonstrate the safety and cost-effectiveness of collagenase for the treatment of Dupuytren’s disease.

Method: Twenty-five patients at our hospital received collagenase injections for treatment of their Dupuytren’s disease. Data from this cohort was compared to a hypothetical group extrapolated from the literature.

Results: Surgical treatment, excluding outpatient visits, costs on average AU$5852 per patient and collagenase costs AU$1176 per patient (gross cost difference AU$4676). Moderating this cost difference by the effect of complications using the incremental cost effectiveness ratio, the cost saving is AU$1137.71 per unit decrease in complications with collagenase treatment.

Surgical fasciectomy has a lower risk of recurrence than collagenase but costs up to AU$543 more for patients for whom the condition does not recur within five years of treatment.

In our cohort, 25 patients had 31 cords injected with collagenase. All but two patients achieved full range of motion of their affected joint and 20 per cent sustained minor skin tears requiring dressings.
Conclusion: This analysis suggests that the investment of public health funds in the treatment of suitable patients with collagenase should produce a substantial cost saving without increasing the risk of complications.

Keywords: Dupuytren contracture, collagenases, clostridium histolyticum, fasciotomy, injections.

Background
Dupuytren’s disease is a disorder of abnormal collagen production that may manifest in the palmar fascia.\(^1\) Contracture of the joints in the hand may ensue and this may adversely affect hand function. Extra-palmar manifestations may involve the knuckles (Garrod’s pads), feet (Ledderhose disease) and penis (Peyronie’s disease).\(^2\) The Dupuytren's diathesis predicts a more aggressive disease course\(^3\) and is defined by disease onset in youth, the involvement of multiple rays including the radial digits and extra-palmar disease.\(^4\)

The precise disease aetiology is unknown. A genetic predisposition is recognised and a northern European heritage portends a greater risk.\(^2\) Known associations include male gender, advancing age, alcohol use, smoking, infection with HIV, diabetes mellitus, anti-epileptic medications and working with vibrating tools.\(^3,5\) The pathogenesis of the disease also remains unknown. Several theories have been proposed including a perpetuating cycle of ischaemia, free radical production, tissue contracture and further ischaemia.\(^6\) The observation that diseased cords have a much higher proportion of reparative type III collagen than normal fascial bands suggests a pathophysiology whose final pathway is tissue injury.\(^1\)

Treatment options vary according to clinical circumstances and historically have included conservative measures such as hand therapy and splinting; minimally invasive modalities such as steroid injections and fasciotomy (percutaneous or open); and surgery, which may involve limited, dermato- or radical fasciectomy with appropriate reconstruction. Fasciectomy is regarded as the gold standard of treatment.\(^7\) Collagenase, an enzyme produced by *Clostridium histolyticum*, is a relatively new modality for the treatment of Dupuytren's disease. The collagenase clostridium histolyticum (CCH) formulation consists of two distinct collagenases (types I and II) and both have been shown to cleave collagen strands in vitro.\(^8\) The drug is injected directly into the target cord, which weakens over the ensuing 48 hours and is then ruptured, either spontaneously or by a controlled extension procedure.

The injection of collagenase into diseased cords in Dupuytren's disease has been shown to increase range of motion and reduce contractures (level 1 evidence).\(^9\) Collagenase has the advantage of a side effect profile and risk of recurrence that is comparable to fasciectomy in appropriately selected patients and a much quicker return to work.\(^10\) Therefore, it would appear that results comparable to surgery could be achieved at a substantially reduced cost. A deterrent to the implementation of this modality in public healthcare is the cost of the drug. At AU$1176 per treatment, the drug is not available through the Pharmaceutical Benefits Scheme (PBS) at the time of writing. Studies analysing the costs and benefits of collagenase in other countries and healthcare systems including Canada, Spain and the United States have found in favour of collagenase.\(^11–13\) Similarly well-designed studies have not yet been performed in Australia.

Aim
The aim of this study is twofold: to show that collagenase is a safe and cost-effective treatment in the Australian public healthcare system; and to demonstrate implementation of this finding in a small public health patient cohort.

Method
A retrospective review of our operating room data was undertaken to identify those patients who had undergone surgical fasciectomy at our institution between 2009 and 2014. Using the transitional II costing system, our finance department calculated all direct and indirect costs associated with admission to our hospital for surgical fasciectomy. The CORD I inclusion criteria were then applied to this population to identify patients who might have been suitable for collagenase injection.\(^9\) These criteria include age 18 years or
older and Dupuytren's contracture affecting one metacarpophalangeal (MCP) joint (contracture $\geq 20$ to $\leq 100^\circ$) or one proximal interphalangeal (PIP) joint (contracture $\geq 20$ to $\leq 80^\circ$).\textsuperscript{10} Costs and benefits were compared between the surgical and hypothetical collagenase groups using the incremental cost-effectiveness ratio (ICER).

The costs associated with supply of collagenase were provided by our local distributor. The additional associated costs were supplied by our hospital pharmacy department. Outpatient costs including initial assessment and post-procedural reviews were assumed to be the same in both groups, though it is likely that patients treated with collagenase would have had fewer outpatient appointments on the basis of collagenase treatment in the local private sector.\textsuperscript{10}

The incidence of complications and the risk of recurrence for each modality were determined from a review of the literature.\textsuperscript{14–16} Complications were stratified according to severity using the Accordion classification (Table 1). These strata were then weighted to give a post-operative morbidity index (PMI) where 0 represents perfect health and 1 represents death. This approach to grading postoperative complications has been validated for this purpose.\textsuperscript{17} The risk of a given complication, represented by its incidence and expressed as a percentage, was then multiplied by its PMI to give a numerical value that is a function of both the severity and the incidence of the given complication. These values were then added together to give an aggregated complication risk as one measure of effect for a specific treatment modality.

The ICER was calculated using the following equation:

$$\text{ICER} = \frac{\text{cost overall of collagenase} - \text{cost overall of surgery}}{\text{effect of collagenase} - \text{effect of surgery}}$$

A second measure of effect is the risk of recurrence, expressed as a percentage. In a recent 20-year review of complications after surgical fasciectomy, the reported recurrence rate was 39 per cent.\textsuperscript{15} A more recent randomised controlled trial comparing surgical fasciectomy and percutaneous needle fasciotomy reported a recurrence rate of 20.9 per cent for surgical fasciectomy at 5 years.\textsuperscript{18} The CORDLESS study continues to follow up 1081 joints injected with collagenase for Dupuytren's disease.\textsuperscript{14} In 2015, the study's five-year recurrence rate was 47 per cent for all joints, 39 per cent for MCP joints and 66 per cent for PIP joints. As our population of patients was similar to those analysed in these studies, we ascribed the risk of recurrence to be 20.9 per cent in the surgical fasciectomy group and 47 per cent in the collagenase group. ICER was calculated twice, using a different measure of effect each time—once with the aggregated complication risk and again with the risk of recurrence.

From 2015, selected patients attending our hospital outpatient hand clinic were offered collagenase injection over surgical fasciectomy if they met the CORD I inclusion criteria (as previously described). Patients who passed screening were offered an appointment. At the initial visit, patients were re-screened for inclusion, assessed with a QuickDash questionnaire and subjected to an examination. The patient's treatment options were then

| Grade | Description                                                                 | Weighting (PMI) |
|-------|-----------------------------------------------------------------------------|-----------------|
| 1     | Treatment complication requires only minor invasive procedures that can be done at the bedside, such as insertion of lines, drainage of infections | 0.11            |
| 2     | Complication requires pharmacological treatment other than drugs allowed for minor complications eg, antibiotics or blood transfusions | 0.26            |
| 3     | No general anaesthesia required to treat the complications. Reoperation without general anaesthesia | 0.37            |
| 4     | General anaesthesia required to treat the complication. Single organ failure has developed | 0.60            |
| 5     | General anaesthesia and single organ failure or multi-organ failure         | 0.79            |
| 6     | Death                                                                      | 1.00            |
discussed and written consent sought. Descriptive data were collected during patient assessment and treatment, including pain scores during injection and extension procedures using a Likert scale. The collagenase was administered at the initial visit using the procedure outlined in the Actelion instruction manual\(^1\) by a certified injector. A follow-up appointment was then scheduled for three days later. Patients were observed for 15 minutes prior to discharge to ensure that they suffered no ill effects. The extension procedure was performed as outlined in the Actelion instruction manual by the senior author. A metacarpal block was performed prior to the procedure using a 50:50 mixture of 2 per cent Xylocaine and 0.5 per cent Marcain (Astra Zeneca, France) made up to a volume of no more than 5 mL. The injection was performed using a 25 g needle.

**Results**

Forty-eight of the 94 patients (51%) who underwent surgical fasciectomy for Dupuytren's contracture at our institution in the past five years would have fulfilled the CORD I indications for collagenase treatment. Gross calculations were made on this cohort. Surgical treatment, excluding outpatient visits, cost an average of AU$5852 per patient (Table 2). The total cost incurred with the use of collagenase, excluding outpatient visits (which were assumed to be equal in both groups) was AU$4676 per patient.

The morbidity index was calculated for each complication in both groups (surgical and collagenase) and is presented with the aggregated complication risk for each modality in tables 3 and 4.

The gross cost difference per treatment (overall cost of surgery minus overall cost of collagenase) was AU$4676 per patient in favour of collagenase. To moderate this cost difference by the effect of complications using the ICER, this gross cost difference must be divided by the difference in the risk of complications (aggregated complication risk of surgery minus aggregated complication risk of collagenase = 6.85 – 2.74 = 4.11). When this is done, the cost saving is AU$1137.71 per unit decrease in complications with collagenase treatment. If the risk of recurrence for surgical fasciectomy is 20.9 per cent and the risk of recurrence for collagenase use is 47 per cent, then 8 and 19 patients, respectively, would recur in our surgical and matched hypothetical cohorts (n=48). In other words, we can infer that 13 patients in our cohort treated with collagenase would not have recurred if they were treated with surgery. The ICER can be recalculated using recurrence as a measure of effect by dividing the gross cost difference by the gross difference in the number of patients who we predict would have recurred (AU$4676/13 = AU$359.69). Therefore, the cost to the healthcare system for each patient who does not recur within five years of surgical fasciectomy is AU$359.69. If collagenase use is limited to pre-tendinous cords and MCP joint contracture, giving a recurrence rate of 39 per cent, the additional cost would be AU$519.55 per patient who does not recur (AUD$4676/9).

These data were presented to Princess Alexandra Hospital's Division of Surgery for consideration of approval to offer collagenase for suitable patients. Approval was granted on the basis that material savings could be made by offering surgical candidates a cheaper modality but also less tangible savings could be made by not having suitable patients appear on a surgical waiting list. Treatment began on 26 May 2015 and 25 patients were treated at our institution.

| Financial year | 2009–10 | 2010–11 | 2011–12 | 2012–13 | 2013–14 | Average |
|---------------|---------|---------|---------|---------|---------|---------|
| Discharges    | 44      | 51      | 40      | 19      | 31      | 37      |
| Average stay (days) | 1      | 1.2     | 1.1     | 1       | 1       | 1.06    |
| TII cost total (AU) | $243,476 | $304,601 | $251,968 | $103,097 | $186,978 | $218,024 |
| TII cost average (AU) | $5534  | $5973   | $6299   | $5426   | $6032   | $5852   |
Table 3: Complications for treatment of Dupuytren's disease with fasciectomy

| Complication                              | Incidence (%) | PMI | Severity |
|-------------------------------------------|---------------|-----|----------|
| Wound breakdown                           | 23            | 0.11| 2.53     |
| Complex regional pain syndrome (CRPS)     | 6             | 0.11| 0.66     |
| Stiffness                                 | 2             | 0.11| 0.22     |
| Infection                                 | 2             | 0.26| 0.52     |
| Digital nerve injury                      | 2             | 0.26| 0.52     |
| Digital artery injury                     | 2             | 0.6 | 1.2      |
| Flexor tendon injury                      | 0             | 0.6 | 0        |
| Amputation                                | 2             | 0.6 | 1.2      |
| TOTAL                                     | 6.85          |     |          |

Table 4: Complications for treatment of Dupuytren's disease with collagenase

| Complication                              | Incidence (%) | PMI | Severity |
|-------------------------------------------|---------------|-----|----------|
| Wound breakdown                           | 10            | 0.11| 1.1      |
| Complex regional pain syndrome (CRPS)     | 4             | 0.11| 0.44     |
| Stiffness                                 | 0             | 0.11| 0        |
| Infection                                 | 0             | 0.26| 0        |
| Digital nerve injury                      | 0             | 0.6 | 0        |
| Digital artery injury                     | 0             | 0.6 | 0        |
| Flexor tendon injury                      | 1             | 0.6 | 0.6      |
| Amputation                                | 1             | 0.6 | 0.6      |
| TOTAL                                     | 2.74          |     |          |

had 31 cords injected over the ensuing 21 months. Most patients were right-hand dominant (92%) with left-hand disease (62%) affecting their ring (65%), little (23%) or middle (1%) finger. One patient had disease affecting the MCP joint of their index finger. There were 24 injections to pre-tendinous cords of the MCP joint, with an average contracture of 34.86 degrees prior to injection (range 20° to 70°; see Table 5). Average pre-injection Tubiana stage was 1.34 and post-injection it was 0.07.²⁰ Patients reported an average of 5/10 pain during the injection.

Nine cords (29%) ruptured spontaneously and 22 (71%) required a formal extension procedure. Patients rated their pain during metacarpal block at an average of 4/10. Five patients (20%) experienced small skin tears during manipulation that were subsequently treated with dressings and other minor reported side effects including local tenderness, bruising and transient regional lymph node enlargement. This rate is less than that reported in the CORD study, where 96.6 per cent of patients receiving collagenase injection(s) reported minor adverse events such as bruising, pain, skin tear and lymphadenopathy.⁹ In our cohort there were no serious adverse events such as anaphylaxis, tendon rupture or nerve injury, and the average pain score during the extension procedure was 1/10.

All but two patients achieved full range of motion at their MCP joint after the extension procedure. One patient likely had administration of the drug in a plane that was too superficial, leading to lysis of the dermis from the underlying cord but not rupture of the cord itself. A clinical decision was made at the time of the extension procedure to perform needle fasciotomy while the hand was blocked. This was undertaken with good effect and full range of motion of the joint was achieved. The second patient was trialling collagenase after failed surgical fasciectomy. While the patient’s MCP and PIP joint range of movement improved
Table 5: Results post-injection of collagenase for metacarpophalangeal and proximal interphalangeal joint contracture

| Joint                        | Cord            | Digit | Pre-injection contracture (degrees) | Post-injection contracture (degrees) |
|------------------------------|-----------------|-------|-------------------------------------|-------------------------------------|
| Metacarpophalangeal          | Pre-tendinous   |       |                                     |                                     |
| Pre-tendinous                | Ring            | 30    | 0                                   |                                     |
|                              | Little          | 45    | 0                                   |                                     |
|                              | Ring            | 15    | 0                                   |                                     |
|                              | Ring            | 45    | 0                                   |                                     |
|                              | Ring            | 30    | 0                                   |                                     |
|                              | Ring            | 25    | 0                                   |                                     |
|                              | Little          | 25    | 0                                   |                                     |
|                              | Ring            | 20    | 0                                   |                                     |
|                              | Little          | 20    | 0                                   |                                     |
|                              | Little          | 50    | 0                                   |                                     |
|                              | Ring            | 30    | 0                                   |                                     |
|                              | Middle          | 25    | 0                                   |                                     |
|                              | Ring            | 25    | 25                                  |                                     |
|                              | Ring            | 57.5  | 40                                  |                                     |
|                              | Index           | 25    | 0                                   |                                     |
|                              | Middle          | 35    | 0                                   |                                     |
|                              | Ring            | 40    | 0                                   |                                     |
|                              | Ring            | 50    | 0                                   |                                     |
|                              | Ring            | 54    | 0                                   |                                     |
|                              | Ring            | 40    | 0                                   |                                     |
|                              | Ring            | 70    | 0                                   |                                     |
|                              | Ring            | 20    | 0                                   |                                     |
|                              | Little          | 30    | 0                                   |                                     |
|                              | Ring            | 65    | 0                                   |                                     |
| Average                      |                 |       | **34.86**                           | **2.6**                             |
| Proximal interphalangeal     | Spiral          |       |                                     |                                     |
| Spiral                       | Little          | 30    | 0                                   |                                     |
|                              | Ring            | 50    | 0                                   |                                     |
|                              | Little          | 50    | 0                                   |                                     |
|                              | Ring            | 45    | 0                                   |                                     |
|                              | Ring            | 67.5  | 30                                  |                                     |
|                              | Little          | 60    | 0                                   |                                     |
|                              | Ring            | 40    | 20                                  |                                     |
| Average                      |                 |       | **48.9**                            | **7.14**                            |
after collagenase injection (57.5° to 40° for the MCP joint, 67.5° to 30° for the PIP joint) the patient did not obtain full joint extension.

For the five patients who had seven spiral cords injected, PIP joint flexion contracture was an average of 48.9 degrees before injection and 7.14 degrees post-injection. Five cords were ruptured with full extension of the PIP joint achieved and the other two had improvements in range of motion from 67.5 to 30 degrees and 40 to 20 degrees post contracture release (Table 5).

**Discussion**

This is the first analysis of cost-effectiveness for the use of collagenase in the treatment of Dupuytren's disease in a public healthcare setting in Australia. It emphasises the importance of moderating the gross cost saving associated with the use of collagenase by measures of its effect. This analysis suggests that the investment of public health funds in the treatment of suitable patients with collagenase should produce a substantially cost saving without increasing the risk of complications. Indeed, surgical fasciectomy comes at a cost, both fiscally and in risk of complications.

The situation with respect to recurrence is different. Surgical fasciectomy has a lower risk of recurrence, even when the use of collagenase is confined to MCP joint contracture but this comes at a cost of up to AU$543 per patient who does not recur within five years of treatment. Though some surgeons find fasciectomy for recurrence after collagenase to be more technically challenging, there is currently no evidence to suggest that complications are greater in this group. Also, it is presumed that all recurrences are clinically significant and warrant treatment. If all recurrent disease requires fasciectomy, then the cost of fasciectomy needs to be added to the total costs of injection alone for those patients in our group who can be presumed to have recurred (47%). When this is recalculated, the cost difference becomes AU$3178.93 per patient with a recurrence rate of 47 per cent after collagenase and AU$3650.37 for a recurrence rate of 39 per cent, both in favour of collagenase treatment. As experience with collagenase increases, both the cost difference and the risk of recurrence may change.

In this study, estimates of cost were conservative and, because of this, favoured surgical fasciectomy. The number of outpatient visits was assumed to be the same for both groups, though it is likely that the surgical fasciectomy group would need more outpatient visits than the collagenase group. Furthermore, the total time required per outpatient visit is likely less for collagenase patients as they rarely require dressings or removal of sutures. The need for hand therapy may also be decreased. These variables and others, including the effect of early return to work, were not measured in this study. A barrier to the implementation of outpatient injections of collagenase in a public hospital may be access to an appropriate facility and the availability of personnel trained in its use. These barriers can be overcome and our study suggests that efforts to do this may be worthwhile, even if there is a material cost involved.

**Conclusion**

The data from our patient cohort who received collagenase injections corroborate findings from previous studies that injection of collagenase for Dupuytren's disease is effective in reducing joint contracture and improving range of motion. Our gains in range of motion are similar to those found in larger studies and the injections have been shown to be well tolerated with low risk of adverse events. In light of the demonstrable clinical benefits to patients, and the apparent cost-effectiveness of this treatment, it is hoped that data from this study will encourage use of collagenase for Dupuytren's disease in the Australian public hospital system.

**Disclosure**

The authors have no financial or commercial conflicts of interest to disclose.

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