The Treatment of Dupuytren Disease

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The treatment of progressive Dupuytren contractures has historically been and continues to be largely surgical. Although a number of surgical interventions do exist, limited palmar fasciectomy continues to be the most common and widely accepted treatment option. Until recently, nonsurgical options were limited and clinically ineffective. However, the commercial availability and recent approval of collagenase clostridium histolyticum now provides practitioners with a nonsurgical approach to this disease. This article presents a comprehensive review of the surgical and nonsurgical treatments of Dupuytren disease, with a focus on collagenase. *(J Hand Surg 2011;36A:936–942.*

Key words Aponeurotomy, collagenase, Dupuytren disease, fasciectomy, fasciotomy.

Dupuytren disease, a benign connective tissue disorder affecting the palmar fascia, was first described by the Swiss physician Felix Plater in 1614. This disorder leads to progressive hand contractures and was later eponymously attributed to Baron Guillaume Dupuytren, a French physician, who in 1831 extensively lectured on this subject. Since that time, we have yet to understand the exact etiology or isolate the specific gene or genes involved.[1] Mediated by myofibroblasts, pathologic cords form, leading to progressive flexion deformity of the fingers, involving the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, and it can also involve the distal interphalangeal (DIP) joint.

Although most commonly seen in older men of northern European descent, Dupuytren disease is seen globally across nearly all ethnic groups, with incidence increasing with advancing age. The inheritance pattern appears to be autosomal dominant with variable penetrance. Men usually present 10 years earlier and have higher prevalence of this disease when compared to women.[2,3]

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Treatment for Dupuytren disease was first described by Henry Cline in the late 17th century and involved sectioning the pathologic cords, later known as *fasciotomy* or *aponeurotomy*.[4] Since then, surgical intervention traditionally has been the most effective and widely accepted treatment for progressive Dupuytren contractures.[1,2] Today's surgical options include limited needle aponeurotomy, open or percutaneous fasciotomy, and the more commonly performed open fasciectomy. Until recently, nonsurgical interventions have proved to be largely ineffective and rejected clinically.[5] Collagenase clostridium histolyticum was introduced to the literature less than 15 years ago as a potential, minimally invasive, nonsurgical option to treat Dupuytren contractures. This has ultimately led to completion of phase 3 clinical trials and its recent approval by the United States Food and Drug Administration (FDA) for clinical use, marketed under the name Xiaflex (Auxilium Pharmaceuticals, Malvern, PA). Collagenase is injected directly into a Dupuytren cord, leading to lysis of the collagen found within the diseased tissue. The patient returns the following day for joint manipulation in an attempt to rupture the cord. Both the injection and the subsequent cord rupture have safely been conducted in an office-based setting. Clinical studies report that collagenase is safe and efficacious when used within the appropriate guidelines; however, studies looking into long-term results and recurrence rates are currently being conducted.[10–12]

SURGICAL MANAGEMENT

Surgery continues to be the gold-standard treatment for progressive Dupuytren contractures. Typically, intervention is recommended in patients with MCP joint contractures of at least 30° and/or any PIP joint contractures with associated functional impairment.[6] A variety of surgical interventions exist and are largely classified by the amount of diseased tissue removed. In general, the amount of diseased palmar fascia excised can be directly related to a decreased recurrence rate but can also be associated with higher rates of complications. When evaluating a patient for surgery, today's surgeon should be adept at multiple surgical techniques and tailor a treatment regimen fitting that individual. Consideration of the patient's age and comorbidities combined with a realistic understanding of the patient's goals are critical for successful outcomes and patient satisfaction.

Needle aponeurotomy

The least invasive of surgical interventions, percutaneous needle aponeurotomy/fasciotomy (PNA) can be considered little more than a modification of the original technique performed by Sir Astley Cooper and later known as the *Cooper fasciotomy*.[4,7] This technique, modified and later revived by the French rheumatologists Lermusiaux and Debeyre,[8] is ideal for elderly individuals with multiple comorbidities because it allows for a rapid increase in finger extension with minimal recovery time and can be safely performed under local anesthetic alone. A small-gauge needle is introduced percutaneously through the skin along the length of the cord, and the cord is incised, using sweeping motions. The cord is weakened to allow an extension force over the finger to rupture the cord. Multiple studies have shown a remarkable decrease in the total passive extension deficit (TPED), with reports showing the greatest improvement in contracture involving the MCP joints and less so with the PIP joints.[9–13] In 2006, Van Rijssen et al published a prospective study evaluating the improvements seen immediately after PNA and the recurrence rates seen after short-term follow-up. They reported that, immediately after surgery, there was a mean reduction of TPED of 77% (88% at the MCP joint and 46% at the PIP joint). At their final follow-up (mean, 33 months), the 42% of the patients available for final follow-up had had a second treatment for recurrence, and another 23% showed signs of recurrence.[9] Van Rijssen et al also directly compared PNA to limited open fasciectomy in a prospective, randomized controlled study.[10] At 6 weeks, they reported TPED to be improved by 63% in the PNA group and 79% in the fasciectomy group. They reported 33 minor complications in the PNA group (29 skin fissures and 4 paresthesias) versus 13 in the fasciectomy group (all paresthesias). There were no reported major complications in the PNA group, but the fasciectomy group reported 3 major complications (digital nerve injury, infection, and hematoma).

Open fasciotomy

Open fasciotomy of pathologic cords has been the original treatment modality for Dupuytren contracture for well over 200 years.[4] Original descriptions of Baron Guillaume Dupuytren's technique describe an open fasciotomy using a transverse incision through the skin and progressing through the pathologic cord at the level of the MCP joint. Unfortunately, there have been no direct comparisons of this technique to percutaneous fasciotomy or open fasciectomy in terms of contracture improvement, recurrence rate, and postoperative complications. A prospective, randomized study was conducted by Citron and Hearnden[14] to determine whether skin tension after skin closure correlates with an increased risk of recurrence. They used open fasciotomies to treat these contractures and either a transverse incision (closing primarily) or a longitudinal incision (closing by Z-plasty). They reported a statistically significant difference in the recurrence rates between the primary closure (50%) and the Z-plasty group (15%).[14] When performing an open fasciotomy, one should pay special attention to the overlying skin incision and be prepared to perform a Z-plasty if needed.

Palmar fasciectomy

The more widely used procedure to treat Dupuytren contractures is regional (subtotal) fasciectomy, which is considered the accepted gold standard for primary contracture release. This procedure involves careful dissection and excision of the involved diseased fascia. This is different from radical fasciectomy advocated by McIndie and Beare,[15] which requires extensive removal of involved and noninvolved palmar and digital fascia. This treatment has fallen out of favor due to its higher complication rates without necessarily lowering the rates of recurrence. Multiple options for skin incisions exist, including Bruner-type zigzag incisions, multiple Y-V advancement flaps, midline longitudinal incisions closed with Z-plasties, and transverse incisions (Fig. 1). Most incisions are closed primarily, but wounds can also be allowed to heal secondarily, as popularized by McCash in his open-palm technique.[16] After surgery, the hand is splinted, with the MCP and PIP joints in an extended position. After a few days, this splint is re-

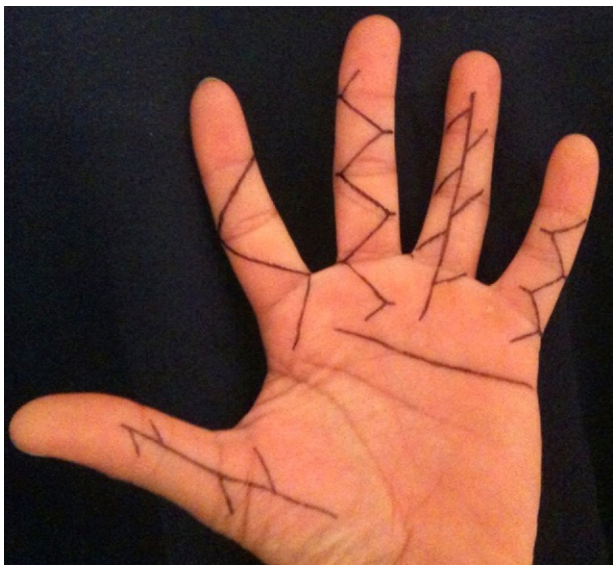

FIGURE 1: Typical incisions used for surgical exposure in Dupuytren disease. Examples of Y-V plasties, Z-plasties, and Bruner's incisions are shown.

moved and active range of motion is initiated. A night extension splint is fabricated to maintain passive extension. Denkler[17] published a comprehensive review of papers analyzing the results of palmar fasciectomies found over a 20-year period. He reported the overall surgical complication rate ranging from 3.6% to 39.1%. These studies reported an average digital nerve injury rate of 3.4% (0% to 7.7%), digital artery injury 2.0% (0.% to 2.6%), wound-healing complications 22.9% (0% to 86.0%) and infection 2.4% (0 to 8.6%). Denkler also reviewed 3 papers that compared complication rates between surgery for primary and recurrent disease. Overall, the reported incidence of digital artery injury in recurrent disease was more than a 10-fold increase compared to surgery for primary disease, and the incidence of digital nerve injury was increased more than 5-fold.[17] Bulstrode et al,[18] in a retrospective series, showed that there was a correlation between the degree of contracture and the rate of complications. However, they did not find the same difference in complication rates between surgery for primary and recurrent disease.

The comparison of recurrence rates among the various studies reporting on palmar fasciectomies has proved to be difficult because there is no universally agreed-on definition of what constitutes a recurrence and because of the variability in follow-up. Although many studies report a rate, they fail to define the criteria used to determine recurrence. Also, there is variation between surgeons regarding how much diseased palmar fascia is initially removed in limited palmar fasciectomy, which can also affect recurrence. Overall, it is widely accepted that recurrence rates increase with time; however, not all recurrence necessitates reoperation.[2,19] A systematic review by Becker and Davis[19] reported rates of recurrence ranging from 0% to 71% in the papers they reviewed. Dias and Braybrooke[20] reported a correlation between the rate of recurrence and the degree of initial contracture; however, this retrospective study is subject to bias, as it involved postal questionnaires sent to patients after surgery. They also reported a correlation between the severity of contracture and final hand function using subjective outcome measures. Skoff[21] reported a prospective study comparing limited fasciectomy in 2 consecutive groups. The first group had an open-palm technique described by McCash.[16] The next group had a local advancement flap combined with a hypothenar-based full-thickness skin graft (FTSG). Overall, they reported a 50% recurrence rate with the open-palm technique (average follow-up, 3.5 y) and 0% recurrence with the FTSG approach (average follow-up, 2.7 y). They failed to define their criteria for recurrence. Citron and Nunez[22] performed a prospective, randomized study to determine whether the type of skin incision used for palmar fasciectomy correlated with a higher recurrence rate. In one group, they used a longitudinal incision closed with Z-plasties, and in another group, they used a modified Bruner incision closed with Y-V plasties. After a minimum 2-year follow-up, they found no statistically significant difference between the 2 groups (18% for Z-plasties vs 33% for Y-V plasties). However, this study might have been under-powered, and a finite conclusion favoring one technique over the other cannot be determined. Ullah et al[23] conducted a prospective randomized trial to determine whether dermofasciectomy combined with FTSG versus Z-plasty over the PIP joint had a lower comparative rate of recurrence. After a 3-year follow-up period, they reported a combined recurrence rate of 12.2% and reported no statistical difference between the 2 groups. Hindocha et al[24] revised and modified the importance of patient factors (known as *Dupuytren's diathesis*) in prognosticating disease recurrence. They isolated and studied a constellation of patient-dependent variables that increase the risk of recurrence after surgery. The presence of all predetermined factors increased the patient's risk of recurrent disease by 71% compared to a 23% recurrence in patients without any factors.

Controversies in Dupuytren surgery still exist. Due to the intrinsic properties of the PIP joint, prolonged contractures of the PIP joint can make full extension of this joint virtually impossible without capsuloligamentous release and possibly surgical shortening of the

now-elongated central slip of the extensor mechanism. Unfortunately, combined capsulectomy with palmar fasciectomy has not shown to have better results than fasciectomy alone.[2,25]

Lilly and Stern[26] recently published a 2-part study of combined carpal tunnel release (CTR) and palmar fasciectomy for Dupuytren contracture. Previous studies have shown an unacceptably high rate of reflex sympathetic dystrophy/complex regional pain syndrome (CRPS) when both procedures are combined.[27,28] Their study initially reported the results of a survey conducted with members of the American Society for Surgery of the Hand to show that combined procedures are still controversial. The second part of their study involved a retrospective review of 70 patients who had combined CTR with palmar fasciectomy. They reported 2 patients with a transient pain flare that subsequently resolved and 1 patient who complained of stiffness. No patients were diagnosed with CRPS. They concluded that both procedures, CTR and palmar fasciectomy, can be safely performed during the same surgical session.

Although there are few available data regarding the management of recurrent disease, the accepted treatment has historically been and continues to be dermofasciectomy and FTSG. However, the studies that advocated this approach did not compare this technique to other treatment options.[29,30] Roush and Stern[31] attempted to compare 3 different treatment options: dermofasciectomy with FTSG, limited fasciectomy with interphalangeal joint arthrodesis, and fasciectomy with local flaps. Although this study did not compare rate of recurrence, the authors did show that patients treated with fasciectomy with local flaps had a substantial difference of total active motion at final follow-up. However, all 3 groups had comparable patient reported outcomes.

NONSURGICAL TREATMENT

Although surgery continues to be the most reliable and accepted method to treat progressive Dupuytren contractures,[1,2] numerous nonsurgical interventions have been tried over the years. These include physical therapy, corticosteroid injections, dimethylsulfoxide injections, topical vitamin A and E, and gamma interferon injections; however, these modalities have largely been found to be ineffective and clinically not acceptable.[5] In the 1960s, Bassot[32] introduced a new method to treat progressive contractures. Using enzymatic compounds injected directly into diseased cords, he effectively allowed for their degradation and subsequent rupture. Hueston[33] later coined this technique as *enzymatic fasciotomy* and used a mixture of trypsin, hyaluronidase, and lidocaine. McCarthy,[34] using a similar technique, reported long-term results showing comparable recurrence rates between enzymatic fasciotomy and surgical fasciectomy. Due to the higher rate of associated complications, he concluded that "enzymatic fasciotomy offers no advantage over surgical fasciotomy."[34] Nonetheless, the search for a nonsurgical approach continued to have an appeal to those afflicted by this condition and the physicians who treat them. Collagenase clostridium histolyticum was first introduced to the medical literature nearly 15 years ago as a potential novel approach to treat Dupuytren disease. Starkweather et al[35] presented the first *in vitro* studies conducted on excised Dupuytren cords for patients having fasciectomy. Before this introduction, there were no commercially available parenteral or injectable medications to treat Dupuytren disease. Since that time, collagenase clostridium histolyticum has completed phase 3 clinical trials and recently received FDA approval for clinical use and is marketed the under the name Xiaflex (Auxilium Pharmaceuticals, Inc.).

Collagenase clostridium histolyticum

Initially purified and isolated from clostridium histolyticum bacterial cultures by Maclennon[36] more than 50 years ago, collagenase has been extensively researched and has had variable clinical success before its introduction to Dupuytren disease. A total of 7 different clostridium histolyticum collagenases have been isolated and are categorized into 2 classes based on protein domain, substrate specificity, and gene of origin. These metalloprotease enzymes of the matrixin subfamily contain a substrate binding site that accepts collagen's triple-helix structure, leading to lysis and breakdown of its 3-dimensional structure.[37,38] Xiaflex is a predetermined mixture of class I and class II collagenases that the manufacturer claims works synergistically when breaking down collagenase. Collagenase in Dupuytren disease involves direct injection of the enzyme into the diseased cord. The patient returns the following day to allow time for the collagenase to digest and lyse the collagen within the cord. An extension force is then applied to the involved finger to rupture the already weakened cord[38–40] (Fig. 2).

Preclinical studies have shown that collagenase has catalytic activity against all types of collagen; however, it has the least activity against type IV collagen. Type IV collagen is found in the basement membranes of blood vessels and perineurium of peripheral nerves and is clinically important because both preclinical and clinical trials have failed to show noteworthy injury to these structures.[38,39,41,42]

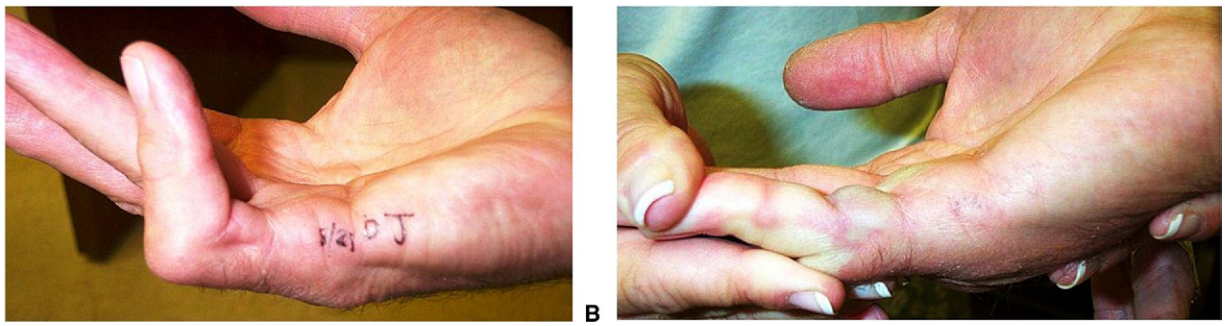

FIGURE 2: Collagenase treatment of a cord causing a PIP joint contracture of the small finger. **A** Before collagenase injection. **B** Passive extension force applied to the finger the following day, causing cord rupture.

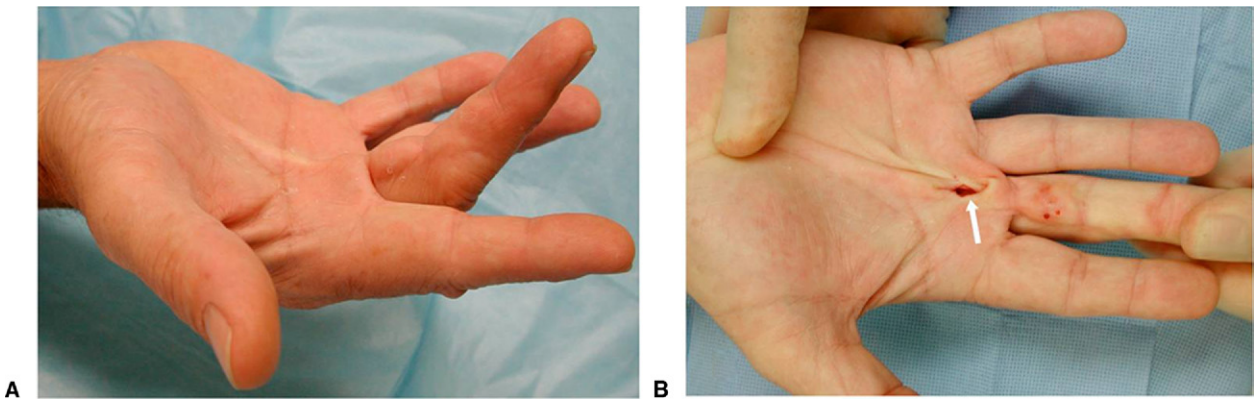

FIGURE 3: Collagenase treatment of a cord causing an MCP joint contracture of the long finger. **A** Before collagenase injection. **B** Passive extension force applied to the finger the following day, causing cord rupture and associated skin tear (arrow).

Numerous clinical studies have been conducted on the effects and outcomes of collagenase in Dupuytren contracture.[38,43] Hurst et al[39] reported the results of the large, multicenter phase 3 clinical trial, known as the Collagenase Option for Reduction of Dupuytren's I study. This randomized, double-blinded, placebo-controlled study enrolled 308 patients receiving a total of 741 (444 collagenase and 297 placebo) injections over 20 centers. They reported that 64% of patients who received collagenase versus 6.8% placebo corrected to within 5° of extension or less ($P<.001$). They also reported an improvement in overall range of motion in the affected joints, from 43.9° to 80.7° in the collagenase group versus 45.3° to 49.5° in the placebo group ($P<.001$). Adverse events were seen in 96.6% of patients in the collagenase group versus 12.2% of the placebo group. Most of these events localized reaction to the injection itself (peripheral edema, pain, contusion, and injection-site hemorrhage) and skin tear (Fig. 3); however, 7 major events were reported in the collagenase group, which included 1 patient developing CRPS and 2 patients having flexor tendon ruptures.[39] The results of another phase 3 trial, the Collagenase Option for the Reduction of Dupuytren II study, have recently been published. This prospective, randomized, placebo-controlled trial with an open-label phase reported a 70.5% decrease in joint contracture in the collagenase group and 13.6% in the placebo group ($P<.001$).[44] The results of these studies were combined with the previous clinical studies (one phase 1, three phase 2, and nine phase 3) and presented to the FDA.[38] A total of 1,082 patients with Dupuytren contractures received 2,630 injections to treat 1,780 distinct cords. Treatment-related adverse events were reported in 97% of patients but were mostly self-limited local reactions. However, major treatment-related adverse events included 3 tendon ruptures, 1 case of CRPS, 1 case of tendonitis, 1 pulley rupture, and 1 finger deformity. The tendon ruptures, pulley injury, and boutonniere deformity were all seen after injections into the small finger. Immunological studies have also been conducted; more than 85% patients tested developed anti-collagenase antibodies after 1 injection, and this percentage increased in patients who received more than 1 injection. Three patients developed clinically significant urticaria after receiving 2 or more injections; it resolved with

oral medications. No reported cases of anaphylaxis were reported across all trials.[38] The long-term immune responses to collagenase are currently being studied in the post-marketing surveillance studies required by the FDA.

The combined results of these trials have led to the FDA approval of collagenase clostridium histolyticum for treatment of Dupuytren disease. However, other long-term effects and overall recurrence rates are still being investigated by clinical trial. Watt et al[45] reported on a series of 8 patients who completed an 8-year follow-up. They reported that the average MCP joint contracture was 9° at 1 week to 23° at 8 years (n=6). The average PIP joint contracture was 8° at 1 week to 60° at 8 years (n=2). Only 2 patients in the study did not have recurrence, and both had MCP joint contractures.

The treatment of Dupuytren disease has been and continues to be largely surgical. However, the recent FDA approval of collagenase clostridium histolyticum for Dupuytren contractures now provides physicians a nonsurgical option to treat this disease. Clinical studies have shown that collagenase is both safe and efficacious when administered correctly. Although no comparison studies of collagenase to standard surgical options have been conducted, the opinions of some experts in the field is that recurrence rates might fall between those seen with a fasciotomy versus fasciectomy. As the financial cost of this new treatment becomes more affordable and long-term effects become better elucidated by clinical trial, collagenase might shift the current treatment paradigm.

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