Journal Club Meeting Date: 24 August 2011
Chair: Mr R. D. Meek
Organiser: Mr David Russell, StR4 West of Scotland Rotation
West of Scotland Orthopaedic Journal Club

Injectable collagenase clostridium histolyticum: A new nonsurgical treatment for Dupuytren's disease

Gilpin D et al
J Hand Surg 2010;35A:2027-38.

Reviewer: Mr Duncan Macdonald

Aim

To investigate the safety and efficacy of injectable collagenase clostridium histolyticum in patients with Dupuytrens contracture.

Study type

Phase 3 clinical trial conducted as a prospective, multicentre, randomised, double blind, placebo-controlled study with extension at 90 days to an open-label study.

Materials and Methods

Inclusion criteria included healthy subjects, aged over 18 years, with at least least one finger with MCP contracture between 20-100 degrees or PIP contracture between 20-80 degrees and the inability to place their hand flat. Exclusion criterion included recent treatment of Dupuytrens, breast feeding, pregnancy, bleeding disorder, cerebrovascular accident, neuromuscular disorders and allergy to collagenase. 72 subjects were screened and 66 included. They were randomised by computer-generated permuted block design with a ratio of Collagenase : placebo of 2:1. There were 45 actively treated (MCP:PIP was 20:25) and 21 placebo treated (MCP:PIP was 11:10). The double blind phase lasted 90 days. The collagenase (0.58mg clostridium histolyticum with lyophilised tris and sucrose) or placebo (lyophilised tris and sucrose) were injection into cord and if required a 'finger extension procedure' performed up to 3 times the next day. Night splints and physio were included for all. All subjects were included in the open label extension study for a further nine months and given up to five collagenase treatments if required. Standardised assessments included ROM, grip strength, enzyme linked immunogenicity assay to detect antibodies. Statistics used included the Cochran-Mantel-Haenszel test for repeated tests of independence controlling for joint type (PIP or MCP) + contracture severity. Two patients withdrew from the initial study and all patients were included in intention to treat and safety analyses. 6 further patients withdrew from open extension. The primary end point was defined as a reduction in contracture to 0-5 degrees within 30 days of the last injection and recurrence was identified as an increase to 20 degrees in a joint which had reached 0-5 degrees.

Results

During the double blind phase more joints in the collagenase group than placebo had reduction in contracture to 0-5 degrees, 44.4%(20/45) vs 4.8% (1/21) $p<0.001$. The median time to reach the primary end point was 57 days and required a mean 1.5 injections. The MCP was more likely to reach end point in the collagenase group, 13/20 vs 1/11, $p=0.003$ but in the PIP the difference did

not reach significance, 7/25 vs 0/10, p=0.69. The mean change in ROM was greater in the collagenase group 35.4+/- 17.8 vs 7.6+/-14.9, p <0.001. Adverse events occurred in all who received collagenase (100%) but these were mostly minor: Oedema (78%), contusion (73%), pain (38%), tenderness (13%), lymphadenopathy (24%), pruritis (11%), vesicles (4%). Antibodies present after 30 days in 95% patients. Two significant adverse events were flexor pulley rupture (1) and proliferation of cord (1).

Study Critique

Strengths

- Well run RCT
- Block randomisation
- Clear protocol
- Proper blinding
- Appropriate placebo used
- Excellent follow up
- Analysed on Intention to treat principle
- Clear reporting, flow diagram
- Appropriate statistics
- Open label extension enabled wider follow up for safety and efficacy

Weaknesses

- Strict primary end point
- Open label extension commenced relatively early and makes the paper more complicated to read.
- Under powered for sub-group analysis (PIPJ effectiveness)
- No power analysis mentioned
- Control group not a comparative treatment eg needle aponeurotomy
- Relatively short term follow up

Clinical relevance

Dupuytrens disease is a common condition and collagenase appears to be an effective new treatment which is licensed for use in the UK and USA. It appears to be safe and potentially cost effective to NHS when compared to open surgery. It is likely to change practice but needs to be taken in conjunction with other studies and long term follow up required.

Should acute scaphoid fractures be fixed? A randomised controlled trial

Dias JJ, Wildin CJ, Bhowal BM, Thompson JR

J Bone Joint Surg [Am] 2005;87-A:2160-8.

Reviewer: Miss Nadia Claire Sciberras

Aim

The aim of the study was to compare the functional outcome and rates of union of acute scaphoid fractures after non-operative treatment with immobilisation in a cast and after internal fixation.

Study Type
The study was a randomized controlled trial.

Materials and Methods
Patients who gave informed consent were randomized using computer generated randomization to two groups: (1) treatment with early internal fixation with use of a Herbert screw without a cast (forty-four patients) and (2) to non-operative treatment for eight weeks with immobilization in a below-the-elbow plaster cast with the thumb left free (forty-four patients). Patients were recruited into the study over a three year period. The patients were evaluated at two, eight, twelve, twenty-six, and fifty-two weeks with respect to the severity of pain, tenderness, swelling, wrist movement, grip strength and symptoms and disability, which were assessed with the Patient Evaluation Measure. In addition, radiographs were taken and assessed at each visit. Patients who were in the conservative group and showed signs of non-union at twelve weeks had a CT-scan at sixteen weeks. If a gap was present at the fracture site, the patient was offered surgery.

Results
The follow-up outcome measures were compared on an intention-to-treat basis using a repeated-measures analysis of variance with adjustment of p values by the Greenhouse-Geisser epsilon. The results at each visit were then compared with t-tests. No difference was detected between the groups with respect to age, sex, hand dominance, side of injury, mechanism of injury, or the occupation of the patients. At the eight-week follow-up evaluation. the range of motion, score on the Patient Evaluation Measure, and grip strength were significantly better in the group managed operatively than in the group managed non-operatively. This was at the time when the cast was removed in the group managed conservatively. Patients returned to work at five to six weeks after the injury in both groups. At twelve weeks, grip strength was better in patients who had had surgery. No significant difference was detected between the two groups with respect to any other outcome measure at any other time. Ten of the forty-four fractures treated non-operatively had not healed radiographically at twelve weeks, and, as a consequence, the treatment was altered. Complications occurred in thirteen patients who had been managed operatively. All complications were minor and were mostly scar related.

Conclusion
With the exception of union, the authors did not find any significant difference in the long term outcomes. Conservative treatment eliminates the risk of surgery which would still be available as a mode of treatment if the fracture fails to unite. Consequently the authors advocate a different approach which they refer to as “aggressive conservative treatment”. With this approach all undisplaced scaphoid fractures and those without a substantial step-off are treated with immobilisation in a below elbow cast for six to eight weeks. If following removal of plaster there is concern about union, a CT scan is performed to identify any gap at the fracture site. If a gap is identified at the fracture site the patient is offered surgery. The authors conclude that acute surgical intervention should only be reserved for patients who cannot return to work in a cast.

Study Critique

Strengths

- One of the major strengths of this study is that it is a randomized controlled trial (RCT) with computer generated randomization.
- Being a RCT, is it a prospective study and hence accurate data collection was possible
- It is a well powered study
- Well defined inclusion and exclusion criteria which were adhered to
- The senior author who is experienced in hand surgery performed most of the operations and was present for all of the operations

Weaknesses

- The study is a well conducted study with few weaknesses
- The study was not blinded and thus an element of bias might have been introduced

Clinical Relevance

This study is clinically relevant as it is a randomised controlled trial addressing the acute treatment of scaphoid fractures which is controversial. The study has shown that patients who are treated conservatively do not have an increase in stiffness or reduced grip strength when compared to those who had acute surgical intervention. This is contrary to what was published in some previous articles.

Long-Term Results of Radial Head Resection Following Isolated Radial Head Fractures in Patients Younger Than Forty Years Old

Antuna SA, Sánchez-Márquez JM, R Barc

J Bone Joint Surg [Am] 2010;92-A:558-66.

Reviewer: Mr Odhran Murray

Aim

Review the long-term results of radial head resection after radial head fractures not associated with elbow instability in patients younger than forty years of age.

Study Type

Retrospective case series

Materials and Methods

The authors review all patients who underwent a radial head resection from1968-1992 (n=72) in their institution. Thirty-three were excluded due to an associated ipsilateral elbow injury or failed conservative or alternative operative management. Twenty-six patients were alive, had complete records and returned for study follow-up. There were 6 Mason type II and twenty type III injuries. The average time to surgery was seven days (1-12) with a minimum follow-up of 15 years (mean, 25). Final clinical and radiological follow-up was performed by one independent observer, including the Mayo Elbow Performance (MEP) and the Disabilities of the Arm, Shoulder and Hand (DASH) scores.

Results
There were no complications and no additional surgery to the elbow or wrist. Twenty-one patients (81%) had no elbow pain, three had mild pain, and two had moderate pain. The mean extension / flexion arc was 130° (70°-145°). The mean pronation was 84° (40°-90°), and the mean supination was 85° (60-90°). The mean MEP Score was 95 points (60-100) (good or excellent for twenty-four elbows (92%) and as fair for two). The mean DASH score was 6 points (0-38). Three patients complained of mild to moderate wrist pain. Elbow instability was detected in four patients and osteoarthritis in all twenty-six. Neither finding was clinically relevant.

Conclusion
Radial head resection in young patients with isolated fractures without instability yields long-term satisfactory results in >90% of cases. Osteoarthritic changes are uniformly present but typically are not associated with functional impairment.

Study Critique
Strengths
- Clinically relevant
- Long-term follow up, (minimum 15 years, average 25 years)
- Young active cohort in manual occupations
- Excluded patients with instability (different problem)

Weakness
- Retrospective
- Low Numbers, underpowered for subgroup analysis
- Method of Obtaining elbow range of motion not stated (potential for large variation)

Clinical Relevance
The long-term results of radial head excision in patients with comminuted isolated radial head fractures (Mason II & III) are at least as good as more complex and expensive methods of fixation in the literature. However, one should exercise caution and must exclude instability including a pull test under fluoroscopic control.