

Continuing Experience with Chemonucleolysis

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Abstract

Chemonucleolysis using chymopapain is the least invasive technique used to treat a herniated lumbar pulposus. After 37 years of clinical experience, multiple clinical trials, a national multicenter, double-blind study mandated by the Food and Drug Administration, and heated controversy in the scientific community, the injection of chymopapain to treat herniated discs has (in appropriately selected patients) proven as successful as laminectomy, with fewer complications and the advantage of considerable cost savings. **Key Words:** Herniated lumbar disc, chemonucleolysis, chymopapain.

IN 1963, LYMAN SMITH (1) was the first to inject chymopapain for the treatment of unremitting sciatica due to a herniated lumbar nucleus pulposus; he coined the term "chemonucleolysis" (CNL) for the procedure. Even after 37 years of clinical experience with CNL, the administration of chymopapain still provokes controversy, especially among those with very strong opinions who have never used the enzyme. Nevertheless, this minimally invasive technique has been the most studied, the most evaluated, the most regulated, and the most closely followed therapy for unremitting sciatica ever utilized by the medical profession.

Pharmacology

Chymopapain is a proteolytic enzyme derived from papaya latex. It acts as a catalyst which promotes rapid hydrolysis of the chondromucoprotein portion of the nucleus pulposus (2). Although the specific substrate(s) remain obscure, it is known that the enzyme inhibits the ability of proteoglycan to adsorb water which then leads to a breakdown of cartilage. Similarly, since proteo-

glycans are crucial in maintaining the integrity of vascular endothelial lining, chymopapain may cause bleeding from the microcirculation if it comes in direct contact with the capillaries. Large vessels are not affected. Recent studies also indicate that chymopapain modulates the activity of phospholipase A and thus exhibits anti-inflammatory qualities (3).

Indications

Proper patient selection is paramount for the success of chemonucleolysis. Only 10% of patients with unremitting sciatica and neurologic changes due to a herniated nucleus pulposus should be considered for discectomy or chemonucleolysis if they do not respond to conservative treatment (4). Not all laminectomy candidates are suitable for chemonucleolysis. Classic indications are symptomatic lumbar disc displacement as indicated by MRI, CT, and/or myelography, and lack of other major cause of symptoms. Conservative treatment should be attempted for a minimum of 6 weeks.

A recent study indicates that the size of the herniated disc is not a factor for a satisfactory outcome, nor is the shape of the spinal canal (5). The disc does not have to be contained; however, a sequestered fragment in certain cases may be a contraindication. Age can be a factor, because patients over 60 years of age may lack sufficient

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mucoprotein for the herniated disc to be hydrolyzed. Among patients younger than 20 years, an 80–90% success rate has been reported (6). A good candidate is one with single level involvement, leg pain exceeding back pain, and good correlation of the findings on physical and imaging examinations.

Contraindications

Known contraindications include: (a) allergy to papaya or papain, (b) pregnancy, (c) severe or progressive neurologic deficit, (d) cauda equina syndrome, (e) arachnoiditis, (f) diabetic polyneuritis, (g) spinal tumors, (h) central or lateral recess spine stenosis, (i) migrated disc, (j) severe spondylolisthesis, and (k) history of discitis. Chemonucleolysis is also contraindicated for patients with recurrent disc herniation after surgery at the same level. Repeat chemonucleolysis is not approved by the FDA.

Clinical Studies

In 1975, when FDA approval of chymopapain was sought, 17,000 patients had already been injected. Nonetheless, some surgeons insisted that a double-blinded study must also be done, to eliminate the possibility of the placebo effect. Others thought this to be contrary to the Helsinki Accord, in which the use of a placebo was strongly criticized in any research study where specific treatment was known to be effective. A multicenter, double-blind study was done in 1981, and the results were reported in *JAMA* in 1983 (7), with a 75% favorable response to the enzyme versus 45% to placebo. To our knowledge, this was the first double-blind study of treatment for a musculoskeletal disorder. Subsequently, a double-blind study in Australia was reported by Gogan et al. (8). In 1988, Dabezies et al. (9) reported a study done in the United States. Both showed positive results for CNL. Ramirez and Javid reported good or excellent results for laminectomy in 77% of their cases (10).

Our prospective one-year study with follow-up of 100 consecutive patients (including 22 workers' compensation cases) who underwent CNL, and 100 consecutive patients (including 24 workers' compensation cases) who underwent laminectomy yielded the following results (11):

At 6 weeks (Figure), the success rate for CNL was 80% (excellent 33%, good 47%). For laminectomy, it was 85% of patients (excellent 52%, good 33%). Although statistically these results seem to favor laminectomy, $p = 0.013$,

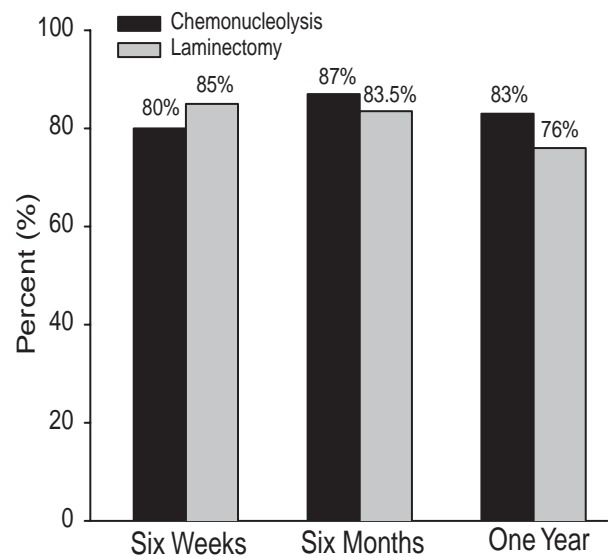


Figure. Comparison of overall successful results of chemonucleolysis versus laminectomy.

improvement in sciatica was similar in both groups. Slight improvement occurred in 7% of CNL patients and 6% of laminectomy patients; 10% of CNL patients and 3% of laminectomy patients remained unimproved.

At 6 months (Figure), results were good-to-excellent for 87% of 100 CNL patients, and for 83.5% of 97 laminectomy patients; 4% of CNL patients and 6.1% of laminectomy patients showed slight improvement; 9% of CNL patients and 5.1% of laminectomy patients showed no improvement; and 4.3% of laminectomy patients had deteriorated to preoperative pain levels.

At one year (Figure), results were good-to-excellent for 83% of 100 CNL patients and for 76% of 97 laminectomy patients who were available at one year; 7% of CNL patients and 14.5% of laminectomy patients showed slight improvement; 10% of CNL patients and 9.5% of laminectomy patients showed no improvement.

There are no statistically significant differences between the two groups. In addition, long-term experience with CNL has repeatedly shown lack of postoperative fibrosis and maintenance of successful results over many years.

Complications

Earlier, anaphylaxis had been a concern, following its occurrence in 0.5% of cases, mostly in the southern states. But, with IgE, chymopapain sensitivity testing and administration of antihistamine agents prior to use, anaphylaxis has been reduced to 0.25% of total allergic reactions in the United States; it is even lower in Europe. There

have been no major anaphylactic complications since April 1987, although seven deaths from anaphylaxis occurred prior to that time.

Since the enzyme is under the jurisdiction of the FDA, all reactions following CNL administration must be reported within 15 days. (This is not true of laminectomy.) The total thus far includes 121 adverse reactions in about 135,000 patients. We often read that chymopapain results in more complications than does laminectomy/discectomy. Actual comparison of usual complications, however, reveals 17 times more infections, 6 times more neurological and vascular problems, and an overall mortality 3 times greater in laminectomy than in CNL (12). In a European study (13) of 43,662 chymopapain-injected patients and 2,051 discectomy patients, ten times as many complications occurred in the open surgery as in the CNL cases.

Reinjection of chymopapain has always been prohibited in the United States, because of fears of sensitizing the individual and thereby creating a greater probability of anaphylactic reactions. The International Intradiscal Therapy Society sponsored a study of 420 reinjected patients in 1997. Five cases had minor reactions that needed no definitive treatment, three had some decrease in blood pressure and transient distress, and one had a full-blown anaphylactic shock that responded to treatment. Two smaller studies came to conflicting conclusions (14, 15). With the availability of IgE chymopapain testing, there is no reason to withhold CNL from these patients. Our own experience with repeat injection in four patients with recurrent disc herniation at the same level and in two patients with the problem at another level revealed no allergic reactions.

Efficacy and Future

The continued practice of chemonucleolysis is dependent upon surgeons who have seen the results personally and are well versed in the body of medical literature supporting the procedure. The responsible use of chemonucleolysis and chymopapain is paramount. From the double-

blind (7) and longitudinal (16) studies and the recent article by Postacchini (17), it is clear that chemonucleolysis and chymopapain are safe and effective in the treatment of lumbar disc herniations for patients who are carefully selected and screened.

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