

# Chemonucleolysis Requires Chymopapain: Should We Accept Its Unavailability?



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The production of chymopapain and its availability in the United States and Europe has been discontinued by its manufacturer. This creates an untenable and unacceptable situation. Our patients are without chemonucleolysis (CNL), a proven treatment for disc related nerve root pain. FDA confirmed that Chymodiactin®, which is injected during the CNL procedure, was not discontinued for reasons of safety or effectiveness.

Chemonucleolysis is the only minimally invasive technique that has undergone extensive study and validation with Level I evidenced based medicine (EBM). Three prospective, randomized, double blind, placebo controlled studies<sup>1,2,3</sup> and at least 32 cohort studies in patients selected using stringent criteria after a well standardized chemonucleolysis procedure demonstrate that it is safe and effective for soft, contained and protruded disc herniations contiguous with the disc space<sup>4</sup>. These studies bring credence to the results of numerous reports of open label level V studies that rate the good results as high as 70 to 80 percent as a stand alone procedure. More recent studies, including my own, conclude that ten percent higher good/excellent results are reached when chymopapain is combined with the endoscopic or percutaneous discectomy. Each year, continued reports of the benefits and efficacy of chymopapain continue to be presented at the annual meeting of the International Intradiscal Therapy Society (IITS). Reports continue in the form of scientific clinical papers presented by surgeons as recently as the 19th annual meeting held in Phoenix, Arizona in April 2006.

What is most unfortunate is that CNL can be used most effectively in adolescents<sup>5</sup> and is also effective in older patients without spinal stenosis who have higher surgical co-morbidities<sup>4</sup>. Surgeons are more reluctant to operate on these patients. Foraminal and extraforaminal herniations, which are sometimes difficult to access from the spinal canal and in transcanal approach to the disc, can be successfully treated by CNL<sup>6</sup>. In studies comparing CNL with surgery, outcomes were generally better with open surgery<sup>7,8</sup>. Some studies, however, raise methodological problems<sup>8</sup>. In these studies, although surgery provides more dramatic short term pain relief, there is little difference in long term outcomes<sup>7,9</sup>. The rate of recurrence is reduced from 4% to 10% when compared with microdiscectomy, and it has now been established that CNL can be repeated a second and even a third time with adequate premedication<sup>10</sup>. In the long term, there is no significant loss of initial benefits by using chymopapain<sup>4,7,9</sup>. In clinical and experimental studies, no evidence of instability was demonstrated by dynamic assessments<sup>4</sup>, unlike traditional surgical decompression and discectomy. There are no specific surgical challenges when operating on patients previously treated with chymopapain<sup>11</sup>. Outcomes are similar to those after primary surgery, and the paradoxical effects of discectomy are lessened.

The risk of adverse events after CNL generated considerable controversy after its introduction, but it should be pointed out that adverse events are

six times less common and serious adverse events ten times less common than after open surgery<sup>12</sup>. Temporary increase in low back pain is fairly common; however, the use of low dose chymopapain and endoscopic removal of chymopapain assisted nucleotomy has reduced the incidence of low back pain exacerbation<sup>13</sup>. The main advantage of chymopapain over surgery is that there is no risk of epidural and perineural fibrosis (14). In a study that took into account both the costs of repeat surgery to treat failed CNL or recurrence and the costs of nonsurgical treatment in patients who did not have surgery, one year costs were 40 percent higher with surgery than with CNL<sup>4,15</sup>. Thus, the medical and financial usefulness of chemonucleolysis has been established.

From the first year of FDA clearance in the U.S., I have utilized chymopapain both as a stand alone procedure and as an adjunct to endoscopic disc excision. I reviewed my visually documented endoscopic results on 63 consecutive cases from October 1995 to February 1998 for difficult to extract extruded and sequestered disc herniations. The results, presented at the 11th annual meeting of IITS in May 1998, concluded a ten percent higher clinical success rate when chymopapain was used in conjunction with arthroscopic microdiscectomy, even when used selectively for the most technically difficult disc excisions.

What follows is a summary of observations and clinical experience with chymopapain used in conjunction with endoscopic disc removal (the YESS Technique).

Chymopapain softens the nucleus pulposus, making it slippery and more easily removed by endoscopic suction-shaver techniques. There is intra-operative evidence of partial endoscopic enzymatic digestion in the specimen removed manually. When combined with the mechanical endoscopic discectomy, nucleotomy is easier and possibly faster.

In over 300 consecutive patients, no symptoms of allergic reactions, i.e. rash, itching, breathing difficulty, anaphylactic reaction, were encountered when chymopapain was used in conjunction with endoscopic discectomy and nucleotomy. Because chymopapain contained in the disc is immediately removed along with the partially digested nucleus pulposus, I elected not to test for antibodies to chymopapain. Even so, now that IgE testing is available routine testing for potential allergic reaction to papaya should be done.

Chymopapain was found to be safe, even if it extravasates into the epidural space and around myelinated spinal nerves as demonstrated by intra-operative chemo-discography, an integral part of the YESS endoscopic discectomy technique. Even with extravasation, post-operative muscle spasm, a common self limiting sequellae of CNL, is minimized. Chymopapain is also inactivated by cystine in the blood stream if any of the

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injected chymopapain reaches the blood stream. Post-operative back spasms, a concern with 15 to 20 percent of stand alone chymopapain treated patients, is dramatically reduced, if it occurs, when used in conjunction with endoscopic disc excision. All procedures are performed on an outpatient basis and only one patient in the entire series was hospitalized for back spasm when the primary care physician admitted the patient without consulting or notifying the surgeon.

### *Rationale for Chymopapain as a Stand Alone or an Adjunct to Mechanical Discectomy*

- The nucleus pulposus is hydrolyzed almost immediately with low dose chymopapaine.
- The mechanical extraction of hard, collagenized disc fragments is aided by having the nucleus partially digested prior to mechanical extraction.
- Any remaining degenerated nucleus pulposus may be altered biochemically to decrease the production of cytokines responsible for chemical sciatica.
- Recurrent herniations are ideal for the combined endoscopic fragmentectomy technique since epidural fibrosis will limit the migration of the recurrent fragment. Treatment of the remaining nucleus may mitigate a third recurrence.
- Future indications and applications for chymopapain may include using it to aid nucleotomy for nucleus replacement.

### *Clinical Study Reported at IITS Meeting, May 1998 (Yeung)*

From 10/95 to 2/98, 47 consecutive patients with narrow based extruded herniations (height greater than width) and 16 consecutive patients with recurrent disc herniations following conventional transcanal discectomy underwent endoscopic percutaneous discectomy aided by low dose chymopapain.

### *Results*

Using MacNab criteria, 59/63 (93 percent) were good/excellent, 3/63 (five percent) fair, and 1/63 (two percent) poor; 16/63 were for recurrent herniations after previous successful laminectomy/discectomy or microdiscectomy; 14/16 (88 percent) of the recurrent herniations were good to excellent and 1/16 (six percent) was fair; 1/16 (six percent) was poor due to unrecognized lateral recess stenosis, but converted to good after lateral recess foraminoplasty.

### *Discussion*

Hoogland, et.al. compared his results of lumbar and cervical percutaneous nucleotomy combined with low dose chymopapain versus nucleotomy alone, and found ten percent better good/excellent results compared with discectomy without chymopapain. In this series, only the more difficult extruded herniations were selected for the combined technique. The overall results of 93 percent good/excellent were slightly better than a similar group demonstrating an 89 percent good/excellent result in 119 consecutive patients reported in the Spine Journal.

### *Conclusion*

Chemonucleolysis using chymopapain utilized as a stand alone treatment for contained disc herniation should be made available again. As an adjunct

to endoscopic discectomy for HNP, it will shorten the learning curve, may improve percutaneous endoscopic discectomy results, decrease the recurrence rate and is safe, even when the enzyme is used for extruded herniations. Future applications may include its use in nucleotomy for nucleus replacement in which a thorough nucleotomy is mandatory. As a stand alone procedure, it is still the first line treatment of choice, especially in adolescent and young patients with painful bulging discs with or without annular tears.

Chemonucleolysis may be utilized as a first line treatment in the spectrum of minimally invasive options for disc protrusions and herniations.

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