Chymopapain chemonucleolysis

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It is nearly 30 years ago that Lyman Smith introduced chymopapain as a possible treatment in lumbar disc herniation (Smith et al. 1963). The enzyme depolymerizes the long chains of proteoglycans in the nucleus pulposus with subsequent loss of water binding capacity. This causes a reduction in the volume and pressure of the nucleus and the herniated fragment. It is also postulated that the inflammatory reaction of the nerve root, a chemical radiculitis, caused by break down products from the leaking degenerated nucleus, is reduced by the chymopapain. This could explain the immediate relief of sciatica that we observe in one third of our patients following chemonucleolysis.

The observed decrease in disc height after chemonucleolysis will also reduce the tension in the nerve root. However, despite numerous studies, the mechanism by which chymopapain exactly resolves the radicular symptoms is still unclear. Discussions on the effectiveness of chemonucleolysis have not subsided completely, but the overwhelming number of publications showing its safety and efficacy cannot be ignored (Deutman 1992).

In 1983 we performed a prospective CT-study of the effects of chemonucleolysis in 30 patients with the herniated lumbar disc syndrome (Konings et al. 1984, 1986). At 3 months follow-up the degree of compression of the nerve root and dural sac was reduced in 74 percent of the patients and was found to correlate with the clinical result. A focal abnormality often remained, as was also reported in other CT- and MRI-studies. Similar serial changes in the intervertebral disc after chemonucleolysis observed by Magnetic Resonance Imaging were recently reported by Kato (Kato et al. 1992). A marked decrease in disc signal was noticed after 2 weeks; reduction in size of the herniated disc fragment began at 4 weeks and continued to diminish gradually over the first year after chemonucleolysis.

The reduction in disc height induces annular bulging. Chemonucleolysis is not indicated in the treatment of dural sac or nerve root compression caused by annular bulging alone as this would increase the problems.

Many authors consider chemonucleolysis as the last step in conservative therapy of the herniated lumbar disc syndrome. The standard indication for chemonucleolysis is a patient with mainly radicular pain and symptoms not alleviated by a well conducted conservative treatment of at least 6–12 weeks including bed rest. At least 3 out of 5 criteria according to McNab and McCullough have to be positive including confirmation of a herniated disc with CT or MRI (McCullough and McNab 1983). Chemonucleolysis is not indicated in patients with root entrapment and stenosis or when MRI demonstrates a migrated disc fragment that has no contact with the disc. Cauda equina compression and fast developing major neurological deficit are probably best treated by immediate surgery.

However, we have to realize that in the vast majority of cases the herniated disc problem is a pain problem. The only indication for invasive therapy, chemonucleolysis, percutaneous nucleotomy or micro-/macrodiscectomy is intolerable radicular pain, not (minor) neurological deficit (Findlay 1991). Minor muscle weakness or sensory changes of long standing existence are often not reported by the patient but discovered by the physician. The neurological recovery after treatment is not predictable and is reported not only after surgery but after chemonucleolysis and conservative treatment as well.

The technique of the disc puncture and chemonucleolysis is well known (McCullough and McNab 1983). Some of the neurological complications attributed to chemonucleolysis may be the result of an incorrect needle placement technique during lumbar disc puncture with violation of the subarachnoidal space or the nerve root sheaths. It has to be stressed that the only allowed approach of needle placement is the lateral approach and certainly not the posterior transdural approach. The safest way to avoid puncturing the nerve root or the lumbar plexus and to avoid penetrating the intervertebral foramen, is to direct the needle just lateral to the facet, with a low point of entry to the disc (Konings and Veldhuizen 1988). There is no general agreement about the use of discography or discometry. Discography can be used to check the position in the center of the nucleus, to observe the spreading of the fluid into the herniation. Epidural leakage can often be observed and is not a contra-indication for

chemonucleolysis. In case of a very rare intra-dural herniation and intra-dural leakage of the contrast the enzyme should not be injected. In a large European survey Bouillet found no adverse effects of discography but on the other hand he also found that the use of discography did not protect against the rare occurrence of neurological incidents and complications (Bouillet 1991). Routine discography of the adjacent discs is not indicated.

In the European survey, Bouillet analyzed allergic and anaphylactic reactions (Bouillet 1991). He could not show benefits of standard desensitization premedication. Anaphylactic accidents did not occur more often with general anesthesia than with local anesthesia.

After chemonucleolysis relief of back pain is slower than relief of sciatica. Many patients (25–40%) experience mild or severe back pain and spasms or stiffness of the lumbar spine for some days or weeks. In a number of studies (Wardlaw 1991, Bonneville 1992, Pegg 1992) was found that a lower dose chymopapain (2.5 nkat in 2 mL) appeared to be as effective as the standard dose (5 nkat in 2 mL), while there was less post-injection back pain and spasm and eventually also less disc height reduction. Other studies evaluating the result of even lower chymopapain dosage are in progress.

The complication rate of chemonucleolysis is low. In the large European surve of 43,662 chemonucleolysis procedures Bouillet (1991) reported 3.1 percent incidents (allergic reactions, urinary problems etc) which required no treatment; 0.14 percent complications of average severity (thrombosis, pulmonary embolism) but without sequelae and 0.44 percent severe complications (discitis, anaphylaxis, cerebral hemorrhage, cauda equina syndrome). The value of a certain treatment also depends on success and complication rates of other possible procedures. In this case it is interesting to mention that Bouillet encountered 10 times more severe complications and 4 times more adverse reactions in a comparable survey of surgical procedures for disc protrusion.

Epidural fibrosis is a recognized complication of disc surgery. It could be symptomatic and it could give diagnostic problems in case of persistent symptoms. Chemonucleolysis does not cause epidural fibrosis. In a rat model LeBlanc (1992) found that chymopapain could prevent epidural fibrosis after laminectomy.

The success-rate of chemonucleolysis in the *short-term* is reported in many retrospective studies. In 43 studies with nearly 8000 procedures, the result was satisfactory in 74 (40–98) percent. In 5 double-blind studies, the result with chemonucleolysis was satisfactory in 72 (58–80) percent, with placebo 50 (42–57) percent. In a double-blind study of chymopapain versus placebo injection, with 10-year follow-up, a sustained better therapeutic effect of chymopapain was demonstrated (Gogan and Fraser 1992). A compilation of *long-term* results in 3130 patients (Nordby 1986) showed satisfactory results in 77 (66–93) percent.

We performed a prospective study on a consecutive group of 200 patients, who were followed up for at least 6 years (Konings 1990). None of these patients were lost to follow-up! 34 percent of the patients had an uneventful, straight forward recovery following chemonucleolysis, in others recovery often took many months. The effect of the treatment at 6 months was satisfactory in 70 percent of the patients. The best results were met in adolescents and in males in their third decade.

In agreement with the literature a better treatment effect and better short-term and long-term condition ratings were seen in patients with the "classic" radicular symptoms. After a mean period of 7 years 76 percent of the patients were in a satisfactory condition. Unsatisfactory short-term and long-term results were encountered in patients receiving a disability pension. The amount of disc height reduction was not correlated with the response to treatment. In many long-term studies the development of root canal stenosis could not be shown.

Most authors agree that the relief of leg pain after chymopapain is slower than after surgery, but that at 3 months the results are the same (Wardlaw 1991). According to the literature the results of postchymopapain surgery are somewhat less than would be expected with primary surgery, satisfactory results are achieved in 50–80 percent. When primary surgery is compared with chemonucleolysis including post-chymopapain surgery the results at 1 year are comparable (Wardlaw 1991).

The important advantages of chemonucleolysis are, however: 1) a lower complication rate; 2) more economical in terms of savings and hospitalization; and 3) no epidural fibrosis.

Surgery of chymopapain failures seems to be easier and more successful than repeated surgery.

The advantages of chemonucleolysis over percutaneous discectomy are: 1) its simplicity; 2) in contrast with percutaneous discectomy hardly/no nerve root lesions; 3) treatment of the L5-S1 disc herniations is technical much easier; and 4) the enzyme will reach a large postero-lateral protrusion better than with the percutaneous instrumentation.

Allergic reactions are rare, at least in Europe; it can be treated without sequelae and its risk can hardly form an argument to choose percutaneous nucleotomy.

During the regular annual meetings of the International Intradiscal Therapy Society, clinical experience with intradiscal techniques, new developments, and

trends are presented. As chemonucleolysis concerns, consistently favorable results are reported in elderly patients (Benoist et al. 1992), in disc herniation at the level of a spondylolisthesis (Nordby 1986, Hoekstra et al. 1990) and in repeat chemonucleolysis (Sutton 1986). In recent years satisfactory results without complications are also reported of cervical chemonucleolysis (Gomez-Castresana et al. 1992). Even in patients with recurrent sciatica after previously operated discs, chemonucleolysis was considered to be a valuable procedure (Deburge 1992).

In the long-term, the frequency of persistent back and/or leg pain, the need for physiotherapy, disability pensions and the frequency of secondary procedures, appears to be very similar for the various treatment modalities for lumbar disc herniation (Weber 1983, Dvorak et al. 1988).

Surgery, percutaneous discectomy and chemonucleolysis will accelerate the degenerative process of the disc and transform the initially unstable disc situation into a more or less stable and asymptomatic situation, as has already been suggested by Hirsch (1959). Our "therapeutic intervention", like Nordby stated, may eliminate or modify the pain a little sooner than nature does (Nordby 1989).

Intolerable sciatica is the most important reason to end conservative treatment. We have to choose a treatment which has a reasonable chance of success and offers the least risk of complications in the short-term and long-term. From our own experience as well as from that of many other authors, we can conclude that chemonucleolysis meets these requirements.

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