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Chemonucleolysis for sciatica

A critical review

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Intradiscal injection of chymopapain for the treatment of sciatica due to disc herniation has been used for more than 25 years, but is still under debate. We review the indications, complications, and clinical results, and discuss the tissue effects of chymopapain.

The results following surgical disc removal versus chymopapain injection indicate that surgery with removal of the disc hernia through a small laminotomy remains the documented treatment of choice for patients with proven disc herniation and sciatica in whom conservative treatment has failed.

The use of chymopapain for intradiscal injection in patients with disc herniation and sciatica was introduced by Lyman Smith in 1964, who called this procedure *chemonucleolysis*. To date, several hundred thousand patients around the world have received lumbar intradiscal injections with this enzyme. Collagenase has also been used in this context, but in a much smaller number of patients, and only on a trial basis (Bromley et al. 1984, Brown and Tompkins 1986, Hedtmann et al. 1987).

The concept of injecting a proteolytic enzyme into the disc to treat disc disease was first suggested by Hirsch (1959). His hypothesis was that an intradiscal injection of a chondrolytic enzyme would speed up the disc degeneration to an end stage where the disc would be stable and asymptomatic. Hirsch's original idea was modified by Smith, who reported the use of chymopapain to dissolve discs in animals and humans (Smith et al. 1963, Smith 1964). The use of chymopapain was based on observations by Thomas (1956), who showed that intravenous injection of papain in rabbits caused cartilage dissolution and drooping of the ears. Papain and its more refined form chymopapain are both extracted from the juice of the papaya fruit (*chymos* is Greek and means juice).

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Effects of chymopapain on disc tissue

Chymopapain, which is a positively charged molecule, attacks the negatively charged proteoglycans of the intervertebral disc, demonstrated both in vitro and in vivo (Stern 1969, Bradford et al. 1984, Suguro et al. 1986), whereas the collagen of the disc seems to be mainly unaffected by chymopapain. Intradiscal injection of chymopapain brings about changes in the mechanical properties of the disc in terms of increased flexibility and loss of torsional stiffness (Kahanovitz et al. 1985, Spencer et al. 1985, Floman et al. 1986). Following chymopapain injection, the disc height decreased within a few weeks to months (Wiltse et al. 1975, Bitz and Ford 1977, Bradford et al. 1984, Takahashi et al. 1986, Szypryt et al. 1987).

Some authors claim that the disc may regain height later (Wiltse et al. 1975), a phenomenon that might be based on the reversible effect of chymopapain on the proteoglycans of the disc as demonstrated in animals by Bradford et al. (1983, 1984). The precise mechanism of action by which chymopapain relieves pain is not known (Brown 1983, McCulloch and MacNab 1983, Editorial 1986), but the general interpretation of this treatment modality is that the enzyme reduces the water-binding capacity of the proteoglycans, thereby decreasing the intradiscal pressure (Takahashi et al. 1986). This would result in a reduction of the pressure by the disc herniation on the nerve root. Reduced nerve root pressure

has also been proposed to be mediated via the decrease in disc height, resulting in slackening of the nerve root (Spencer et al. 1985). Recent MRI studies do show rapid loss of water, which does not reconstitute in 12 months (Szypryt et al. 1987).

Toxicity and allergenicity

Before discussing the clinical efficacy of chymopapain treatment, we would like to consider some aspects of the potential side effects of this enzyme. There has been an intensive debate on this obviously controversial topic, and different opinions regarding incidence, severity, and underlying causes of various complications have been put forward (Brånemark 1975, Wiltse 1977, Rydevik et al. 1978, Eguro 1983, Weitz 1984, Dabezies 1985, Sridhar 1985, Brown 1985, Fager 1985, Taylor and Ghosh 1985, Javid 1985, Gupta et al. 1986, Knox 1986, Javid 1986, Sutton 1986).

The most frequent complication is *anaphylaxis*. In large materials from the United States and Canada, this complication has occurred in about 0.5 to 0.7 percent (Hall and McCulloch 1983, Agre et al. 1984); and in a European survey of 4,880 cases, an anaphylaxis rate of 0.06 percent was reported (Bouillet 1984). The higher incidence of systemic allergic reactions in North American studies might be due to the fact that the population there is generally more exposed and sensitized to chymopapain through its frequent use in meat tenderizers, toothpaste, beer, and fruit juices (Brown 1983). Intradiscal chymopapain injection can induce increased serum levels of IgE and IgG with reactivity against chymopapain (Sagona et al. 1985), and therefore repeated injections of chymopapain should not be given. By preinjection screening to detect and exclude risk patients, i.e., individuals with IgE antibodies to chymopapain, and by skin testing (Cogen et al. 1985), the incidence of anaphylactic reactions has been reported to be decreased (McCulloch and Macnab 1983, Mayer et al. 1986). It has also been proposed that chymopapain injection under local rather than general anesthesia would be associated with a lower risk for anaphylaxis (Agre et al. 1984). Another advantage of enzyme injection under local anesthesia is that the patient will react if the injection needle comes in close contact with the nerve root (Brown 1983, McCulloch and Macnab 1983, Kitchel and Brown 1987).

Injection of chymopapain into a nerve root must be avoided because chymopapain can induce significant *neural injury* if it comes in direct contact with the nervous tissue (Shealy 1967, Brånemark et al. 1969, Rydevik et al. 1976, Zook and Kobrine 1986). Generally, there is in every case of intradiscal injection of chymopapain a potential risk of exposure of other tissues than the disc to the injected enzyme solution. Epidural leakage from the disc space probably occurs in several cases of intradiscal injection; up to 25 percent has been proposed, based on experience from discography (Wiltse et al. 1975). In cases of epidural leakage, different tissues may be exposed to the enzyme solution: epidural fat, dura, and local nerve endings. Garvin et al. (1965) have shown that chymopapain applied in the epidural space of rabbits and dogs, in doses up to 100 times the therapeutically effective doses, is tolerated without neurologic changes. However, a careful analysis of the tissue reactions following chymopapain application in the epidural space seems to be lacking in the literature.

Intrathecal application of the enzyme may occur if the injection needle has violated the dura. Several animal investigations indicate that intrathecally injected chymopapain, even in small amounts, can induce subarachnoid hemorrhage, paralysis, etc. (Garvin et al. 1965, Shealy 1967, Widdowson 1967, Ford 1969). These observations have led to recommendations on very careful injection techniques in order to avoid dural puncture. Nevertheless, there have been reports on severe neurologic lesions following chymopapain injections. These complications have been, for example, subarachnoid hemorrhage associated with acute paraplegia or a transverse myelitis, the latter occurring 2–3 weeks after the enzyme injection (Eguro 1983, Agre et al. 1984, Weitz 1984, Dyck 1985, Brown 1985). In 80,000 cases of chymopapain injection, there were 46 serious neurologic complications reported, equal to about one in 1,860 injections (Agre 1985). There were, in this series, 15 cases of cerebral hemorrhage, 28 cases of paraplegia, 1 case of quadriplegia and 2 cases of subarachnoid hemorrhage. It was concluded that: "... it appears likely that chymopapain injections at multiple disc levels, the use of general anaesthesia as opposed to local or supplemental local anaesthesia, and performing discography at the time of chymopapain injection all increase the risk of developing a serious neurolo-

gic adverse event. In addition, discography appears to play a negative role in determining the reversibility of these events" (Agre 1985).

The mortality rate associated with chymopapain injection has been reported to be about 0.025 percent (Watts 1977, Agre 1985), which seems to be comparable to the death rate following laminectomy (Spangfort 1972, Watts 1986). Due to the above-mentioned dangers, the use of chymopapain in the United States has been rapidly diminishing.

Clinical results

The results obtained after chymopapain injection vary to a great extent according to different authors, and this matter is obviously also a controversial issue. Before summarizing the available data, we would like to emphasize that it is often difficult to compare the results from various studies because there may have been differences in preinjection evaluation, indications, as well as methods of assessment. In the first clinical series of 75 patients published, 75 percent good results were reported (Smith and Brown 1967). These authors also noted that 39 percent of their patients had severe muscle spasms and a substantial increase of their back pain for a few days. Later, this has also been reported by others (Brown 1983, McCulloch and MacNab 1983). In several clinical studies, conducted over the last few years, a success rate of about 60–80 percent has been reported (Ravichandran and Mulholland 1980, Benoist et al. 1982, Brown 1983, McCulloch and Macnab 1983, Fraser 1984, Javid 1985, Lorenz and McCulloch 1985, MacDiamid 1985, McDermott et al. 1985, DuToit and Usdin 1985, Maciunas and Onofrio 1986).

However, one has to put these above results in relation to important factors, such as the natural history of disc herniation and sciatica (Hakelius 1970, Roslund 1974), as well as the results of other relevant treatment alternatives, such as partial laminectomy with surgical disc removal (Spangfort 1972, Weber 1978). In reviewing the literature, we could not find any study comparing the effects of chymopapain treatment with the natural history of the disease. This issue was discussed in an editorial article in the *Lancet* (1986). A careful analysis of the natural history of disc herniation and sciatica has been performed by Weber (1978, 1983). He performed a prospective, controlled investigation comparing the results of surgical treatment and conservative treatment of disc herniation, with 100 percent follow-up for 10 years. A study comparing the results of chymopapain injection with the known natural history of disc herniation and sciatica is currently being undertaken by Weber. With the study near completion (> 80 cases), there seems to be minimal differences in the results compared with the natural history (Weber 1983, personal communication 1987). The final results of this study should answer some of the controversial questions regarding the efficacy of chymopapain injection. The types of control in other studies have consisted of, for example, the same volume of saline (Javid et al. 1983, Fraser 1984), and these double-blind studies have demonstrated that injection of chymopapain is more effective than saline. However, there are theoretical disadvantages to using intradiscal saline injections as controls, for the saline in itself may negatively influence the disc tissue causing swelling and increased pressure (Editorial 1986).

Clinical studies evaluating chymopapain injection when compared with surgical disc removal have generally indicated that surgery gives better results (Watts et al. 1975, Ejeskär et al. 1983, Crawshaw et al. 1984) or comparable results (Leavitt et al. 1980, Nordby 1985, Weinstein et al. 1986). Microsurgical discectomy has been reported to give better results than chemonucleolysis (Zeiger 1987). In the study by Ejeskär et al. (1983) the prospective randomized trial was abandoned when more than half of the patients who received chymopapain had failed clinically so that they had to undergo surgery. Crawshaw et al. (1984) in a similarly designed study also noted a higher failure rate in chymopapain-treated patients (52 percent) than in surgically treated patients (11 percent). Thus, these and several other studies indicate that, with proper patient selection, one can predict about 80–90 percent good results with surgical disc removal, whereas chymopapain injection may be expected to be successful in only about 50–70 percent. Another important aspect of the treatment is that if there is failure following chymopapain treatment, the result of surgery may be less successful, especially

if the operation is delayed (Crawshaw et al. 1984). We prefer to operate on the noninjected patient with disc herniation and sciatica who does not respond to conservative treatment within 3 months of onset of symptoms. There are numerous reports in the literature that further delay in patients with clear indications gives less good results (Spangfort 1972, Surin 1977, Weber 1978). There is an inherent risk that with a chymopapain injection that fails this time limit can be exceeded, resulting in chronic, irreversible tissue changes in the nerve root and/or induction of central nervous system pain mechanisms. Therefore, the evaluation of the patients who are undergoing chymopapain injection treatment must be performed not too late after the injection. Crawshaw et al. (1984) felt that failure after chymopapain treatment could be predicted within 1 months after the injection.

Proper patient selection is obviously of great importance. With respect to chymopapain treatment, a number of conditions have been listed that would disqualify a patient (McDermott et al. 1985) – for example, previous laminectomy, rapidly progressive neurologic deficit especially with involvement of bladder and bowel dysfunction, spinal tumor, spinal stenosis, spondylolisthesis, multiple level disc herniation, severe allergy, diabetes, and pregnancy. If one can exclude these conditions, one still has to deal with a large number of cases in which a decision must be made if they are suitable for chymopapain injection. Attempts have been made to come to a more precise diagnosis with respect to the possibilities of predicting the result after chymopapain injection. Postacchini et al. (1986) correlated the size of the disc herniation as measured on the CT scan with the results following chymopapain injection and surgery, respectively. They found that the best results with chymopapain treatment were obtained in patients with small herniations, whereas surgery gave the best results in cases with large herniations. Troisier and Cypel (1986) used discography and Edwards et al. (1987) used CT discography in the preinjection evaluation. These authors found that if the contrast dye passed from the center of the disc out into the disc herniation the results of chymopapain injection was much better than if the dye remained in the center of the disc, away from the disc herniation. Thus, discography, possibly combined with CT, might give an indication if a certain patient is likely to have a successful outcome after a chymopapain injection. However, a potential risk with discography is the fact that x-ray contrast media have been shown to potentiate the neurotoxic properties of chymopapain in laboratory animals (Agre 1985). Clinically, it has also been noted that in several of the reported cases of serious neurologic deficits, after chymopapain injections, discography had been performed closely prior to the chymopapain injection (Agre 1985). The role of MRI in this context has not yet been entirely clarified (Gibson et al. 1986).

Costs of chemonucleolysis and surgery

There are several factors influencing the cost of these treatment modalities, for example, the required length of hospitalization and the time before returning to work. Chemonucleolysis has been reported to require shorter hospitalization than surgery for disc excision (Brown 1983, Ramirez and Javid 1985), and it has even been performed on an outpatient basis (McCulloch and Ferguson 1981). Comparisons of the costs for the treatment during hospitalization with surgery have indicated that chemonucleolysis may be less expensive (Ramirez and Javid 1985), or of comparable cost (Watts and Dickhaus 1986). However, if one takes into account the number of patients who do not respond successfully to chemonucleolysis within the first 1 to 2 months, and which thus have to be operated on, the total cost for treating disc herniation with chymopapain injection may in fact be higher than for surgery (Watts and Dickhaus 1986, Norton 1986).

Concluding remarks

Chymopapain injection for the treatment of symptoms from lumbar disc herniation has been used for more than 20 years in hundreds of thousands of patients. Still, there is controversy regarding the efficacy, safety, costs; and thus, the overall role of this treatment modality must be debated. In part, this is due to the fact that the treatment results have been evaluated in only a few properly controlled, prospective studies. Fur-

ther clinical research in this area should focus on the problems related to proper patient selection for various treatment modalities for disc herniation, including possibly other substances that might become available for intradiscal injection therapy in the future. At the present time, surgery with removal of the disc hernia through a small laminotomy incision remains the scientifically proven treatment of choice for the patient with sciatica in whom proper conservative treatment has failed and in whom a disc hernia at the suspected side and level has been demonstrated by water-soluble contrast myelography, CT, or MRI.

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