

# Five-Year Results From Chemonucleolysis With Chymopapain or Collagenase

## A Prospective Randomized Study

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**Study Design.** A 5-year clinical follow-up assessment of a prospective randomized study of chemonucleolysis using chymopapain (4000 IU) or collagenase (400 ABC units) was performed.

**Summary of Background Data.** Intradiscal therapy can be performed for patients with contained discs by chemonucleolysis, percutaneous discectomy, or laser ablation. The oldest intradiscal therapy is chemonucleolysis with chymopapain.

**Objective.** The purpose of this study was to compare prospectively the efficacy of chymopapain and collagenase for intradiscal injection.

**Methods.** In this study, 100 patients with indication for intradiscal therapy were prospectively randomized to treatment with either chymopapain or collagenase. All the injections were performed by the double-needle technique with the patient under general anesthesia. The mean age of the patients was 35.5 years in the chymopapain group and 38 years in the collagenase group. An equal number of injections was performed at L4–L5 and L5–S1.

**Results.** After 5 years, good and excellent results were observed in 72% of the chymopapain group and 52% of the collagenase group when the surgically treated and lost patients were graded as poor. Using a scale of 0 (no pain) to 10 (intractable pain), the pain level dropped from 8.5 to 0.7 in the chymopapain group and from 8.6 to 0.9 in the collagenase group. Microdiscectomy at the injected level was required for 23 patients (14 in the collagenase group and 9 in the chymopapain group).

**Conclusions.** After 5 years, no deterioration had occurred, as compared with the 1-year follow-up assessment. Chymopapain has proved to be safe, with one minor anaphylactic reaction, and effective even over the long term. Collagenase may need further study and cannot be recommended at this time. [Key words: chemonucleolysis, chymopapain, collagenase, disc, intradiscal therapy, lumbar spine, sciatica] **Spine 2001;26:1835–1841**

For enzymatic intradiscal therapy, two enzymes have been described as effective when used *in vivo*: chymopapain, which catalyzes the hydrolytic cleavage of glycosaminoglycans from proteoglycan aggregates in the disc, and collagenase, which splits the Type 2 collagen fibers with relative particularity.

The therapeutic concept of the intradiscal chymopapain injection is the hydrolytic splitting of the noncollagen protein connections of proteoglycans. This mechanism decreases the water-binding capacity of the polysaccharide side chains.<sup>14,29,60,64</sup> The pressure in the disc is lowered, so the disc protrusion decreases, which relieves the tension on the nerve root.<sup>66</sup> The effect of chemonucleolysis can be demonstrated by the aspiration of a milky fluid from the disc immediately after injection.<sup>45</sup> Already 30 minutes after injection, immunoreactive chymopapain can be detected in the plasma, and the half-life is 3 days.<sup>45,47</sup>

Allergic reactions have arisen in 1.5% to 2% of the patients studied.<sup>5,20,75</sup> More serious complications have been lumbar subarachnoid hemorrhage and paraplegia.<sup>2,12</sup> Experimental investigations have shown that peripheral and intrathecal injection result in the clinically described changes.<sup>49,50,55</sup> Because of improved and more controlled injection techniques, these complications have not occurred at all since 1987.<sup>48,71</sup> The potential risk of allergic reactions and other complications has generated a serious interest in enzymes such as collagenase with less allergic potential for intradiscal injections.<sup>37,43</sup>

Purified collagenase was tested in animals and found to have very low allergenicity. The basic enzyme synthesized by *Clostridium histolyticum* consists of varied subenzymes that split the collagen fibers at different locations.<sup>32,74</sup> The purified collagenase is relatively specific for Type 2 collagen, seen mainly in the nucleus pulposus, which consists of 15% to 20% collagen in its dry weight. The annulus has approximately 60% collagen, Types 1 and 2, and the total collagen amount in the dry weight is 50% to 60%.<sup>1,23,25</sup>

After successful animal experiments, collagenase (Nukleolysin) was used in a chemically purified preparation for clinical studies.<sup>7,8,28,67–69</sup> In a double-blind study, 80% of the patients treated with collagenase showed good and excellent results, as compared with 30% in the placebo group.<sup>9</sup> There were no reports about allergic reactions or sensitivity to collagenase, but endplate erosions of the adjacent vertebra, mimicking the picture of discitis, were reported.<sup>10,12,36,39,40</sup> Even 7 to 10 times the therapeutic dose injected into the disc or intravenously in dogs and monkeys caused no toxic effects.<sup>8,69</sup> After intrathecal injections of lower doses in dogs, anterior horn cell degenerations were seen. Hemorrhage and paraplegia occurred only after a high dose of 2000 U.<sup>28,71</sup>

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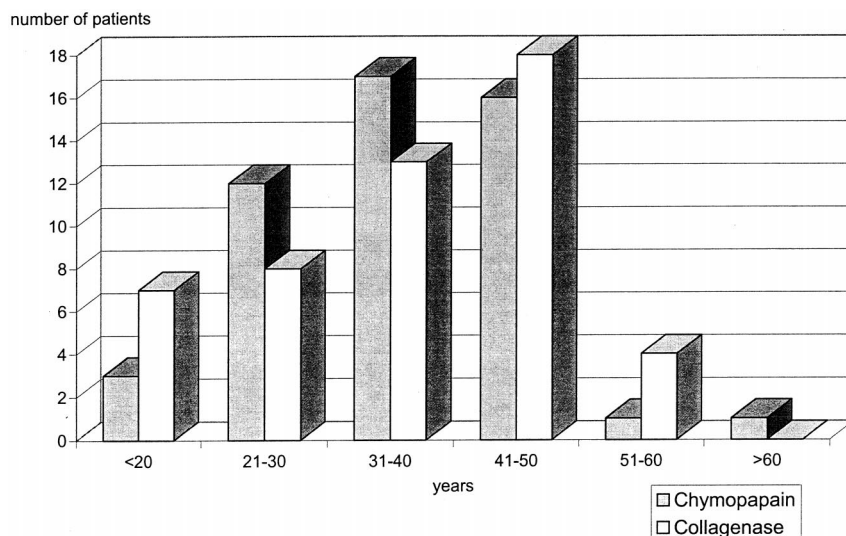


Figure 1. Age distribution of the patients treated with chymopapain or collagenase.

The purpose of this study was to determine the clinical efficacy and relative safety of chymopapain (4000 IU) and collagenase (400 ABC units) as well as the midterm outcome after 5 years. Therefore, 100 patients with sciatica were prospectively distributed randomly to one of two treatment groups.

## Methods

The participants in intradiscal therapy were 100 patients with sciatic back pain who fulfilled the following inclusion criteria:

- sciatic leg pain stronger than back pain
- a 6-week minimum of unsuccessful conservative treatment
- a straight leg raising test positive below 60°
- clear clinical signs for nerve root irritation
- a correlation between the clinically identified segment and magnetic resonance imaging (MRI) or computer tomography (CT) findings
- distinctive functional impairment.

The following were exclusion criteria for intradiscal therapy:

- back pain greater than leg pain
- increasing neurologic deficits
- cauda equina syndrome
- osseous root compression
- extradiscal sequestration on MRI, CT scan, or discography
- pregnancy
- known allergy to the injection substance
- previous surgery at the same segment

If chemonucleolysis was indicated and the patients had none of the exclusion criteria, they were scheduled for intradiscal therapy. The 50 patients were randomized into two equal groups by having them draw cards the day before injection. Before the enzyme injection, the participants received H1 and H2 blockers as well as corticosteroids, consisting of diphenhydramine 25 to 50 mg and cimetidine 400 mg four times before surgery. At 30 minutes before injection, they received an additional dose of cimetidine 200 mg and prednisolone 500 mg intravenously. All the patients in both treatment groups received H1 and H2 blockers and hydrocortisone.

For all the patients, the disc injection was performed under fluoroscopic control from the lateral, extraspinal approach us-

ing the double-needle technique with the patient under general anesthesia.<sup>24,76</sup> After placement of the second, smaller needle securely in the nucleus, a water-soluble dye (Solutrast 250M, BYK Gulden, Konstanz, Germany) was injected and radiographic documentation performed. Patients with free sequestered discs or severe epidural dye flow were excluded from the study. In all the patients, the discography was classified according to the criteria described earlier.<sup>33,34</sup>

The patients were closely supervised for 2 hours immediately after injection, and then for another 24 hours. Allowed to ambulate with a brace the day of injection, they were mobilized immediately in an exercise program. They also received low back school training and therapeutic swimming. A lumbar orthosis was worn 6 to 12 weeks to compensate partially for postinjection segmental instability.

After the injection, the patients were investigated clinically for segmental sensations, reflexes, and motor functions to detect neurologic deficits. After discharge, the patients were seen in regular follow-up visits after 2, 6, and 12 weeks, and then for 1-year, 3-year, and 5-year follow-up assessments. Statistical analysis was performed using the  $\chi^2$  test and the Student's *t* test.

## Results

At the time of injection, the mean age was 35.5 years for the patients in the chymopapain group and 38 years for those in the collagenase group. Those younger than 30 years included 16 patients in the chymopapain group and 14 patients in the collagenase group. Only two patients in the chymopapain group and five in the collagenase group were older than 50 years (Figure 1). The 32 men and 18 women in the chymopapain group nearly equaled the 33 men and 17 women in the collagenase group. The mean duration of symptoms before injection was 26 weeks in the chymopapain group and 22 weeks in the collagenase group.

Injections were performed at L4–L5 (chymopapain 24/collagenase 22 patients) and L5–S1 (chymopapain 24/collagenase 27 patients) in both groups, whereas one patient in each group got both levels injected, and one

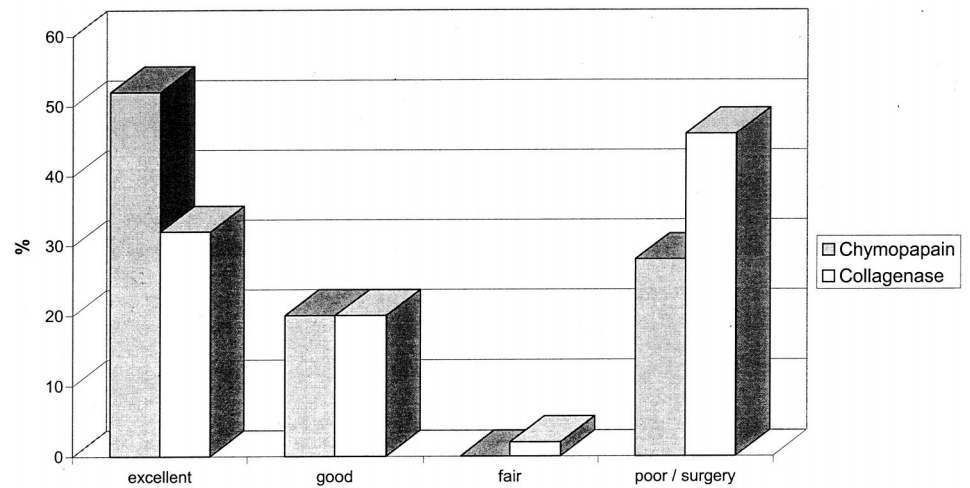


Figure 2. Clinical outcome of the patients 5 years after chymopapain or collagenase injection, including the patients who underwent surgery because of poor results and those lost to follow-up evaluation ( $n = 100$ ).

patient in the chymopapain group was injected at L3–L4. In the chymopapain group, 12% of the patients showed allergic reactions. Of these, 10% were flush phenomena and itching, but one patient had a slight anaphylactic reaction. None of the patients had an early or late disc infection.

Although intradiscal therapy was performed, 18% of the chymopapain group and 28% of the collagenase group underwent microdiscectomy at the injected level. The indication leading to surgery was severe increasing pain for seven patients in the chymopapain group and five patients in the collagenase group, whereas it was an increasing neurologic deficit for two patients in the chymopapain group and nine patients in the collagenase group. A cauda equina syndrome developed in three of the nine patients in the collagenase group. Except for one patient who underwent surgery after 66 weeks, all surgery was performed within the first year: after an average of 14.9 weeks in chymopapain group and after 8.9 weeks in the collagenase group.

The clinical results, according to the modified criteria by McNab,<sup>42</sup> were graded in four categories: excellent, good, fair, and poor. After 5 years, six patients in the chymopapain group and ten in the collagenase group had been lost to follow-up evaluation. They could not be located, even after an intensive search, because of several changes in their location. Of the reexamined patients who had only the enzyme injection, 100% of the chymopapain group and 93% of the collagenase group had good and excellent results. If the unexamined patients and all those who had undergone surgery were rated as poor, these success rates dropped to 72% in the chymopapain group and 52% in the collagenase group who experienced good and excellent results (Figure 2). Patients undergoing microdiscectomy after intradiscal injection showed a success rate with good and excellent results of 75% after chymopapain injection and 83% after collagenase injection. When these patients were in-

cluded with their real outcome, the results improved considerably (Figure 3).

When the patients were asked to grade their pain from 0 (no pain) to 10 (intractable pain), the average leg pain score was 8.5 in the chymopapain group and 8.6 in the collagenase group. These scores dropped to 0.7 and 0.9, respectively, after 5 years, and the back pain score also was reduced significantly.

When the patients were grouped according to their weight using the Broca index, there was no significant difference ( $P < 0.05$ ) between the good and excellent results in the chymopapain group. However, in the collagenase group, 14 patients who were overweight showed significantly fewer excellent results than 14 patients whose weight was normal. When the patients were graded in three categories from little to heavy back aggravation or physical stress during sport activities or work, no significant difference was observed between office workers and hard-working patients in both groups.

When the results were investigated with respect to the discogram classification, two of the three patients with a normal discogram grade underwent later microdiscectomy. Three patients with little epidural leakage after collagenase treatment experienced an excellent result. Four of 10 patients with chymopapain injection and little epidural leakage underwent microdiscectomy, and the other six had good or excellent results. Therefore, a prediction of the outcome from the discogram classification was not possible.

At follow-up assessment, none of the patients showed a significant decrease in lumbar spine range of motion, and none showed lateral bending differences. The average floor–fingertip distance was 9 cm in the chymopapain group and 11 cm in the collagenase group. The straight-leg-raising test yielded positive results for the contralateral side in two patients of the collagenase group and for the affected side in one patient of the chymopapain group and two of the collagenase group. All

these tests were only at 50° positive. No differences between the affected and nonaffected sides were observed for the patella tendon reflex, but three patients in the chymopapain group and one in the collagenase group still showed a decrease in the Achilles tendon reflex.

No difference between the affected and nonaffected side was observed in the active function of the following muscles: quadriceps, extensor hallucis, and triceps. Sensation was still decreased in the affected segments of three patients in the chymopapain group and eight patients in the collagenase group.

Patients in the chymopapain group started work in the same job an average of 8 weeks after injection, whereas patients in the collagenase group returned to work after an average of 11 weeks. Besides those who returned to their previous job at 5 years, a total of six patients in each group had to change to an easier occupation within the company (3 and 4 patients, respectively) or in another company (3 and 2 patients, respectively). There was no correlation between clinical outcome of patients who had to change jobs and hard-working patients who returned to their initial position.

## ■ Discussion

Until 1975, more than 16,000 patients with sciatic disc disease were treated with chymopapain injection. The clinical outcome varied between 70% and 90% good and excellent results.<sup>3,11,20,26,41,42,51-54,57-59,65,72,73,75</sup> A double-blind study initiated by the American Food and Drug Administration (FDA) showed no significant difference between good and excellent results for chymopapain (58%), as compared with placebo (49%). Therefore, the general use of chymopapain was denied by the FDA.<sup>18,56</sup> The study, which had numerous faults and flaws, was followed by two well-designed double-blind studies,<sup>27,35</sup> both of which showed a preferable effect of chymopapain, as compared with placebo.<sup>30,35</sup> In large studies, chymopapain has been proved effective, although serious side effects were observed in a number of patients.

In this study, the average age of the patients in both groups matched that of other studies published in the literature. Also, the predominance of male patients, with a male-to-female ratio of approximately two-to-one, was typical for sciatic leg pain and intradiscal therapy or discectomy.<sup>21,27,35,46</sup> The follow-up assessment at 5 years was 88% in the chymopapain group and 80% in the collagenase group. The average rate of good and excellent results in the chymopapain (72%) and collagenase (52%) groups fell in the range reported from the literature if the results of the patients who underwent microdiscectomy and those lost to follow-up evaluation were rated as poor. In a comparative study, Brown and Tompkins<sup>13</sup> reported a satisfactory outcome after surgery of 95%, 68% after chymopapain injection and 67% after collagenase injection. Only the early chymopapain stud-

ies in the late 1960s showed success rates of 90% or more.<sup>21,57,59,65</sup> Studies that followed in the 1970s and 1980s with a larger number of patients showed success rates of 70% to 87%.<sup>4,46,48,58</sup>

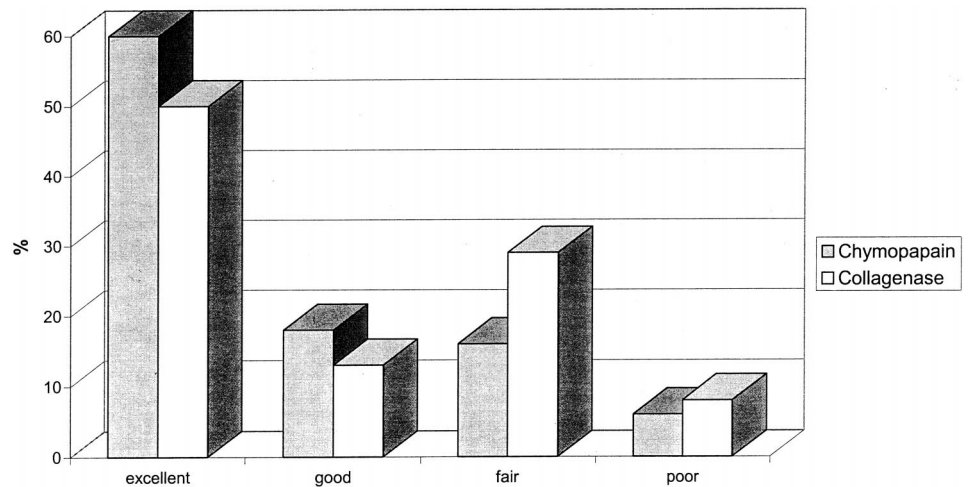
Whereas the 70% to 85% success rate for chymopapain has been established in large numbers of patients, fewer studies are available for collagenase. The clinical experience with collagenase started in the early 1980s, with success rates between 69% and 88%.<sup>9,10,12,17,36,40</sup> Results from a randomized double-blind dose-finding study of 20 *versus* 450 ABC units of collagenase in 85 patients showed a significant pain improvement in 76% of the high-dose group, as compared with 54% of the low-dose group.<sup>62</sup>

These comparisons with other studies are as interesting as the development of the clinical outcome over 5 years for both enzymes. Three months after injection, only an equal distribution among excellent, good, fair, and poor results was observed in both groups. Already after 1 year, 68% of the chymopapain group and 64% of the collagenase group showed good and excellent results. This did not change significantly after 3 years (70% in the chymopapain group and 56% in the collagenase group),<sup>33</sup> nor after 5 years. These results and those of other comparable studies contrast with speculations that the destruction of proteoglycans by chymopapain and Type 2 collagen fibers by collagenase might result in a distinct disc degeneration that would get worse over the years and could result in an unstable painful motion segment.<sup>30</sup>

The somewhat discouraging fact is that nine patients in the collagenase group experienced a neurologic deficit. Five recovered immediately after surgery, but two patients with cauda equina syndrome recovered slowly. The five patients with fast and the two patients with slow neurologic recovery represented 7% of the patients. This was a much higher incidence than the 0.5% and 2% reported in other large studies.<sup>1,5,46</sup> In a well-documented study, the incidence of transient increased neurologic deficit was 14% with chymopapain and 17% with collagenase, which was interpreted to mean that an increased swelling pressure occurred after injection of chymopapain and collagenase causing transient neurologic deficits.<sup>13</sup> However, 230 patients treated additionally in the authors' institution with chymopapain since the current study showed an incidence of neurologic deficits in the range of 2% to 3%, which accords with the other studies published in the literature.<sup>1,5,21,46,75</sup>

When the results of surgery after chemonucleolysis failure were compared with the results from microdiscectomies performed without prior injections, slightly more good and excellent results were observed in the primary surgery patients.<sup>38</sup> Worse results had been found by Crawshaw et al,<sup>19</sup> who experienced only 30% successful disc surgery after chemonucleolysis. Other authors such as McCulloch and McNab<sup>45</sup> stated that open surgery was easier after prior chemonucleolysis, and still other studies reported successful

Figure 3. Clinical outcome of the patients 5 years after chymopapain or collagenase injection, including the patients who underwent surgery with their actual outcome at the 5-year follow-up visit and those lost to follow-up evaluation (n = 100).



result rates of 65% and 75%. These surgical results are comparable with those found in the current study, with good and excellent result rates of 75% for chymopapain and 83% for collagenase.<sup>15,16</sup>

When the results of primary microdiscectomy and intradiscal therapy were compared, the results of microdiscectomy showed a success rate of approximately 80% to 90%, which was higher than that reported for intradiscal therapy. This might be partially attributable to the intradiscal therapies (chemonucleolysis, percutaneous nucleotomy, laser ablation), whose indications exclude free sequestration and target the lesser degrees of disc displacement. The best indication for open surgery, however, is the presence of a free herniated disc fragment. If the best indication is excluded, this explains the inferior clinical outcome. When Spangford<sup>61</sup> analyzed disc pathology with respect to the clinical outcome, he found a significantly reduced success rate in patients who underwent open surgery for disc protrusion. In another publication Mayer and Brock<sup>44</sup> compared the effect of percutaneous endoscopic discectomy and microdiscectomy in 40 patients with contained or small noncontained disc herniations suitable for intradiscal therapy. Sciatica had disappeared in 80% of the patients who underwent percutaneous endoscopic discectomy and in only 65% of those who had open surgery. Furthermore, only 72% of the microdiscectomy group, in contrast to 95% of the percutaneous endoscopic discectomy group, returned to their previous occupation. These results support those from the previous study by Spangford,<sup>61</sup> which show that microdiscectomy probably is not the best treatment method for patients with contained disc herniations.<sup>44</sup>

Another reason for unacceptable results after intradiscal therapy reported in the literature involved osseous nerve root compressions.<sup>22,45,53</sup> These should be diagnosed before the injection by myelography, CT scan, or MRI, but were not seen in the current study.

The safety of the two reported substances was compared. In the chymopapain group, one patient experi-

enced an anaphylactic reaction resulting in slight laryngospasm and hypertension. Five other patients experienced flush phenomena and itching. In the collagenase group, no allergic or anaphylactic reactions occurred. Therefore, the whole allergy rate was 12% for chymopapain, far above what has been published in large multicenter studies (Europe 1.9% and 2%).<sup>5,6</sup> If only the clinically obvious allergic reactions are considered, this rate drops to 2% in the current study. Even in North America, where exposure to papain is higher and an increased allergy rate is therefore expected, this was the maximum that had been reported.<sup>31,46,70,75</sup>

In summary, this prospective randomized study of chymopapain *versus* collagenase has shown that the good and excellent results for both substances are not significantly different. There was no significant decrease in the good and excellent results from the 1-year visit to the 3- and 5-year follow-up visits. The results from chemonucleolysis were still worse than those observed after microdiscectomy. Chymopapain was shown to be relatively safe, whereas collagenase needs further studies and cannot be recommended at this point for general clinical use.<sup>62,63</sup>

#### ■ Key Points

- Chymopapain is more effective than collagenase in the treatment of sciatica.
- Chymopapain showed slight anaphylactic reactions.
- No deterioration of the clinical outcome occurred between the 1- and 5-year follow-up visits.

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## Point of View

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The findings in this prospective randomized study with a clinical follow-up period of 5 years verified the results of a study published by this author and a colleague in 1989.<sup>1</sup> The current study demonstrated new neurologic deficits in 4% of the chymopapain group and 18% of the collagenase group. By comparison, the previous study demonstrated new neurologic deficits in 14% of the chymopapain group and 17% of the collagenase group.

In the current study, 3 of the 50 patients in the collagenase group had a new onset of cauda equina syndrome after the injection. This complication did not occur in the previous study. In that study, a worsening of an existing neurologic deficit was noted in 3% of the chymopapain group, as compared with 8% of the collagenase group and no change in the existing neurologic deficit in 20% of the chymopapain group and 33% of the collagenase

group. The data from the previous study suggested that collagenase produced more postinjection pain, a higher incidence of transiently worsened neurologic deficits, and a higher incidence of no change in existing neurologic deficits as compared with chymopapain. The authors of this previous study also demonstrated an unacceptably high incidence and severity of neurologic deficits in the group treated with collagenase.

The authors of the current study concluded that chymopapain for chemonucleolysis is a safe and effective treatment for lumbar disc herniation, and that collagenase requires further study. These conclusions are similar to those reported for the previous study 1989.

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