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Treatment of the Herniated Nucleus Pulposus Syndrome by Chemonucleolysis with Chymopapain*

Eugene J. Dabezies

1. Introduction

The syndrome of lower back pain associated with sciatic pain has probably plagued man since the upright position was first assumed. The terms lumbago, sciatica, and lumbar fasciitis were used to describe this problem, but in 1937, Barr delineated herniation of the nucleus pulposus as the pathologic entity. As a result of that report, the standard surgical treatment became laminectomy with disk excision, or laminectomy and disk excision combined with fusion. Primarily the surgery was done for the disks between L4-5 and L5-S1.

Lindblom studied the interior architecture of disks by means of diskography, and Hirsch in 1959 proposed injecting the symptomatic intervertebral disk with a sclerosing agent.

The world of low-back surgery was jolted when Lyman Smith introduced intradiskal injection of chymopapain for the treatment of this herniated lumber disk syndrome. Considerable controversy in the U.S.A. raged about this modality and when the Food and Drug Administration (FDA) approval was not forthcoming in 1975, Baxter-Travenol withdrew its New Drug Application (NDA). The drug could then be used only under strict investigational protocol; however, surgeons continued to pressure for approval and on November 10, 1982, the FDA approved chymopapain for use as intradiskal therapy for the herniated lumbar disk syndrome. Dr. Smith's leadership in this achievement is acknowledged.

Now that the drug is an accepted modality of treatment in the U.S.A., a review of our experience is appropriate to provide insight into the drug complexities, proper usage, and expectations.

2. Biochemistry

Chymopapain is a proteolytic enzyme extracted from the juice of the carica papaya plant. It has a selective action on the chondromucoprotein of the intervertebral disk. Water-insoluble components of the nucleus pulposus are rapidly dissolved in vitro. Chymopapain is immediately tissue-bound and free enzyme has never been detectable in tissue extracts of the nucleus pulposus after injection. Recent work by Bradford et al. has shown that the effect is primarily on proteoglycans, and in animals the drug action is reversible.

Urinary excretion of acid mucopolysaccha-

* Department of Orthopedic Surgery, Louisiana State University, School of Medicine, 1542 Tulane Avenue New Orleans, Louisiana, U.S.A. 70112

* 대한의용생체공학회 주최 Pacific Area Conference on Orthopaedics and Biomechanics에서 강연한 내용을 발췌한 것임.

ride temporarily increases after intradiskal injection in man, probably as a result of the chemical reaction within the disk. The urinary mucopolysaccharide level returns to normal within a few days.

The enzyme is significantly toxic when injected intrathecally because it produces a breakdown in the capillary microcirculation. Rydevik et al. demonstrated changes in the tibial nerve as evidenced by demyelination and electrical conduction changes, and attributes these alterations to a breakdown in the microcirculation. Other body tissues tolerate the drug well at the clinical dosage level.

3. Anaphylactic Reactions

The incidence of anaphylactic reaction has ranged from 0.82 percent (Travenol) to 0.35 percent. This phenomenon is manifested by sudden vascular collapse. There may be a prodrome of conjunctival injection, skin flushing, piloerection, or bronchial spasm; however, the usual episode is reported to be an unexplained rise in heart rate followed by a dramatic fall in blood pressure. This problem can be extremely difficult to manage and, indeed, under general anesthesia, deaths have occurred. McCulloch and McNab reported fifteen (0.35%) episodes of anaphylaxis in patients in whom the procedure was done under sedation. All were successfully resuscitated, perhaps because the early warning signs of tachycardia, shortness of breath, malaise, and a faillng blood pressure were not obscured by general anesthesia.

Allergy and anesthesia are special concerns, Recent data indicate that the H_1 and H_2 receptors should be blocked, using diphenhydramine hydrochloride (Benadryl) and cimetadine (Tagamet). Theoretically the mast cell membrane can be stabilized by use of steroids. Our present premedication regimen consists of dexamethsaone (Decadron), 4mg; diphenhydramine hydrochloride (Benadryl), 50 mg; and cimetadine (Tagamet), 300 mg, given orally at 6 : 00 p.m. and at midnight. Four milligrams of dexamethasone is administered intramuscularly on call. Fifty milligrams of diphenhydramine is given intravenously when the I.V. is started at surgery. Using this regimen, we have had no anaphylacatic reactions in 500cases.

4. Technique

The procedure has been done in the operating suite or in the x-ray special procedures room. The capability for biplane fluoroscopy can be achieved with a portable Carm image intensifier.

The patient, premedicated with the above drugs, is positioned in the left lateral decubitus(Fig. 1). (This position is more suited for the architectural style of the rooms in our hospital). The operation is done under sedation that is aimed at keeping the patient drowsy but responsive to voice inquiry. The amount of intravenous drug is individually titrated. One-half to 1 cc of combined droperidol and fentanyl (Innovar) is given at the onset. Five to 15 mg of diazepam (Valium) is given intravenously to supplement the sedation. One to 4cc of fentanyl (Sublimaze) is usually required to relieve discomfort during the procedure.

Next, by the lateral approach, a diskogram is accomplished to study the pattern and pressure integrity of the disk, as discussed in more detail below. After the offending level is identified, chymopapain is injected. The usual dosage is 8mg (2 cc) per disk with a

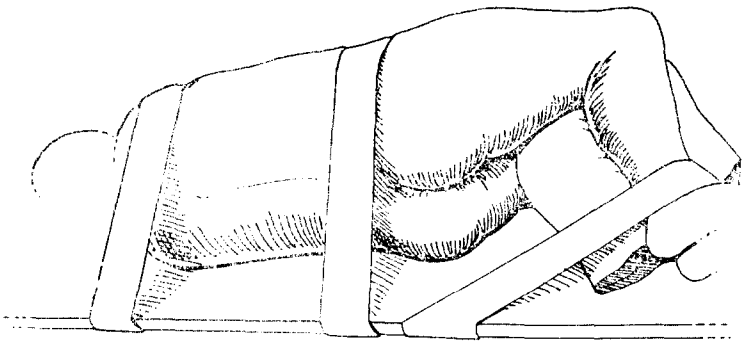

Fig. 1. The patient is in the left lateral decubitus position with the hips and knees flexed 30 degrees. The body is stabilized with tape

maximum of 10 mg (5 cc) per patient.

After the injection, the patient stays in the recovery room for about one hour, before being returned to his room.

On the day after surgery, each patient is allowed to become ambulatory to tolerance, to take hot showers, and to increase activities progressively. We have found that a ten-day course of nonsteroidal anti-inflammatory medication (naproxen[Naprosyn], 375 mg, twice daily) and a muscle relaxant (meprobamate and ethoheptazine citrate with aspirin[Equagesic], 1 three times daily) eases the early convalescence.

5. Diskography

An abnormal diskogram by itself should not be considered an indication for surgery. Holt believed that diskography was valueless because the cervical diskogram pattern was abnormal in 93 percent of 143 disks in fifty nonsymptomatic normal volunteers. He also reported that 34 percent of 72 lumbar diskograms in 30 nonsymptomatic volunteers were abnormal. He concluded that pain was produced by intrusion of the contrast fluid into the annulus or extradiskal tissues.

Simmons and Seigal reassessed the value of diskography and concluded that for cer-

Table 1. Comparative data on leakage patterns of normal disks from cadavers and disks from symptomatic patients

Age (years)	Clinical (suspected disk pathology) Degenerated(%)	Postmortem ("normal disks")	
		Normal(%)	Degenerated(%)
14~34	55 (Majority L4 and L5); ruptured L5 to L4 ratio 2 : 1)	90	10 (None at L3; one rupture at L5)
35~45	75 (Majority at L4 and L5)	25	75 (Incidence of dye extravasation 50% less than in clinical series)
46~59	85	25	74

* From Gresham JL, Miller R: Evaluation of the lumbar spine by diskography and its use in selection of proper treatment of the herniated disk syndrome. Clin Orthop Rel Res 67 : 29~41, 1969.

vical disk problems, the accuracy of myelography wsa 46 percent and diskography was 91 percent in localizing the symptomatic level. In the lumbar area, the assessment of accuracy showed that myelography was 46.5 percent, and diskography was 82.5 percent. The criteria for accuracy was the outcome of surgery determined by relief of pain. This study reported satisfactory results in 78.7 percent of cervical spine surgeries, and 94.4 percent of lumbar spine surgeries.

Gresham and Miller studied normal spines (cadaver) and those of symptomatic patients and found an increasing incidence in leakage patterns with age (Table 1). They noted that in patients on whom operations were done, the preoperative meylogram findings were confirmed in 42 percent, and there was a 91 percent confirmation if the patient also had a diskogram. The incidence of abnormal patterns was 75 percent in the normal and abnormal disks for persons in the 35-to 45-year age range. The incidence of abnormal diskograms was 85 percent in the symptomatic group aged 46 to 59 years.

For chemonucleolysis, the lateral approach (Fig. 2) should be used to avoid dural penetration. If the angle of approach using this technique is too anterior, the needle will

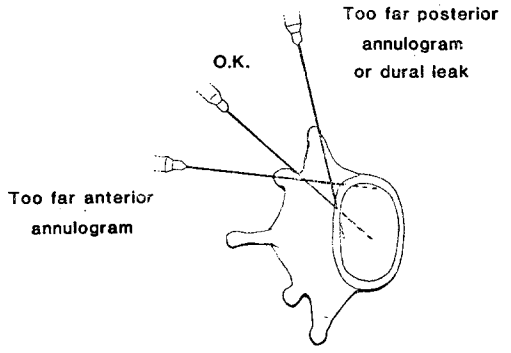

Fig. 2. Proper placement of needle for lateral diskogram

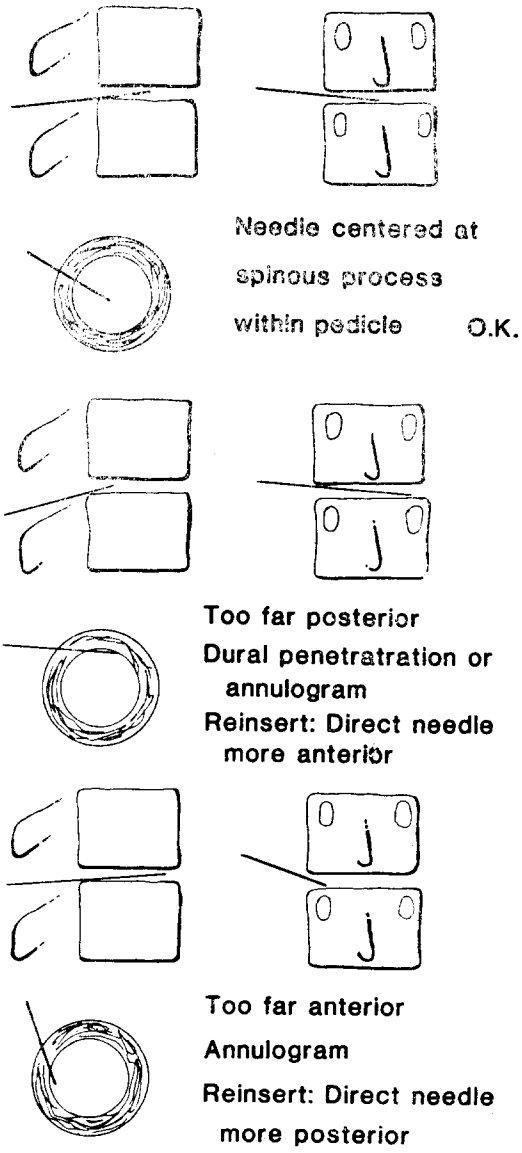

Fig. 3. Evaluation of needle placement as viewed by fluoroscopy

stay within the anulus and not enter the nucleus pulposus. If the angle of approach is too posterior, then the needle may penetrate the dura or may again stay within the anulus (Fig. 2).

We recommend that when the needles are placed under fluorscopic control, the needle be docked at the posterior margin of the disk

space. The fluoroscopic evaluation of placement of needles is diagrammed in Fig. 3. The stylette from this six-inch, 18-gauge spinal needle should be removed, and if there is a flow of spinal fluid, then the procedure should be terminated. It may be assuming an unnecessary risk to proceed with chymopapain injection fluid because of the possibility of intrathecal contamination with enzyme. The spinal fluid is under positive pressure, as we all know from experience with dural tears; however, in the lateral position, with inspiration, the possibility of negative pressure exists, and the enzyme has the potential of being sucked into the dura.

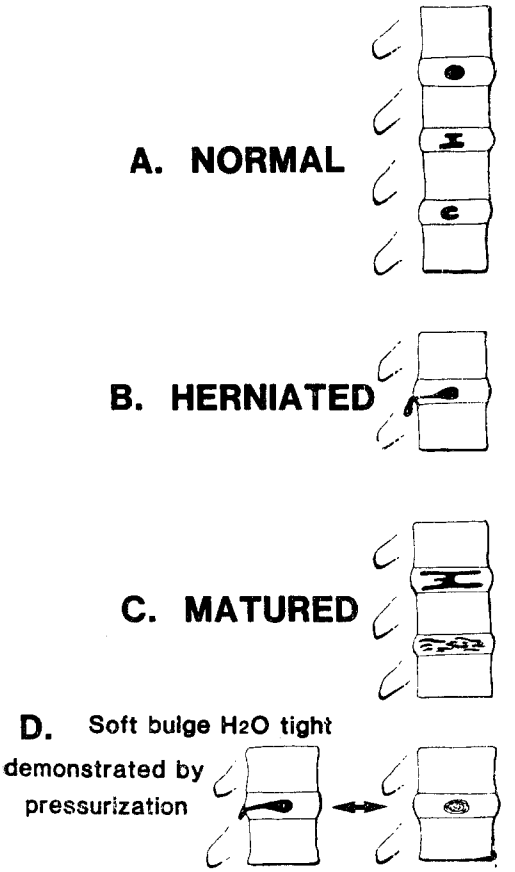

Fig. 4. Diskography patterns

The watertight, normal patterns of a diskogram may be either globular, lobular, or crescentic (Fig. 4). The herniated pattern will show a definite bulge posteriorly (Fig. 4-B). Occasionally, a watertight disk will bulge with pressurization, and then, with release of the pressure, the contrast fluid will flow back into the syringe, leaving a matured pattern within the disk space (Fig. 4-C).

When doing a diskography, one should be aware that it takes about 100 psi to pressurize a normal disk; matured and pathologic disks have no back pressure. Epidural extravasation of contrast fluid not only indicates an incompetent disk, but if excess amount of the fluid is injected, affects interpretation of other-level diskograms. Observe while injecting so that a minimal amount of contrast fluid is used.

6. Clinical Experience

(1) Materials and Methods

Three hundred and nine patients with the diagnosis of herniated nucleus pulposus syndrome were treated with chemonucleolysis with chymopapain from 1971 until 1975. We were able to retrieve and review 232 charts.

We also examined and analyzed in 1978 a group of 100 patients taken from the original patient population of 309 patients, who had been followed up for two years after chemonucleolysis.

To confirm the effectiveness of this treatment, we reviewed data on the first 50 patients who had received injections since the release of chymopapain by the United States Food and Drug Administration in 1982 (Group Ⅲ) with a minimum follow up of six months.

The diagnosis was established based on

history, physical examination, and myelography or CT scan. Diskography was done in all cases to isolate the level of herniation.

A result was classified "excellent" when the patient had no pain or restriction of activities and normal findings on physical examination. A result was classified "good" when the patient experienced occasional back and/or leg pain, insufficient to interfere with his lifestyle, and findings on physical examination were normal. The condition was considered "unimproved" if the symptoms were unchanged or if surgery was later required.

(2) Results

Group Ⅰ: Original Patients Before 1975

Two-hundred thirty-two charts were reviewed with a follow-up period of six months to two years. A good-to-excellent (G-E) result was achieved in 164 patients (70.4%); 69 patients (29.6%) were classified as unimproved. One hundred patients were interviewed by telephone; 72 were classified, G-E, and 28 were unimproved. This chart review and telephone interview produced equivalent patient populations and results.

Long-lasting results were achieved in 86.6 percent of patients originally classified G-E, with a gradual deterioration to point of failure occurring in 13.4 percent of patients.

Levels of Injection: Chymopapain was injected at one level in 26.6 percent of patients, with G-E results in 64 percent. Sixty-three percent of patients received injections at *two levels*, and 70 percent had G-E results. Ten percent were given injections at *three levels*, with G-E results in all.

Eighty-seven percent of patients who originally achieved G-E results with one-to two-level injections had long-term G-E results, whereas 67 percent of those receiving three-level injections had enduring results. The numbers are too small for statistical validity; however, these findings suggest multiple-level disk disease may ultimately prove disabling (Table 2).

Group Ⅱ: Two-Year Follow-Up Group

In 1978, data from 100 patients followed up for two years after chemonucleolysis were analyzed. G-E results were achieved in 71 percent, which was a higher percentage than what had been achieved within a comparable group having traditional lower-back surgery (Table 3). An analysis of this group indicated that significantly better results were achieved in private patients than in patients

Table 2. Levels of injection and results of chemonucleolysis

Group and Results	Number of Patients (%) Per Level		
	1 Level	2 Levels	3 Levels
Group Ⅰ (N=94*)	25(26.6%)	60(63.8%)	9(9.6%)
Initial G-E results	16(64%)	42(70%)	9(100%)
Long-term G-E results	13(54%)⁺	33(59%)⁼	6(67%)
Durability	13/15⁺(86.6%)	33/38⁼(86.8%)	6/9(67%)
Group Ⅱ (N=100)	29(29%)	64(64%)	7(7%)
Group Ⅲ (N=50)	37(74%)	11(22%)	2(4%)
Good-to-excellent results	29(78.4%)	7(63.3%)	1(50%)

* Levels known in 94 of the 100 patients contacted
⁺ Excluding 1 reinjury
⁼ Excluding 4 reinjuries

Table 3. Results from treatment after two-year follow-up

Rating	Chemonucleolysis (100 Patients)		Laminectomy With or Without Fusion (100 Patients)	
Excellent	42	71	11	63
Good	29		52	
Unimproved	29		37	

who had a compensation or litigation facet in the case. This finding emphasizes the need for careful selection because G-E results were achieved in 86 percent of private patients and 50 percent of compensation patients (Table 4).

Of the 29 unimproved patients, six had no further treatment, 21 underwent subsequent surgery, and two were lost to follow up. Seven obtained relief from the surgery that followed unsuccessful chemonucleolysis.

G-E results.

We conclude that with careful analysis of the pre-injection data (history, physical examination, x-rays, lumbar myelogram or CT scan and diskography), the primary offending level can be detected for chymopapain injection. One should not, however, hesitate to inject into more than one level if there is uncertainty about the primary offending level.

(3) Disk Space Narrowing

In the Group Ⅱ patients who were followed up for two years, disk-space narrowing averaged 1.7 mm. Four patients had extreme narrowing (more than 5 mm); of these four patients, results were good in two and poor in two.

In the current study group of 50 patients, the disk-space narrowing averaged 2 mm. We

Table 4. Results of treatment of private and compensation patients

Rating	Chemonucleolysis				Laminectomy With or Without Fusion			
	Private Patients(%)		Compensation Patients(%)		Private Patients(%)		Compensation Patients(%)	
Excellent	33(56)	50(86)	10(24)	21(50)	9(16)	42(77)	2 (4)	21(45)
Good	17(30)		11(26)		33(61)		19(41)	
Unimproved	8(14)		21(50)		12(23)		25(55)	
Total	58		42		54		46	

Group Ⅲ: Current Patients

Data on the first 50 patients injected after the release of chymopapain were reviewed. Thirty-seven patients (74%) were classified as having G-E results; 13 (26%) were unimproved.

Seventy-four percent received injection at one level, with G-E results in 78.4 percent of these patients. Twenty-two percent received injections at two levels, with 63 percent having G-E results. Four percent were injected at three levels, with 50 percent achieving

conclude that disk-space narrowing after chymopapain injection could not be used as a prognostic indicator. About 2 mm of narrowing usually occurs after chemonucleolysis, and does not adversely affect the end result.

(4) Causes of Failure of Chymopapain Injection

For the reason for failure to be understood, the findings of surgical pathology at laminectomy were reviewed. We were able to obtain an adequate description of surgical pathology in 14 cases from the original group of patients

Table 5. Findings of surgical pathology of laminectomy

	Levels explored	Free disk fragment	Bulging herniation	Flat disk
Original group (n=14)	23	2	5	16
Current group (n=5)	8	2	4	2*
Late failures (n=4)	7	1	5	1

* An inflamed nerve root was noted at surgery in one case.

treated before 1875; in five cases from the current study group of 50 cases (Group Ⅲ), which had 13 failures; and in four cases that were considered late failures. Table 5 shows the number of free disk fragments, bulging disks, and flat disks found in our analysis of those data.

The concept that the procedure will fail if chymopapain does not get to the offending disk material is appealing and we can account for failure in a situation in which a free fragment of disk material is encountered. It is harder to understand why failure has occurred when the disk space is flat. The finding of a persisting bulging disk is even more puzzling, but this circumstance undeniably accounts for failure.

7. Discussion

We reviewed all of cases of herniated lumbar disk syndrome that were treated with chemonucleolysis utilizing chymopapain. Good-to-excellent results were achieved in 70.4 percent of 232 patients (Group Ⅰ, before 1975) whose charts were available for review.

Seventy-one percent of 100 patients who were followed up for two years achieved G-E results. Seventy-four percent of the first 50 patients who were injected since release of the drug in 1982 achieved G-E results. Thus, analysis of all three groups indicates that G-E results can be anticipated in at least 70 percent of patients, a finding that correlates with reported results.

Eighty-six percent of Group Ⅰ patients (before 1975) had enduring G-E results. Fifty-eight percent of all patients injected had G-E long-term results. From the telephone interview, we found that 13.4 percent of cases failed late, but surgery was necessary in only 7.5 percent of these patients. The results achieved with chemonucleolysis at ten years are equivalent to results achieved by DiPalma and Rothman in their long-term follow-up of patients treated with laminectomy and fusion.

Disk-space narrowing at the injected levels averaged 2 mm. The degree of narrowing was found to be unrelated to the result.

We could draw no firm conclusions for the reason for failure of this treatment. That failure can be caused by free fragment that chymopapain has not reached or by a bulging disk that has not been solubilized by the chymopapain injection is understandable. Why symptoms persist, however, when a flat disk is encountered and surgical entry into the disk routinely reveals no disk material is difficult to explain.

If the offending level cannot definitely be established or when we are uncertain whether the syndrome is caused by one-level disease, we recommend injecting two levels.

Concerns about allergy and anesthesia must be addressed, although we have had no anaphylactic reactions in any of our cases. From the beginning we have premedicated the patients with steroids. That the H_1 and H_2

receptors should also be blocked is also presently recommended. We do the surgery with the patient under sedation and follow the premedication and operative protocol as outlined above. With this regimen we have had no problems in doing the procedure, and, more important, have had no anaphylactic reaction in what is now more than 500 cases. McCulloch and McNab reported 15 (0.35%) episodes of anaphylaxis in patients in whom the procedure was done under sedation All were successfully resuscitated, perhaps because the early warning signs could be recognized.