Double-blind evaluation of intradiscal chymopapain for herniated lumbar discs

Early results


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The authors report 66 patients with signs, symptoms, and a myelographic abnormality of herniated lumbar disc, who were not responsive to conservative treatment. The discs were injected at random with either chymopapain or a placebo. Neither patient nor surgeon knew which agent was used until after the results had been tabulated. Unless early laminectomy was necessary for intractable pain, all patients were followed for 2 months or more. There was no statistically significant difference in incidence or quality of improvement between the two groups: chymopapain was successful in 58% while placebo was successful in 49% (p = 0.15). Early results from this study indicate that most, if not all, of the putative effectiveness of chemonucleolysis probably derives from a placebo effect.

Key Words: chemonucleolysis, herniated nucleus pulposus, chymopapain

In 1963, Smith injected the enzyme chymopapain intradiscally into patients with symptomatic lumbar disc disease and termed his new treatment chemonucleolysis. Many investigators have subsequently studied the physical properties, chemistry, pharmacology, and toxicology of chymopapain, and their results have been reviewed thoroughly in recent articles. Since Smith's early reports, more than 10,000 patients have undergone chemonucleolysis by neurosurgeons as well as orthopedists. Successful results reported in 50% to 80% of those so treated have led to demands by both the general medical community and the public for increased use of chemonucleolysis. Some have opposed this demand on grounds that chemonucleolysis has not been evaluated by carefully controlled clinical therapeutic trials and therefore has yet to be proven effective. This study arose out of our desire to assess objectively the efficacy of chemonucleolysis in treating herniated lumbar discs.
Clinical Material and Methods

Selection of Patients

Between December 20, 1974, and October 1, 1975, 130 patients were admitted to the Walter Reed Army Medical Center with the diagnosis of herniated lumbar disc. Herniated lumbar disc as used in this paper is a clinical diagnosis applied to patients with pain in the low back that radiates into the lower extremity in a sciatic distribution; the condition is assumed to be caused by a bulging or protruding disc, or by a portion of the disc that has completely extruded from the disc space and comes to rest in the spinal canal. None of the 130 patients had had previous surgery or chemonucleolysis. Each patient met all the following criteria for inclusion into the study:

1. Patients were between 18 and 65 years of age
2. Symptoms had been treated conservatively (bedrest plus other symptomatic measures) for at least 3 weeks without significant improvement
3. Acute paralysis or loss of sphincter control was not a part of the clinical picture
4. A Pantopaque lumbar myelogram demonstrated an abnormality that correlated with the clinical picture
5. One or more of the signs of herniated lumbar disc were present such as abnormal deep tendon reflexes, radicular sensory deficits, positive straight-leg raising, positive cross-straight-leg raising or nonprogressive lower extremity weakness.

Patients with compensation claims pending, profound or progressive weakness, or sphincter dysfunction were excluded from the study, as were those thought to have degenerative disc disease or those who were pregnant.

After a complete evaluation to rule out other disease, each of the 130 patients was offered the opportunity to participate in the study or to undergo standard laminectomy. After being counselled thoroughly in accordance with the guidelines set down for this study by the Walter Reed Army Medical Center Human Use Committee, 68 patients chose to participate. Those who refused to participate in the study did so because of the 50% chance of not receiving the active agent, the presumed greater probability of success with laminectomy, the uncertainty of not knowing what is really wrong with the disc without surgical exploration, an aversion to being an experimental subject, or because of adverse publicity regarding chymopapain.

Chemonucleolysis Procedure

The procedure was carried out under local anesthesia in the X-ray Department using biplane image intensification fluoroscopy. We used the technique of disc injection described by Wiltse, et al. Before disc injection, the patient received intramuscularly 100 mg of hydrocortisone, 50 mg of Benadryl (diphenhydramine hydrochloride), 0.4 mg of atropine sulfate, and meperidine hydrochloride as necessary. An intravenous line was established and kept open with lactated Ringer's solution. An anesthetist monitored continuously the patient's vital signs and electrocardiogram. The patient was placed in the left lateral decubitus position and the lumbar area was prepared and draped to render the field sterile. Lidocaine hydrochloride was used for local infiltration anesthesia. A No. 18 spinal needle 5 in. long was used to penetrate the skin at the level of the abnormal disc about 8 cm lateral to the midline. Using biplane fluoroscopy, we angled the needle 45° toward the midline and passed it to within 1 cm of the disc. The stylette was removed and a No. 22 needle 6 in. long was inserted through the large needle and allowed to penetrate the annulus so that the needle point penetrated the depths of the disc as indicated by fluoroscopy. The position of the needle point was checked by injecting 1 cc of meglumine iothalamate (60% Conray) into the disc after which radiographs in frontal and lateral projection were made. The levels to be injected were determined in the same manner commonly used to determine the level of laminectomy, that is, by clinical findings and myelogram. Discography was not used to determine whether a particular disc was to be injected but only to verify the position of the needle within the disc. In all cases the level indicated as abnormal by myelogram was injected. In some instances an additional level was injected because of the clinical findings. Fifteen minutes after the Conray was injected, the agent, identified only by code number, was injected and allowed to remain for 5 minutes. Any material that refluxed was reinjected and the
nerves removed. The patient was observed in the recovery room for 1 hour and then returned to the ward. The patients were allowed to walk, if they desired, the evening of the injection.

**Preparation of Agents**

The material to be injected was specially prepared for this study by Travenol Laboratories and supplied in vials identified only by a randomly assigned number in consecutive sequence. All vials contained a 3.5 mg of cysteine HCl monohydrate and 0.37 mg of disodium edetate USP. In addition, vials with placebo contained 20 mg of sodium iothalamate; vials with chymopapain contained 20 mg of the enzyme. Immediately before injection, 5 ml of water for injection was added to the vial and 1 ml of the resulting solution was injected into each symptomatic disc.

**Follow-up Studies**

Patients were scheduled to be seen in follow-up examinations at roughly 6 weeks, 3 months, 6 months, and 1 year after injection; at each time the history was taken and physical examination was performed. Three patients, who were unable to return for evaluation, were examined by the referring orthopedist and the results mailed to us. These patients were also interviewed by one of us by telephone. Follow-up studies thus far have been accomplished as scheduled for all patients.

**Data Analysis**

The response to the intradiscal injection was categorized as a failure if preinjection symptoms changed little or became worse. A successful response was divided into three categories as follows:

- **Excellent** = Completely asymptomatic with no limitation of activity
- **Good** = Greatly improved. Residual symptoms are mild and do not interfere with normal activities; no analgesics and working full time
- **Fair** = Moderately improved. Residual symptoms partially limit activities. Works full time at light duty. Requires periodic analgesics. Degree of improvement although modest eliminates the need for surgery.

The result each patient achieved was determined and recorded before the code was broken, and characterization of the results achieved by each patient was not changed. Once a patient was identified as a failure, he remained a failure. Except for those individuals who required early laminectomy for severe and unremitting pain, no patient was identified as a failure unless at least 8 weeks had elapsed since injection.

**Summary of Patients**

Of the 68 patients admitted to the study, 66 remained for analysis. One patient was eliminated because he had been improving rapidly during the week preceding the injection, and the other because the anatomy of his spine prevented the needle from penetrating the disc. Of the remaining 66, 35 patients received placebo and 31 chymopapain. Randomization yielded two groups that were
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comparable as regards age, sex, distribution of active duty personnel and civilians, duration of chief complaint, and treatment before injection (Table 1), as well as levels injected (Table 2).

When this analysis was performed, the shortest follow-up period from time of injection was 2 months and the longest 11 months. Average follow-up intervals for successfully treated patients are recorded in Table 1. There was no statistically significant difference in the success rate between the two groups (Table 3). The overall success rate irrespective of the agent used was 49% for active duty personnel, which did not differ significantly from 57% achieved by civilians (p = 0.14; Fisher exact probability test). There were no complications or adverse reactions in either group.

Discussion

Chymopapain was no better than the placebo in relieving symptoms of herniated lumbar discs. It follows that most, if not all, of the apparent effectiveness of chemonucleolysis may be due to a placebo effect. For the present we are reluctant to consider chemonucleolysis as worthless since our results contradict a large experience collected over 12 years by many different and respected investigators.4,6,8,12,14 Our data reflect early results only, and it is possible that a significant difference favoring chymopapain may yet emerge with a longer follow-up period.

This study may be criticized on a number of points. First, the follow-up period is short. Continuing analysis of the results will overcome this objection. It can be argued, however, that 8 weeks is sufficient time to wait for symptoms to improve after chemonucleolysis. Onofrio6 holds this view and we tend to agree. After chemonucleolysis, one encounters patients who remain with disabling symptoms for many months before they ultimately make a good recovery. The question can reasonably be asked: Is the recovery due to chemonucleolysis or to the natural course of the disease as influenced by prolonged limitation of activity?

The second criticism might be that our patients may not be representative of the general population. Disc disease among government employees is felt by many to be difficult to treat successfully by any method, and yet 44% of our patients were civilians not employed by the government, and the overall success rate among this group was not significantly different from the group on active duty.

The third reservation might be that the length of time we treated our patients conservatively before offering them disc injection or laminectomy was too brief. The average length of treatment was about 5 weeks for the placebo group and 7 weeks for the chymopapain group. In view of our criteria for admission to the study, we believe that the length of time these patients were treated conservatively was reasonable and probably longer than the average neurosurgeon would as a rule conservatively treat a similar population. No doubt some experienced surgeons would have treated some of these patients conservatively for a longer period of time. Yet all of our patients were treated conservatively much longer than the 1 week of bedrest proposed as a minimum in a standard neurosurgical text.9

Finally, our ability to perform chemonucleolysis may be questioned. Compared to others, our experience with chemonucleolysis is small. Before embarking on this study, two of us (PRS and AR) spent time with Dr. Wiltse, observing firsthand his technique of chemonucleolysis.14 In addition, before beginning this double-blind study, we performed routine chymopapain chemonucleolysis on 12 patients. Biplane fluoroscopy and discographic documentation ensured proper needle placement in each case. With these aids chemonucleolysis is not a particularly exacting procedure. In any event, whatever the

### Table 3

<table>
<thead>
<tr>
<th>Result</th>
<th>Placebo (%)</th>
<th>Chymopapain (%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>success rate</td>
<td>49</td>
<td>58</td>
<td>.15</td>
</tr>
<tr>
<td>good or excellent</td>
<td>31</td>
<td>29</td>
<td>.21</td>
</tr>
<tr>
<td>good or excellent after 72 hrs</td>
<td>37</td>
<td>26</td>
<td>.13</td>
</tr>
<tr>
<td>no improvement after 72 hrs</td>
<td>14</td>
<td>29</td>
<td>.08</td>
</tr>
<tr>
<td>returned to full activity within 3 mos</td>
<td>26</td>
<td>29</td>
<td>.21</td>
</tr>
<tr>
<td>laminectomy rate among failures</td>
<td>83</td>
<td>69</td>
<td>.22</td>
</tr>
</tbody>
</table>

*p = probability that difference occurred by chance; Fisher exact probability test.
shortcomings of this study were, as variables they were applied equally to both groups through randomization, while the double-blind design controlled observer bias.

Why was the placebo apparently so effective? Two explanations come to mind. Its efficacy was due either to an unanticipated pharmacological action, or to a true placebo effect. A priori, the agents comprising our placebo are not likely to be therapeutically active when injected intradiscally into herniated lumbar discs. We favor the view that placebo was successful in half of the patients because of a true placebo effect. This study was performed at a time when chemonucleolysis was widely publicized as a safe and effective treatment for some patients with herniated lumbar discs.\(^{5,18,14}\) It was readily accepted and preferred to surgery by most patients. As therapists we assumed that chemonucleolysis was effective, at least for some patients. Since all concerned possessed a positive attitude toward chemonucleolysis, and since herniated lumbar disc symptoms frequently improve without surgery if given sufficient time, we should not be surprised to observe a substantial placebo effect in this setting.

The success rate in the group given chymopapain is lower than most reported series.\(^{12}\) We attribute this disparity to differences in criteria for patient selection, to differences in observer bias, and to differences in the interpretation of patients' symptoms after injection. Moreover, since our patients did not know whether they had received an active or inactive agent, they may have been more forthright in reporting their symptoms and less inclined to minimize their complaints.

Before disc injection, patients in the chymopapain group received an average of 7 weeks of conservative treatment while those in the placebo group received 5 weeks of conservative treatment. It is difficult to assess what bias if any the 2-week difference introduces into the results. It can be argued on the one hand that because we tended to treat the placebo group for a shorter period of time, by chance that group included a greater proportion of patients more likely to improve spontaneously as time passed. On the other hand, the figures may indicate that the placebo group had by chance a greater proportion of patients who required earlier active intervention because they had more pain. In either case, the 2-week difference is not likely to impair the validity of this study since all patients in both groups received more than 3 weeks of conservative treatment before being injected.

The results of this study have implications beyond those that failed to demonstrate therapeutic superiority of chymopapain over placebo. First, one third of the patients identified by our criteria as requiring surgery for relief of their pain improved significantly within 3 months of being treated with placebo. If, as we assume, the placebo was in fact inactive, then our criteria for laminectomy are probably too liberal. Second, because of this substantial placebo effect, one must use proper controls to assess accurately the efficacy of any treatment for symptomatic disc disease. Long-held assumptions about the value of many forms of treatment for disc disease that are based upon uncontrolled studies must be reexamined in this light. Finally, we should avoid repetition of the chymopapain chemonucleolysis experience by insisting that any new enzyme advocated for disc dissolution begin its clinical evaluation as part of a controlled double-blind therapeutic trial.

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References

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