Chemonucleolysis with chymopapain: results in 150 patients

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Chemonucleolysis with chymopapain has been advocated for the treatment of lumbar disc disease. When polled by a mail questionnaire, 150 consecutive patients who had undergone chemonucleolysis reported an overall success rate of only 40% and a failure rate of 60%. However, 57% of the patients were active or had only mild restriction of daily activities. Of those patients employed prior to injection, only 63% had returned to work. Those with workmen's compensation benefits fared considerably worse than those covered by third-party insurance (17% vs. 51% success). These results cast doubt on the long-term benefits of chymopapain in the treatment of lumbar disc disease.

KEY WORDS • chemonucleolysis • chymopapain • lumbar disc • outcome

HEATED controversy has clouded the history of chemonucleolysis with chymopapain since its introduction in 1964 by Smith. Arguments have revolved about its efficacy, safety, and cost compared to that of surgery. Intermediate and long-term success rates have been reported to be from 40% to 90%. Explanations for poor results have included inadequate patient selection, inexperience of the surgeon, poor needle placement, and use of inadequate drug dosage. A series of 150 consecutive patients who underwent chemonucleolysis with chymopapain was studied retrospectively, with success rates analyzed with respect to overall pain relief and ability to return to work.

Summary of Cases

Treatment

From July, 1979, to June, 1985, 150 patients underwent chemonucleolysis with chymopapain for treatment of symptomatic lumbar disc disease at the Division of Neurological Surgery, University of Louisville. Their ages ranged from 17 to 78 years, with an average age of 43 years. Each of the 72 female and 78 male patients had suffered a lumbar disc protrusion or extrusion, confirmed clinically and documented radiographically. Clinical criteria consisted of low-back pain and radiculopathy localized to one dermatome, with the intensity of leg pain being greater than or equal to the back pain. There was always limitation of the straight-leg raising test on the involved side as well. At least one objective sign, such as numbness, weakness, and/or reflex change corresponding to the involved nerve root, was present. Nonoperative treatment consisted of complete bed rest for 10 to 14 days, weight loss if overweight, and administration of analgesic and muscle relaxant medications. Following unsuccessful nonoperative therapy, lumbar myelography (using Panopaque (iophendylate) in the early part of the series and subsequently metrizamide) was performed on each patient. When metrizamide was used, a postmyelographic computerized tomography (CT) scan was also performed 2 to 4 hours later. After confirmation of the correct disc level from the combined clinical, myelographic, and CT scan evaluations, the alternatives of therapy were considered: 1) continued nonoperative therapy; 2) chemonucleolysis with chymopapain; or 3) conventional lumbar discectomy. If chemonucleolysis was chosen, the patient was apprised of the technique, potential risks, and expected results. Those patients who had a rapidly progressive neurological deficit, bowel or bladder dysfunction, prior injection with chymopapain, an allergy to meat tenderizer or papaya, were pregnant, or who demonstrated a complete myelographic block were not offered chemonucleolysis as an option of therapy.

Prior to 1982, patients received no medication before chemonucleolysis, but subsequently steroids (hydrocortisone sodium succinate (Solu-Cortef), 500 mg/6 hrs intravenously for 12 hours), cimetidine (Tagamet, 300
mg three times daily for 12 hours), and diphenhydramine hydrochloride (Benadryl, 25 mg on call in the operating room) were administered for their theoretical benefit in preventing an allergic reaction.\textsuperscript{13} Chemonucleolysis was performed in the operating room utilizing the C-arm image intensifier for precise needle placement.\textsuperscript{10} Patients were awake, but lightly sedated with neuroleptic analgesia. Patients were placed in the prone position,\textsuperscript{12} with needle entry 10 cm to the left of the midline immediately above the iliac crest. Discography was not performed. Chymopapain, 2 cc, was injected after the correct needle position was confirmed and documented by spot radiograms. The patient's vital signs, level of consciousness, and any untoward signs such as pruritis, dyspnea, and pain were closely observed for 15 minutes in the operating room and for another 2 hours in the recovery room. The duration of postinjection hospitalization was 1 to 3 days. Postinjection assessment was carried out at 1, 3, and 6 months.

\textbf{Study Method}

A follow-up questionnaire (Fig. 1) was mailed to all 150 patients 7 to 70 months after injection (average 26 months). With minor modifications, its format closely followed that developed by Javid.\textsuperscript{13} Results were assessed by the patient's estimate of the percentage of overall pain relief (Table 1). Patients with an excellent or good response were considered treatment successes, whereas those with a poor or fair response were considered treatment failures. Relief of back and leg pain was considered together, with no attempt made to assess the effectiveness of chemonucleolysis with respect to the back or leg individually. Widely accepted criteria for evaluating the success of any type of spinal surgery are 1) the patient's assessment of pain relief, and 2) his or her ability to return to work. These criteria were the basis for our evaluation of the efficacy of chemonucleolysis for lumbar disc disease.

\textbf{Results of Follow-Up Study}

Of the 150 patients to whom questionnaires were mailed, responses were obtained from 126 (84\%), six by telephone interview. Of the respondents, 35 (28\%) believed they had obtained an excellent result and 15 (12\%) a good result, for an overall success rate of 40\%. Twenty-three patients (18\%) assessed their result as fair and 53 (42\%) considered that they had a poor outcome or no improvement, for an overall failure rate of 60\%. No patient had worsening of symptoms after chemonucleolysis (Table 1). Of the failures, 23 (30\%) subsequently underwent surgery, the most common findings being foraminal stenosis and the redundant anulus syndrome (Table 2). Multiple abnormalities

\begin{table}[h]
\centering
\caption{Results of chemonucleolysis questionnaire returned by 126 patients}
\begin{tabular}{|c|c|}
\hline
\textbf{Result*} & \textbf{Cases} \\
\hline
excellent & 35 \\
good & 15 \\
fair & 23 \\
minimal or no relief & 53 \\
\hline
\end{tabular}
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\begin{table}[h]
\centering
\caption{Findings at operation in 23 patients}
\begin{tabular}{|c|c|}
\hline
\textbf{Findings} & \textbf{Cases} \\
\hline
foraminal stenosis & 11 \\
bulging disc (redundant anulus) & 7 \\
extruded fragment & 3 \\
mechanical instability & 3 \\
spinal stenosis & 1 \\
scar & 1 \\
no abnormality & 5 \\
\hline
\end{tabular}
\end{table}

FIG. 1. Sample of the chemonucleolysis questionnaire sent to 150 patients 7 to 70 months after injection.
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were occasionally noted, making the total number listed greater than the number of patients undergoing surgery. The patient’s ability to return to work or resume daily activities was also addressed. Only 28 (22%) of the respondents had returned to full activity without limitation, whereas 44 (35%) were active, with mild restrictions such as avoiding lifting heavy weights or performing strenuous exercise. Thus, 57% had returned to activities of daily living with mild or no limitations, 45 (36%) were active with moderate restrictions, and nine (7%) were restricted in their activities to a major degree.

Sixteen (13%) of the respondents had previously undergone lumbar disectomy at the same level as their chymopapain injection. Of this small group, six patients had a successful outcome and in 10 the operation failed. Only patients who had had a successful lumbar disectomy with good results lasting for months or years, in whom a recurrent disc protrusion/extrusion subsequently developed, were considered for injection.

The patient’s ability to return to work was considered highly pertinent in determining the success of chemonucleolysis. Fifty-eight (46%) of the respondents were working at the time of the study; 38 (30%) had returned to their preinjection occupation, 16 (13%) had returned to a light-duty job, and four (3%) who had not worked prior to chemonucleolysis were working at the time of the surgery. Thus, 68 (54%) of the patients were not employed when polled; however, half of these had been unemployed prior to their injection. Of 50 patients with a successful outcome, 35 (70%) were working, while only 24 (32%) of the 76 in whom the procedure failed were working.

Eighty (64%) of the patients were covered by third-party insurance carriers, 37 (29%) were recipients of workmen’s compensation benefits (or settlement was pending), and nine (7%) were covered by other means. The success rate of the 89 patients with third-party coverage was 51% (49 cases), whereas only 17% of the 37 patients covered by workmen’s compensation (six cases) were considered successes (Table 3).

Of the 10 cases with complications (8%), the drug could be directly implicated in seven (Table 4). There were no deaths or anaphylactic reactions. Five patients developed skin rashes: four delayed and one immediate. One patient developed transient causalgia at the level of the needle placement, which totally resolved within 9 months. One patient with unrecognized von Willebrand’s disease developed a retroperitoneal hematoma within 6 hours following injection, which resolved spontaneously. One patient committed suicide 2 years after injection, and one had a cholecystectomy 3 weeks following the injection.

Discussion

Since the Food and Drug Administration released chymopapain in North America in 1982, over 150,000 patients have been injected, with both its efficacy and safety being closely scrutinized. Successful results following chemonucleolysis have been reported in 40% to 90% of cases. Outcome of most series has been determined by the physician’s personal assessment of the patient after an interval of 6 to 24 months. Potential bias may result from a physician’s enthusiasm for a certain form of therapy, or a patient’s tendency to minimize symptoms in order to please his physician. Mail questionnaires largely circumvent these problems by allowing the patient to report his results objectively, free from outside pressure, although questionnaire design may significantly alter the results.11 The 12-year results reported by Parkinson23 and the 3- to 6-year results of Javid, et al.,14 both obtained by mail questionnaires, had a respective 70% and a 73% success rate, compared with our success rate of 40%. Thus, different methods of information retrieval alone cannot explain the disparate results.

Comparison of the results of chemonucleolysis versus lumbar disc surgery has been difficult because different criteria have been used to assess success or failure, such as relief of leg and/or back pain, resumption of daily activities, and the ability to return to work. We believe that the patient’s overall satisfaction with respect to relief of both back and leg pain and the ability to return to work are the most important criteria in judging the efficacy of treatment of lumbar disc disease. A procedure which relieves leg pain alone, leaving the patient with continued incapacitating back pain, is of little value. Our patients’ success rate of 40% was considerably worse than in most other published reports of chemonucleolysis and surgical lumbar discectomies,25 although it was virtually identical to the long-term outcome described by Day, et al.,5 and Loew, et al.15 Although other criteria could have been chosen which might have provided better results, the above features were simple to evaluate and of the greatest

<table>
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<td><strong>Success rate correlated with medical insurance coverage</strong></td>
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<tr>
<td>Medical Insurance Coverage</td>
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<td>third-party carrier</td>
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<td><strong>Complications of chemonucleolysis</strong></td>
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<tr>
<td>Complication</td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>anaphylaxis</td>
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<tr>
<td>rash or urticaria</td>
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<td>other*</td>
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* One case each of: retroperitoneal hematoma; thrombophlebitis; cholecystitis; and causalgia. One patient committed suicide.
importance to the patient's overall well-being, which contributed to his or her satisfaction with chemonucleolysis.

The response rate to our questionnaire was only 80% (120/150). Telephone interviews were attempted after non-return of the second questionnaire (six telephone interviews). Kentucky has a large rural and moderately mobile population which may account for the low response rate. We were unable to contact 24 patients. The 60% failure rate in our series was unexpected. Severe, persistent low-back pain lasting longer than 6 months or radiculopathy lasting more than 6 weeks accounted for the fair, poor, or no benefit categories, which were considered failures. Of the 76 failures, only 23 (30%) subsequently underwent surgery. The other patients complained of predominant back pain, displayed little or no radiculopathy, and had no evidence of mechanical back instability and so were not considered candidates for surgery. This low rate of surgery of chymopapain failures is noted in other series as well, ranging from 42% to 68%. McCulloch has operated on 24 (52%) of 46 failures, including 21 patients for low-back pain. Those patients who were operated on often demonstrated foraminal stenosis, redundant partially calcified anulus, or mechanical instability (P Camp, unpublished data); these findings were not suspected before chemonucleolysis and were presumably caused by a late effect of vertebral-body settling following disc dissolution. Only three patients (12%) had a sequestered fragment at operation in our series, which is less than the 50% to 70% rate reported elsewhere. Deburge, et al., reviewing their chymopapain failures, reported results similar to our own, except in their series nerve root entrapment occurred in the lateral canal rather than at the foramen. They noted the occurrence of lateral recess stenosis in 40%, subligamentous herniation (redundant anulus) in 32%, sequestered disc in 10%, and no abnormality in 8%. Surgery was successful in 70% of their postchymopapain failures, with greatest success noted in patients with lateral recess stenosis or a sequestered disc. We believe that many patients with extruded fragments did respond favorably to chemonucleolysis but those with sequestered fragments did not. The disc space was empty in all patients who had undergone chemonucleolysis, and in no instance was a normal amount of nucleus pulposus removed. Surgery was successful in 57% of the 23 chemonucleolysis failures who had a subsequent operation. Magnetic resonance imaging may provide a clear differentiation between a protruded, extruded, or sequestered disc, providing greater reliability in identifying patients likely to respond to chemonucleolysis.

Prior surgery at the same level was not an absolute contraindication to chemonucleolysis. Only if the patient developed a sudden onset of recurrent symptoms, displaying myelographic and CT changes consistent with a disc protrusion, after having obtained a good-to-excellent surgical result lasting months or years, was chemonucleolysis performed. Other studies have demonstrated inferior results in patients who had previously undergone surgery (60% success in males and 50% in females) compared to the 70% success in patients injected at a nonoperated level. Seventeen patients in our group had prior surgery at the injected level and the outcome was similar (41%) to that of patients who had not undergone prior surgery (39%).

Watts has reported complications occurring in 401 of 13,700 patients whose cases he reviewed. He reported allergic reactions to chymopapain (1.5%); neurological reactions including mild foot weakness, transient bladder dysfunction, and causalgia (0.4%); cardiovascular reactions (0.3%); and miscellaneous complications (0.7%). One patient developed quadriplegia secondary to a progressive cervical spinal cord tumor which was not recognized prior to cervical disc chemonucleolysis. Since that time, 34 patients have developed paraplegia (acute transverse myelitis or cauda equina syndrome). We believe that the admixture of chymopapain and positive contrast agent (used for discography), which may reflux through a dural hole into the subarachnoid space, is largely responsible for this dreaded complication. Watt has suggested that the efflux of chymopapain from the disc space into the venous system, with its rapid adherence to circulating protein fractions, may produce a toxic effect on, or affect the microvasculature of, the thoracic cord or cerebral cortex. During the past 2 years, the use of chymopapain has decreased as a result of reports of major complications such as paraplegia and cerebrovascular accidents. The potential medicolegal liability, and concern as to the effectiveness of this procedure when compared to that of surgery, has prompted withdrawal of this product from the market. Since June, 1984, when discography was largely discontinued, no case of paraplegia caused by chymopapain has been reported in North America. Neither paraplegia nor anaphylaxis occurred in our series, but a mild cutaneous allergy to chymopapain has been recognized in five patients.

All 150 of our patients injected were believed to have had lumbar disc disease and clearly were candidates for surgical intervention. In a double-blind series, in which we were a participating center, the success rate following chemonucleolysis was 70% (HA Wilkinson, et al., in preparation). No patient was included in both series so that the patient populations are totally independent. One explanation for the discrepancy may be that the follow-up period of the double-blind study was 6 months compared to the average follow-up period of

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2½ years for this series. Not infrequently, patients considered a success at 6 months developed subsequent recurrence of back and leg pain requiring further treatment. It is conceivable that, with further investigation (tomography, magnetic resonance imaging, neuropsychological tests) and more rigorous exclusion of some cases, our results might be improved; however, we believe that these results accurately reflect the results of chemonucleolysis in a standard neurosurgical practice.

References


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