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Intraoperative chymopapain in lumbar laminotomy for disc disease: a less invasive technique

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The use of chymopapain in the treatment of lumbar disc herniation has been widely studied since Smith first described its use in humans in 1963. The authors describe the use of chymopapain intraoperatively in open lumbar microdiscectomy in 63 patients. When combined with the results of a previous study performed at the same institution, the authors found that this technique significantly reduces the rate of recurrent disc herniation when compared with traditional laminotomy with discectomy. This procedure maximizes the benefits of each approach taken separately, allowing for decompression of the nerve root from a free fragment or sequestered disc and preventing recurrence through dissolution of the nucleus pulposus. Overall, outcome was good or excellent immediately postoperatively in 73% of the 63 patients and in 64% at last follow-up evaluation. Additionally, this procedure is safe with no complications noted in the immediate perioperative period or at follow-up evaluation.

Key Words * chymopapain * chemonucleolysis * lumbar microdiscectomy * sciatica * recurrence * disability

Chymopapain is a proteolytic enzyme derived from fresh papaya latex[19] that targets the chondromucoprotein of an intervertebral disc[37] and results in the degradation of the nucleus pulposus. Since Smith's[36] description of the use of chymopapain in humans, many studies have been performed to evaluate the efficacy of chymopapain in the treatment of patients with lumbar disc disease.[2,16,18,21,22,24,26,28,29,35] The results of randomized, double-blind trials of chymopapain compared with placebo have supported the use of percutaneous, intradiscal chymopapain for the treatment of patients with herniated nucleus pulposus with sciatica.[7,14,15,23,34] There have been retrospective series in which chemonucleolysis has been compared with traditional lumbar laminectomy combined with discectomy and the results have been conflicting.[6,20,25,31,39,40] Dabezies and Brunet[6] found that 71% of patients who were treated with chemonucleolysis had good to excellent results as opposed to 63% of those who underwent surgery. In contrast to these results, Maroon and Ablak[25] more recently showed a 90% marked improvement for those patients undergoing microdiscectomy compared with 58% improvement in those treated with chemonucleolysis. Likewise, there are studies in which surgery has been directly compared with chemonucleolysis in prospective, randomized trials.[5,12,30,38] Crawshaw, et al.,[5] demonstrated a significantly increased number of

poor results following chymopapain therapy (52%) compared with surgery (11%) at 1 year. Van Alphen, et al.,[38] had the largest study group consisting of 151 patients, 73 treated with chemonucleolysis and 78 who underwent surgery. They found a significant difference, favoring open discectomy over chemonucleolysis at 12-month follow up, with regard to treatment failure (3% compared with 25%, respectively) and satisfactory outcome (85% compared with 63%, respectively). Muralikuttan, et al.,[30] found in a trial of 92 patients, each treatment arm with 46 individuals, that there was a significant difference in the number of failures: 2.2% for surgery compared with 19.6% for chemonucleolysis. Outcome favored surgery at 6 weeks and 3 months but was not statistically different at 12 months. In all three studies it was found that failures were common in patients with sequestered discs and lateral stenosis treated with chemonucleolysis and with recurrent disc herniation treated by laminotomy and discectomy. In an attempt to address the failures of percutaneous chymopapain administration, the use of intraoperative chemonucleolysis as an adjunct to lumbar discectomy was developed at the University of Virginia and described by Sagher, et al.[33] In that study, 104 patients underwent the traditional lumbar laminotomy with intraoperative chymopapain injection, followed by discectomy for some patients and none for others. This patient population was compared with a group of historical control patients treated concurrently with standard laminectomy and discectomy. Sagher's study revealed that this method was safe and, preliminarily, efficacious, with 70% of patients reporting good or excellent pain relief, and that there was a reduction in the incidence of recurrent disc herniation. The present study was undertaken to extend the evaluation of both symptomatic outcome and recurrence, to evaluate the safety of this procedure, and to examine specific factors affecting outcome.

CLINICAL MATERIAL AND METHODS

Patient Selection

Patients were considered for treatment with intraoperative chymopapain as an adjunct to lumbar laminotomy, with or without discectomy or foraminotomy, if they presented with a history of intractable low-back pain and associated radicular complaints. Patients were first treated nonsurgically with 1 to 2 weeks of bedrest, nonsteroidal antiinflammatory drugs, and subsequently with a 4- to 6-week course of physical therapy (PT). Those individuals who reported persistent symptoms despite this trial were further evaluated to define the source of their complaints. Myelography followed by computerized tomography (CT) scanning or magnetic resonance (MR) imaging of the lumbar spine was used to confirm the presence of an appropriately localized nerve root cut-off, disc herniation, or disc bulge. All patients were tested for sensitivity to the chymopapain antigen (Chymopapain immunoglobulin E RIA; Roche Laboratories, Rochester, MN).

Patients with low-back pain and radicular findings who demonstrated a sensitivity to chymopapain were not considered candidates for this study. Also excluded were patients with lumbar radiculopathy secondary to spondylolisthesis or superior facet hypertrophy without associated compressive disc disease.

Surgical Procedure

Preoperatively, all candidates received a single 100-mg dose of hydrocortisone, 50 mg of diphenhydramine, and 150 mg of ranitidine. All operations were performed by the senior author (J.A.J. Sr.) through a midline skin incision and a partial hemilaminotomy. Through this limited exposure, the anatomy of the disc and the medial superior facet were examined to determine the nature and degree of nerve root distortion. If free or sequestered fragments were discovered, they were removed prior to the augmentation of the osseous exposure. If mass effect from a persistent disc bulge was noted without a

significant defect in the posterior longitudinal ligament or annulus fibrosus, the patient was treated with an intradiscal injection of chymopapain (Chymodiactin, 4000 U/2 ml; Boots Pharmaceuticals, Nottingham, UK). The operative site was irrigated concurrently with the injection to ensure maximum dilution of chymopapain leaking from the disc space. The decision to perform a formal discectomy was based on a finding of significant nerve root tension as a result of a persistent bulge in a pharmacologically treated disc. This assessment was delayed for 2 minutes after the injection to observe the effect of the enzymatic degradation of the nucleus pulposus. Following this process, the extent of osseous compression was evaluated, and a foraminotomy was performed accordingly.

Postoperative Management

Postoperatively, patients were mobilized immediately after surgery and normally discharged on the 1st postoperative day. Routine follow-up assessment was conducted at 1 and 6 weeks postoperatively. Patients with persistent or recurrent postoperative pain despite receiving a course of postoperative PT and nonsteroidal antiinflammatory drugs were evaluated by either CT myelography or MR imaging. Individuals who demonstrated persistent nerve root compression were offered a revision surgery. The word "recurrence" is strictly applied to describe individuals with a recurrent disc herniation documented at surgery. Recurrence, in this sense, can be viewed as a failure of chymopapain to completely dissolve the nucleus pulposus.

Outcome Evaluation

Demographic and clinical data were obtained by chart review. Follow-up information was collected by both a review of the patient record and telephone interview. A series of six questions was used to obtain an understanding of patient welfare, surgical efficacy, the nature of persistent or recurrent symptoms, and the duration of postoperative PT. Outcome was classified as either excellent or good when patients reported either an absence of pain or a significant improvement in symptoms. A fair or poor outcome was noted in patients who only experienced a mild improvement, no change, or a worsening in their symptoms when compared with their preoperative condition. Patient condition was recorded in both the immediate postoperative period and at the point of latest follow-up evaluation.

To assess the efficacy of intraoperative chymopapain administration in combination with laminotomy either with or without discectomy compared with laminotomy and discectomy alone, this population was evaluated in isolation and concurrently with a cohort of 120 previously reported patients who were also treated at the University of Virginia.[33] Clinical outcome and the incidence of recurrence are compared with the results reported by Rish[32] and by Sagher, et al.[33]

Statistical Analysis

Statistical analysis was performed using STATISTICA for Windows 5.1 (StatSoft Inc., Tulsa, OK). Student's t-test was used to compare group means. Fisher's exact test was used to analyze the 2 X 2 table in the univariate analysis. The level used to determine statistical significance was 0.05.

RESULTS

Patient Profile

Between 1994 and 1997, 63 patients were treated with chemonucleolysis during lumbar laminotomy (Table 1). Of these, 37 (59%) were contacted by telephone and interviewed. The average age of the

population was 41 years and 39 patients (62%) were men. The average duration of symptoms was 11.1 months, and 62 patients (98%) presented with back pain, leg pain, or both. Four patients (6%) had previously undergone lumbar discectomy. Twenty-two patients (35%) were working preoperatively, and 17 (27%) were either involved in litigation, claimed a work-related injury, or had initiated a process to acquire disability payments; these circumstances were used to define a subpopulation of individuals with "secondary gain" factors. Patients with secondary gain were more likely to be men ($p = 0.010$), more likely to be unemployed preoperatively ($p = 0.019$), and were also more likely to undergo an operation for a disc bulge rather than for a frank herniation ($p = 0.026$).

Characteristic	Mean	Standard Deviation
demographic data		
age (yrs)	40.75	10.39
male	62%	0.49
working preop	35%	0.48
secondary gain	27%	0.45
prior surgery	6.3%	0.25
symptoms		
duration (mos)	11.07	14.38
back pain	98%	
lower-extremity pain	98%	
numbness	73%	0.45
weakness	49%	0.50
signs		
sensory	48%	0.50
deep tendon reflexes	24%	0.43
motor	32%	0.47
op findings		
disc bulge	73%	0.45
disc herniation	30%	0.46
discectomy	63%	0.49
postop symptom relief		
improvement immediately*	73%	
improvement at last follow up*	64%	
length of follow up (mos)	17.6	14.7
duration of PT (mos)	3.6	3.8
working at follow up	63%	0.49
return to premorbid activity	62%	0.47
recurrence rate per year	5.4%	
* Improvement is qualified as significant improvement or no pain.		

Operative Findings

Thirty-four patients (54%) had disease at L4-5, 27 (43%) at L5-S1, and five (8%) at L3-4. Forty-six patients (73%) were found to have disc bulges as documented at surgery. Forty patients (63%) were subjected to a formal discectomy after injection with chymopapain. Reoperation for recurrent disc herniation was performed in five of 63 patients, for a recurrence rate of 5.4% per year.

Patient Outcome

The average follow-up period was 17.6 months. Clinical outcome was evaluated on the 1st postoperative day and at last follow-up evaluation. Forty-six patients (73%) experienced a good or excellent outcome immediately postoperatively, declining to only 64% at last follow-up review.

TABLE 2 OUTCOME IN PATIENTS TREATED WITH AND WITHOUT DISCECTOMY			
Outcome	W/O Discectomy (23 patients)	W/ Discectomy (39 patients)	p Value*
immediate relief (good or excellent)	12 (52%)	34 (87%)	0.006
last follow-up relief (good or excellent)	11 (48%)	28 (76%)†	0.050
recurrence	0 (0%)	5 (12.8%)	NS
secondary gain factors	7 (30%)	10 (26%)	NS
* NS = not significant.			
† Two patients were lost to follow up.			

Several medical and demographic variables seemed to influence outcome. Patients who also underwent a discectomy during their surgery were more likely to benefit both immediately postoperatively ($p = 0.006$) and at latest follow-up review ($p = 0.050$) (Table 2). An absence of secondary gain factors also correlated with relief of symptoms at latest follow-up review ($p = 0.036$), although it did not influence outcome in the immediate postoperative period (Table 3). The presence of secondary gain factors also correlated with individuals who were more likely to be unable to return to their premorbid level of activity ($p = 0.041$), although there was no correlation with postoperative employment status. Recurrence was not influenced by the presence of secondary gain, but a trend toward a significant increase in recurrence was identified in patients who were treated with a discectomy in conjunction with laminotomy and chymopapain injection.

TABLE 3 OUTCOME IN PATIENTS WITH AND WITHOUT SECONDARY GAIN FACTORS			
Characteristic	No. of Patients (%)		p Value*
	W/O Sec- ondary Gain	W/ Sec- ondary Gain	
preop			
no. of males	24 of 46 (52)	15 of 17 (88)	0.010
working preop	19 of 43 (44)	2 of 17 (12)	0.019
disc bulge	30 of 46 (65)	16 of 17 (94)	0.026
outcome			
immediate relief (good or excellent)	34 of 46 (74)	12 of 17 (71)	NS
last follow-up relief (good or excellent)	32 of 44 (73)	7 of 17 (41)	0.036
recurrence	3 of 46 (6.5)	2 of 17 (11.8)	NS
return to premorbid activity	20 of 27 (74)	5 of 13 (38)	0.041
working postop	20 of 38 (53)	9 of 16 (56)	NS
* NS = not significant.			

DISCUSSION

When used as an adjunct to traditional laminotomy and discectomy, the intradiscal injection of chymopapain reduces the rate of recurrent disc herniation. A 5.4% recurrence rate was achieved in a population of 167 patients; this includes 104 patients previously reported by Sagher, et al.,[33] as well as the current group of 63 individuals. This is a significant improvement from the 12.6% recurrence rate reported by Rish[32] ($p = 0.02$). A proportion of patients who received intraoperative injection of chymopapain did not undergo disc-space exploration. This subgroup seemed to gain the most benefit from chemonucleolysis because no patient required reoperation for recurrent disc herniation. To our knowledge, this is the first study to demonstrate that the intraoperative use of chymopapain in the

treatment of lumbar disc disease statistically reduces the recurrence rate, a benefit of not opening the posterior longitudinal ligament. However, this benefit is counterbalanced by the fact that patients who did not have discectomy suffered a worse outcome both immediately postoperatively ($p = 0.006$) and at follow-up review ($p = 0.05$) (Table 2). It is important to note that there were no confounding factors found to explain this difference. In particular, patients with secondary gain were evenly distributed between the two groups, those with discectomy (26%) and those without (30%). Furthermore, for those patients not undergoing discectomy, closer inspection revealed that 50% of the patients without secondary gain had a good or excellent outcome compared with 57% of the patients with secondary gain who had a similar outcome. This poor outcome may ultimately be related to issues in patient selection.

This study supports the idea that removal of a free or sequestered fragment without extensive disc space exploration and discectomy could decrease the recurrence rate and increase the probability of a good outcome. Ideally, a small incision in the posterior longitudinal ligament permitting the removal of a fragment would grant the benefit of nerve root decompression without increasing the risk of recurrence through an iatrogenically caused rent in the annulus. This procedure may be augmented by the intradiscal injection of chymopapain if a defect in the annulus is not detected. The benefit obtained by surgical decompression and chemonucleolysis addresses the failures that result when either percutaneous chymopapain or laminotomy/discectomy is used in isolation. Patients with free or sequestered disc fragments are poor candidates for percutaneous chemonucleolysis because enzymatic degradation must occur within the boundaries of the disc space; patients with associated radiculopathy from lateral recess stenosis are poor candidates as well.[1,2,4-6,12,25,30,38] A major factor in the failure of the traditional surgical treatment of lumbar disc disease is reherniation, which is seen in approximately 13% of patients and requires reoperation.[13,32] The use of our surgical protocol permits the immediate decompression of the nerve root granted by surgery and a reduced risk of recurrence afforded by chemonucleolysis.

As has been noted in nearly all of the papers written to date on the use of chemonucleolysis, the benefit obtained from injection progresses slowly when compared with the benefit of immediate root decompression obtained from surgery. Although not statistically significant in our study, patients who underwent discectomy required less PT than those who did not undergo discectomy. This, combined with our short follow-up period, may be the reason for the worse outcome seen in the patients without discectomy.

Clinical outcome in patients who reported a history of work injury, involvement in litigation, or application for either Worker's Compensation or disability was also compared with those who did not report any of these secondary gain factors (Table 3). These groups demonstrated significant differences in the distribution of gender ($p = 0.010$), preoperative work status ($p = 0.019$), and presence of disc bulge compared with disc herniation ($p = 0.026$). Interestingly, the initial postoperative outcome was the same, with good or excellent outcome in 74% of those patients without and 71% of those with secondary gain factors. As may be expected, these numbers changed significantly at follow-up review, with only 41% of patients with good or excellent outcome compared with 73% without secondary gain factors ($p = 0.036$). Similar percentages are seen when return to premorbid activity was evaluated ($p = 0.041$).

There were no complications resulting from administration of chymopapain seen intraoperatively or at follow up.[3,7-11,15,17,23,24,27,36,41] That is, no anaphylactic reactions, neurological complications, or postoperative discitis were observed. Additionally, patients did not report an aggravation of back pain in the immediate postoperative period. Reasons for the relative safety of this technique are the routine use of preoperative chymopapain sensitivity testing, the advantage of accurate injection into the nucleus

pulposus facilitated by direct visualization, and the implementation of generous irrigation at the time of injection.

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