Association between peridural scar and activity-related pain after lumbar discectomy

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The purpose of this study was to investigate the correlation between activity-related pain six months after first surgery for herniated lumbar disc, and the extent of lumbar epidural fibrosis present at the surgical site, assessed by magnetic resonance imaging. The 298 patients who underwent surgery for lumbar disc herniation were studied in a randomized, controlled, double-blind multicenter clinical trial to test the effectiveness of the scar-inhibiting device ADCON®-L. Clinical assessments were conducted pre-operatively and at 1, 3, and 6 month intervals post-operatively, and included wound examination, magnetic resonance imaging scar assessment, and the Johns Hopkins activity-related pain questionnaire. In addition, a longer-term follow-up assessment was conducted at 12 months post-operatively. The association between the presence of epidural scar and activity-related pain was analyzed at the 6-month interval, when successful surgical excision of protruding disc material should have eliminated chronic pain. Logistic regression analysis demonstrated a significant association ($p = 0.02$, odds ratio $= 0.7$) whereby the odds of extensive scar decreased by 30% for every 31% decrease in activity-related pain score. In addition, those patients receiving ADCON®-L at surgery developed significantly less scar in the months following operation ($p = 0.01$, 6 and 12 months post-operatively). Repeated measures analysis demonstrated that patients who received treatment with ADCON®-L at the time of surgery experienced less activity-related pain through the 12-month assessment ($p = 0.05$). A significant association between extensive epidural scar and activity-related pain is demonstrated. Patients with less scar had less activity related pain, confirming the finding that the use of the scar inhibitor ADCON®-L has a positive effect on surgical outcome. [Neurol Res 1999; **21 Suppl 1**: S37–S42]

Keywords: Activity related pain; epidural fibrosis; radicular pain; clinical outcome

INTRODUCTION

It is of considerable consequence to the lumbar discectomy patient that surgery improve his/her ability to perform activities of daily life. More important than magnetic resonance imaging (MRI) results or straight leg raising angles, is the post-surgical pain which inhibits a patient's ability to perform daily activities and is most frequently a marker of surgery failure. Different groups of patients can be identified according to the time when activity-related pain (ARP) first appears[1]. Pain seen immediately after surgery would most probably indicate surgical failure, i.e. a retained disc fragment or inadequate decompression. On the other hand, pain occurring one year or more after surgery often results from a recurrent reherniation at the same or a new site, possibly indicating the need for a second operation. A third group, those patients who initially report little or no pain, but who gradually develop ARP several months after surgery, comprise a category of special clinical interest. In these patients, it appears that surgical success is compromised by exuberant epidural scar causing compression or limiting the normal movement of nerve roots and therefore leading to pain in the course of normal daily activities[2]. In such cases, where epidural scar is likely to be the main or exclusive cause of symptom recurrence, a second surgery is typically contra-indicated, since scarring would only be exacerbated by further trauma. It is therefore best to prevent epidural scar before it forms. To that end, surgeons have over the years tried a variety of surgical techniques and treatments, including Silastic®, Dacron®, methacrylate, synthetic membranes and foams, free and pedicle fat grafts, and steroids, though with inconsistent results[3–8]. Of considerable interest is a new antifibrotic device, ADCON®-L, a carbohydrate polymer gel which was studied in a full-scale controlled, randomized, double-blind multicenter clinical trial conducted in Europe from 1992 to 1995, and which is being studied in a similar trial in the United States.

PATIENTS AND METHODS

Clinical study

This prospective trial included a total of 298 patients, male and female, between the ages of 17 and 60 years, who were seen at nine centers in three countries (*Table 1*). ARP data were collected from 267 of the 298 enrolled patients. Patients with acute or subacute unilateral herniated lumbar disc at a single spinal level

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Table 1: List of investigators/study sites

Investigator	Location	Total patients[a]	Evaluable patients[b]
N. deTribolet, MD F. Porchet, MD	Lausanne, Switzerland	53	47
T. Lutz, MD O. Gratzl, MD	Basel, Switzerland	47	43
H.A. van Alphen, MD	Amsterdam, The Netherlands	35	35
E.A.M. Beuls, MD	Maastricht, The Netherlands	20	19
R.E.H. van Acker, MD	Amsterdam, The Netherlands	50	46
A. Benini, MD	St. Gallen, Switzerland	30	28
K.N. Strommer, MD R. Bernays, MD	Zurich, Switzerland	13	8
J. Brotchi, MD, PhD	Brussels, Belgium	30	26
J. Goffin, MD	Leuven, Belgium	20	17
Total		298	269

[a] Patient selection criteria satisfied, patient number assigned, and randomization envelope opened.
[b] Evaluable for 6-month analysis.

(either L4/L5 or L5/S1), manifested by radicular pain, with or without significant low-back pain were selected after having failed conservative therapy for at least two weeks, and having MRI evidence of disc pathology consistent with the compression of a nerve root, or existence of disc fragment of sufficient degree to warrant surgical intervention. Additionally, patients were to be in good general health, be able to cooperate with the prescribed follow-up procedures and visit schedules, and have given informed consent.

Patients were excluded if they had previous lumbar surgery, had signs or symptoms consistent with multi-level, bilateral, or far lateral herniated disc(s), had severe scoliosis, or had any other severe spinal condition that would affect patient outcome. Other exclusion criteria were pregnancy, poor health, any immuno-deficiency disease, diabetes, high blood pressure, thrombocytopenia, or any bleeding disorder or systemic condition which might influence patient outcome. Also excluded were patients who had been administered peridural steroid therapy within four weeks of surgery, anti-coagulant therapy within seven days, or platelet-inhibiting medications such as aspirin, oral steroids, or nonsteroidal anti-inflammatory drugs within the prior 24 h before entry into the study. Furthermore, patients who had a myelogram or lumbar puncture within 24 h of surgery were excluded. Intra-operatively, patients were excluded if an incision or nick of the dura or any other intra-operative complication had occurred.

Clinical study methods

All surgeries were performed via midline approach using open visualization of the affected interspace by surgical loupes or operating microscope. Surgeons were free to perform the degree of bone removal necessary to assure adequate visualization and decompression of the affected nerve root. All findings and procedures were recorded on case report forms. If any intra-operative complications occurred, or if the surgeon discovered pathology other than a herniated disc, the patient was not assigned a randomization number and was excluded from the study.

At the completion of surgery, immediately before wound closing, the patient was randomly assigned to either the device group or the control group according to a pre-established schedule. Patients either received treatment with ADCON®-L or received no further treatment, depending on assignment, followed by routine closure. The surgeon was unaware of the group assignment of the patient until just before closure. The follow-up evaluations were conducted by qualified personnel other than the surgeon. Neither patients nor evaluators were aware of individual group assignments, and patients were not remunerated for participation in the study.

MRI evaluation

Gadolinium-enhanced MRI studies were performed on all study patients. Each MRI series consisted of five contiguous nonoverlapping 4-mm axial scans centered on the operated inter-vertebral space. Images were enhanced through the use of a gadolinium contrast medium shown to be effective in differentiating scar from disc and other soft tissues[2,9]. The relative position of the MRI scans is illustrated in *Figure 1*. The middle slice (#3) was centered at the middle of the disc space. The slice just cranial (#2) was cut through the region closely approximating the location where the affected nerve root sleeve separates from the thecal sac. The slice just caudal (#4) completed the area of the operated disc space. The first and fifth slices overlapped the adjacent vertebral bodies and were used for visual orientation purposes. They were not included in the scar analysis. Each of the MRI slices analyzed was divided into four spatial quadrants centered on the thecal sac, shown diagrammatically in *Figure 2*. All MRI scans were

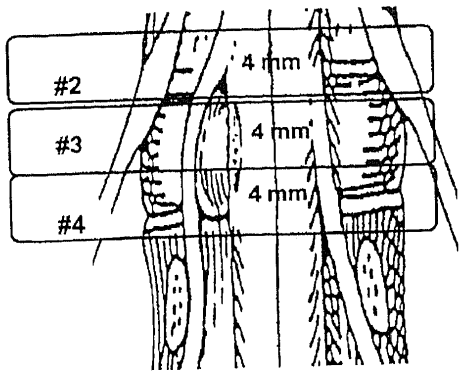

Figure 1: Five enhanced MRI transversal slices were taken. The three central slices, marked 2, 3, and 4 were used for assessment of epidural scar

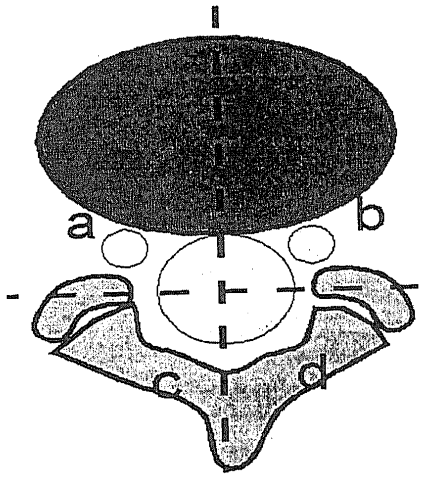

Figure 2: Of each representative MRI slice, four quadrants centered on the spinal canal were examined

interpreted by a single neuroradiologist blinded as to patient group assignment and not associated with any of the investigational sites. A scar score was assigned to each quadrant as follows: a score of 0 if the quadrant area showed no fibrosis or only a trace amount; a score of 1 if the quadrant was $>0\%$ and $\leq 25\%$ filled with fibrosis; a score of 2 for $>25\%$ and $\leq 50\%$ fibrosis; a score of 3 for $>50\%$ and $\leq 75\%$ fibrosis; and a score of 4 for $>75\%$ fibrosis. Scar scored as 0 or 1 was characterized as 'minimal', that which scored 2 or 3 was characterized as 'moderate', and a score of 4 was considered 'extensive'. The scar score for each patient was the maximum score assigned to any quadrant in slices 2–4.

Activity-related pain assessment

Activity-related pain was evaluated pre-operatively and at six months post-operatively for 12 different activities of daily living. The ARP questionnaire was the same as that used for the National Low Back Pain Study coordinated by the Johns Hopkins University Medical School[10]. Each patient indicated whether pain was increased, unchanged, or decreased when each of the activities was performed. Exploratory analyses performed on the data, which were subsequently substantiated by factor analyses, revealed that two factors accounted for most of the systematic variance. The six activities with significant loading characterized the first factor and included those involving walking, standing, and climbing, and are associated with pain of musculo-skeletal origin. The five activities with significant loading on the second factor, including those involving sitting, bending, lifting objects, and riding in or driving a car, are associated with pain of radicular (involving nerve root compression) origin. The twelfth activity, 'lying down', did not load significantly on either factor. For the purposes of this study, the five activities with high loadings on the second factor (involving nerve root compression) were selected for use in evaluating the relationship between post-operative fibrosis and ARP. The five activities were: sitting for less than 15 min; sitting for longer than 15 min; bending forward; lifting objects heavier than 10 pounds; and riding in or driving a car for 20 min. Each of the activities was scored as either 0 (for decreased or unchanged pain) or 1 (for increased pain), and weighted, according to coefficients developed by analyses performed at Johns Hopkins. For each patient, the weighted scores were summed to provide Activity-Related Pain (wARP) scores used in this study.

Purpose of the study

The hypothesis was that the amount of epidural scar seen at the MRI is predictive of wARP evaluation results, with extensive scarring correlating with increased ARP, thus underscoring the clinical relevance of scar tissue in determining the success or failure of surgery. It was also assumed that six months following surgery is an adequate time for healing to take place, and for epidural scar to mature, based on a previous study[11].

Statistical methods

The relationship betweeen the amount of scarring and ARP at six months was evaluated by computing the Spearman correlation coefficient for each clinical center, followed by combining the results across centers using the method of Han[12]. The null hypothesis that the combined correlation coefficient equals zero was then tested. To assess the predictive value of the amount of scarring on ARP, logistic regression analysis was used. The significance of the coefficient for scarring was assessed with a likelihood ratio test. The Hosmer–Lemeshow goodness-of-fit statistic was used to check the fit of the model.

RESULTS

The analysis included 267 patients for whom both wARP evaluations and MRI assessments were available. Patient demographic data are summarized in *Table 2*. Overall, there were no demographic differences within the patient population, except for the operative level. However, when further statistical analyses 'accounted'

Table 2: Patient demographics

Parameter	ADCON®-L $n=128$	Control $n=141$	p-value
Gender [Number (%)]			1.0[a]
Male	79 (62)	88 (62)	
Female	49 (38)	53 (38)	
Age			
Mean (%)	38.2 (10)	39.9 (9)	0.13[b]
Pre-operative clinical signs [Mean (SD)]			
Radicular pain score[c]	7.8 (2)	8.0 (2)	0.40[b]
Low back pain score[c]	6.0 (3)	5.4 (3)	0.10[b]
SLR angle (degrees)[d]	50.0 (21)	52.4 (22)	0.37[b]
Operative level [Number (%)]			0.04[a]
L4/L5	38 (30)	59 (42)	
L5/S1	90 (70)	82 (58)	
Surgical procedure [Number (%)]			
Laminectomy	2 (2)	4 (3)	0.95[a]
Laminotomy	22 (17)	25 (18)	
Hemilaminaectomy	49 (38)	53 (38)	
Hemilaminotomy	55 (43)	58 (41)	
Foraminotomy	0 (0)	1 (1)	
Disc pathology [Number (%)]			
Sequestration	57 (44)	53 (38)	0.27[a]
Extrusion	43 (34)	61 (43)	
Protrusion	28 (22)	27 (19)	

[a] p-value for comparison of distributions between treatment groups (Fisher's exact test). [b] p-value for comparison of means between treatment groups (two-sample t-test). [c] Visual Analogue Scale (0–10 cm), pain when most severe. [d] For the SLR examinations, ADCON®-L $n=121$, Control $n=135$.

Table 3: Scar assessment, 6-month evaluation

Extent of scar	ADCON®-L ($n=127$) Number (%)	Control ($n=139$) Number (%)	p-value
Score 0 (None, 0%)	4 (3.2)	1 (0.7)	0.01[a]
Score 1 ($>0\%$, $\leq 25\%$)	13 (10.2)	4 (2.9)	
Score 2 ($>25\%$, $\leq 50\%$)	16 (12.6)	24 (17.3)	
Score 3 ($>50\%$, $\leq 75\%$)	46 (36.2)	41 (29.5)	
Score 4 ($>75\%$)	48 (37.8)	69 (49.6)	

[a] p-value for comparison of distributions between groups using the CMH procedure stratified by center.

for this difference, the conclusion of the study did not change.

The extent of epidural scar tissue was significantly reduced in ADCON®-L patients compared to the control group, as shown in *Table 3* ($p=0.01$) This represents an increase in the percentage of ADCON®-L patients having minimal post-surgical scarring, and a decrease in the number having extensive scarring (*Figure 3*).

The number of patients who experienced an increase in radicular pain for any of the five activities in the radicular factor group of the Activities of Daily Living questionnaire are summarized in *Table 4*. The greatest difference between treatment groups occurred for the activity of riding or driving more than 20 min, for which 25% of patients in the ADCON®-L group indicated an increase in pain *vs.* 45% of control patients. The wARP scores were lower in the ADCON®-L group than in the control group with mean scores of 1.24 *vs.* 1.58, respectively (*Table 5*). This represents a 21% improvement in outcome ($p=0.026$). Since ADCON®-L

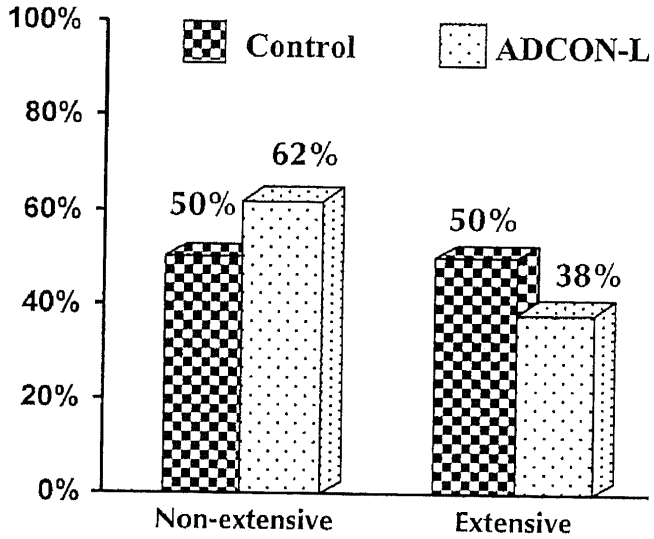

Figure 3: Six months post-operatively, patients receiving ADCON®-L showed a 24% reduction of extensive scarring ($p=0.002$). [a] p-value for comparison of distributions between treatment groups using the CMH procedure stratified by center

Table 4: Incidence of activity-related pain (evaluable patients)

Activity (Radicular factor)	ADCON®-L $n=88$ Number (%)	Control $n=84$ Number (%)	ADCON®-L benefit
Sitting ≤ 15 min	12 (13.6)	21 (25.0)	44%
Sitting >15 min	40 (45.5)	44 (52.4)	13%
Bending forward	41 (46.6)	43 (51.2)	8%
Lifting >10 lbs	50 (56.8)	56 (66.7)	15%
Riding/driving >20 min	22 (25.0)	38 (45.2)	44%

Table 5: Mean score of wARP, radicular factor (evaluable patients)

Linear combination[a]	ADCON®-L $n=88$	Control $n=84$	p-value[b]
Weighted score	1.24 ± 1.02	1.58 ± 0.99	0.026

[a] Linear combinations based on Johns Hopkins University National Low Back Pain Study.
[b] p-value for comparison of means between treatment groups (t-test).

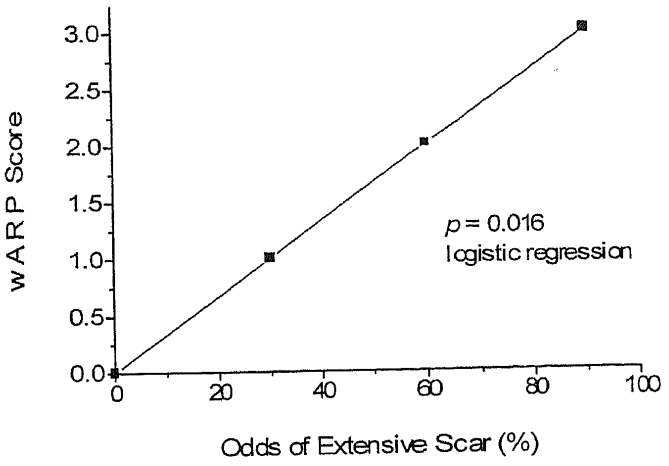

Figure 4: The linear correlation shows association between scar and activity-related pain six months after surgery

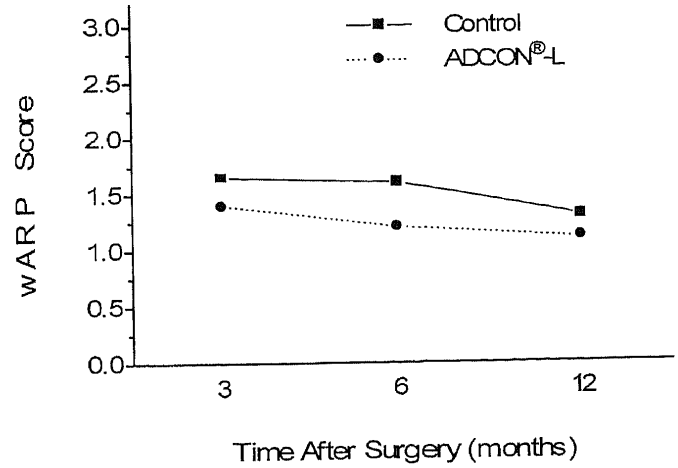

Figure 5: Repeated measures of activity-related pain through 12 months post-operatively show significant improvement in ADCON®-L treated patients ($p = 0.05$; repeated measures)

patients evaluated both less post-surgical epidural scar and better wARP evaluations, the relationship between reduced scarring and improved wARP evaluations was tested by logistic regression, with extensive epidural scar at six months as the dependent variable, and the change from baseline to six months in wARP (wARP at six months minus wARP at baseline) as a continuous exploratory variable. This relationship was statistically significant at the 5% level ($p = 0.016$). The estimated odds ratio of 0.7 refer to the odds that nonextensive scar decreased by 30% for every increase of 1 in wARP from baseline to six months (*Figure 4*).

A follow-up assessment on the same patients at the 12-month point showed that patients who received ADCON®-L had significantly less epidural scar than control patients at this longer post-operative interval ($p = 0.03$, Cochran–Mantel–Haenszel). In addition, these patients experienced less ARP through the 12 month time point ($p = 0.05$, repeated measures), as shown in *Figure 5*.

DISCUSSION

Scar formation is a normal part of the process of tissue healing. However, extensive scarring can have deleterious effects. There is ample evidence which demonstrates that poor surgical outcome can be a direct result of excessive epidural fibrosis. For example, Finnegan *et al.* reported in 1979 that in a study of 67 multiply-operated back patients, none with a finding of extensive fibrosis had a good outcome two years post-operatively[13]; Shiraishi and Crock, in a review of 23 lumbar re-operations, reported in 1995 that recurrent pain could be attributed to scar tissue formation around the nerve roots in 32% of cases[14]. It is, therefore, of primary importance to reduce or eliminate epidural scarring following lumbar surgery to increase the chances for surgical success.

CONCLUSION

This study represents one facet of a large, prospective, controlled, randomized, double-blind multicenter study of post-lumbar surgery epidural scarring and its relationship to clinical outcome. The clinical study shows that ADCON®-L is effective as an antifibrotic device and improves surgical outcome following lumbar disc surgery. Furthermore, a significant correlation between extensive epidural scar and poor patient outcome, as measured by ARP, is demonstrated.

ADCON-L STUDY GROUP

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