Prevention of peridural fibrosis: Current methodologies

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Lumbar discectomy is a common surgical procedure with a physician-reported 'good' outcome of 85%–95% for successfully relieving pre-operative sciatic pain. Up to 40% of patients post-operatively, however, have persistent limitations in activity. Peridural fibrosis is a natural consequence of the normal post-operative healing that can cause symptoms by tethering the nerve roots. ADCON®-L was developed to decrease the peridural fibrosis reaction. Cell culture analysis demonstrated that ADCON®-L blocked the ingrowth of fibroblasts, and animal laminectomy models demonstrated a major decrease in the amount of peridural fibrosis. ADCON®-L has been studied in two prospective randomized multicenter trials, one in Europe with 298 patients and the other in the United States with 223 patients at the interim analysis. Noting the differences in the quantity of peridural scar on post-operative MRI and in clinical outcome between the two groups assessed the effect of the addition of ADCON®-L to the surgical procedure. Both studies had statistically significant positive beneficial effects in both the radiologic index and the clinical outcome scores. These two studies provide the evidence for the clinical use of ADCON®-L to improve outcomes after lumbar discectomy. [Neurol Res 1999; **21 Suppl 1**: S9–S22]

Keywords: Epidural fibrosis; lumbar discectomy; fibrosis; pain; scarring; surgery; radiculopathy; peridural scar; recurrent radicular pain; peridural fibrosis; adhesions; prevention

INTRODUCTION

Currently there are about 200,000 lumbar laminectomies per year performed in the United States and an estimated 800,000 cases per year performed worldwide. 'Good to excellent' results of a single level lumbar disc surgery have been reported to be 85% to 95%[1–5]. Despite these relatively high physician-reported favorable outcomes, up to 40% of the patients continue to report limitations in activities, although the majority experience a significant post-operative decrease in pain[6–13]. Additionally, at 5 years approximately 15% will have another operation at some level[14–16]. The second operation is often noted for dense post-operative epidural fibrosis in the surgical site, which makes the dissection more difficult for the surgeon, and inherently has a higher potential for nerve damage compared to the original surgery. It appears that significant residual clinical impairment remains after a lumbar discectomy in many patients and that there is a significant rate of symptomatic disc herniation recurrence. Thus, it is reasonable to search for medical therapeutic methods to minimize the residual clinical disability and make a repeat operation both easier and safer.

PERSISTENT PAIN AFTER LUMBAR DISCECTOMY

There are several mechanisms potentially responsible for a bad outcome after a lumbar disc surgery[12,17–35]. These can be divided according to the time frame of pain onset as immediate failure to relieve the pain, temporary relief of pain with relapse of the original symptoms in weeks to months, and late failure after a prolonged period of pain relief. When there is no pain relief, the diagnosis should be questioned[10,13,36]. The cause of the pain may not be a herniated disc but rather a tumor, infection, psychosocial factors, associated effects from metabolic or endocrine disorders, discogenic or facet degenerative changes, or nerve root damage from acute or chronic compression. Technical errors during the surgical procedure should also be considered. These include an operation at the wrong level, persistent compression, or a surgically battered root. The persistent compression can be from either a residual fragment, a 'new' herniation while the patient coughs during emergence from anesthesia, or inadequately dealing with the spinal stenosis component of the compression. A conjoined nerve root is noted for having a higher incidence of intra-operative nerve damage as a result of its abnormal anatomic presentation.

When the patient has temporary relief and then the radicular pain recurs within a few weeks, a diagnosis of infection or meningeal cyst should be considered. After a few weeks to several months, the radicular pain may recur, either similar to the pre-operative pain or in the same distribution but of less intensity. A recurrent disc herniation, a battered root, arachnoiditis, epidural tethering from scarring/fibrosis of post-operative tissue, or unrealistic patient expectations can cause this type of pain. Long term failures with return of the radicular pain years after the original surgery can be due to progression of the degenerative disease, often aggravated by disc

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space collapse, recurrent central or lateral stenosis or mechanical instability.

Two of the reasons for failure of the lumbar disc operation to provide lifelong relief symptoms are potentially amenable to new therapeutic considerations. Adhesive arachnoiditis and peridural fibrosis have been felt to be at least partially preventable at surgery, and some treatment options have recently become available for adhesive arachnoiditis[37,38]. By minimizing the contribution of these two modalities to poor or limited outcome after lumbar disc surgery it is hoped that better patient outcome and satisfaction can be obtained[22].

Adhesive arachnoiditis is an inflammatory reaction inside the dura of the pia-arachnoid membrane. It is radiographically diagnosed by matting of the nerve roots of the cauda equina. The patient experiences pain, which is poorly localized and is often described as burning, aching or stabbing. The pain may increase with walking or standing and limit the function of the individual. This is believed to be a lingering pathologic reaction of the nerves to the trauma they experienced from the disease process.

Peridural fibrosis is a reaction that occurs outside the dura and is a natural consequence of the normal healing process after lumbar disc surgery[39]. It has been reported to occur in 6%–24% of patients with failed low back surgery[40–42]. Clinically, the patient has a return of the lumbar or radicular pain[34,43,44]. Peridural fibrosis affects the normal neural dynamics of the exiting nerve root and ganglion by tethering them at the operative site. Normally the nerve root and ganglion slide as the spine and limbs move in activities. Although everyone has some component of peridural fibrosis after lumbar disc surgery, the quantity is variable. Furthermore, although there is a correlation of poorer outcome with increasing amounts of epidural scar, there remains a high degree of variability of the amount of discomfort with a particular amount of peridural fibrosis imaged. Root ischemia caused by tethering may be an important contributing cause for the generation of radicular pain[45–51]. Peridural fibrosis can be imaged with MRI and differentiated from recurrent disc material[42,52–62].

Re-operation of lumbar discs has shown that peridural fibrosis is well formed by four months post-operatively. This fibrosis is dense scar tissue and sharp dissection is often required to mobilize the traversing nerve root and dural sac. Often the nerve root is difficult to locate within the dense scar and thus subject to increased risk of intra-operative damage.

ASSOCIATION BETWEEN EPIDURAL FIBROSIS AND POST-OPERATIVE PAIN

A significant association has been shown between extensive scar as noted on post-operative MRI scans and clinical outcome. There is an increased activity related pain at 6 months ($p=0.02$) and an increased recurrent radicular pain ($p=0.02$, logistic regression)[57,63,64].

The formation of the epidural fibrosis is part of a natural healing process. Fibroblasts originate from the muscle tissue that was removed from the lumbar spinous processes and lamina. The formation of dense tissue is necessary for the healing of the muscle back onto the spinous process and lamina. When the spinal canal has been surgically opened and the ligamentum flavum resected, then the fibroblasts have access to the epidural space. Thus, fibrosis and tethering in the epidural space represent an anatomic spillover of the natural reaction to heal the muscle back onto the bony elements of the spine.

PAST TECHNIQUES TO MANAGE EPIDURAL FIBROSIS

Surgical techniques and various treatments to minimize epidural fibrosis have been discussed in the literature[28,30,31]. Minimally invasive surgery with a smaller incision and muscle dissection has been credited with minimizing epidural fibrosis. Limited manipulation and adequate hemostasis at surgery has been reported to decrease the amount of epidural fibrosis[65]. Lavage of epidural space to remove foreign material or toxins may also reduce it. Talc on gloves and cotton fibers from sponges have been shown to promote a more virulent reaction in the epidural space[66], while anti-inflammatory drugs of both nonsteroidal and steroidal forms have been credited in the literature[67–69] with causing a decrease in epidural fibrosis. Hemostatic agents[70] and mechanical barriers have been tried to lessen epidural fibrosis and some anecdotal reports of good results have been presented. Dissection in the epidural space with the CO_2 laser has been suggested to reduce epidural fibrosis[71].

Fat grafts were the first treatment tried for the prevention of epidural fibrosis after lumbar discectomy[72,73]. The fat was derived from the subcutaneous supply at the surgical incision site and placed over the dura at closing. The use of fat grafts is reported to reduce dural adhesions although it does not prevent the formation of epidural fibrosis[74–76]. Other reports did not support any clinical effectiveness in preventing symptomatic fibrosis[77,78] and fat grafts have been shown to be responsible for a cauda equina syndrome[77,79,80].

Various synthetic materials including Dacron®, Vicryl mesh[81], polyethylene oxide/polybutylene terephthalate[82], polylactic acid foam, Silastic®[83], sodium hyaluronate[84,85], and membranes have been surveyed in experimental models. The results were not considered positive enough to continue development. Gelfoam has been advocated as a covering sheet for the dura but it enhances scar formation and has not been shown to prevent epidural fibrosis.

Polytetrafluoroethylene has been reported to function as an interpositional membrane after lumbar laminectomy in a canine model and compared favorably to fat grafts, Silastic sheeting and nonimplanted control animals[86]. The polytetrafluoroethylene was implanted in 10 humans after lumbar discectomy and compared with 10 nonimplanted patients on post-operative MRI at three and six months. The implanted patients had far less epidural scarring noticed than the control patients[87].

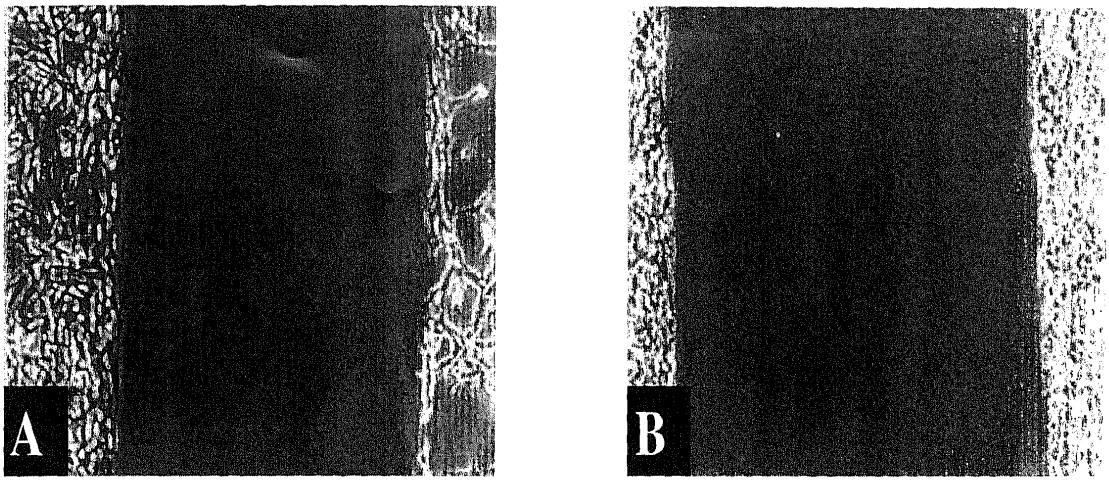


Figure 1: *In vitro* strip assay results in cell culture demonstrates that fibroblasts do not grow into the area where the test substance was placed at **A:** 24 h and **B:** 72 h

Clinical trials to show efficacy of this membrane in clinical outcome have not been performed.

Re-operation and surgical decompression of the tethered nerve root have only a limited role[21,88]. Although the fibrosis can be surgically removed, it often reforms with tethering of the nerve root within weeks and the patient again experiences the same pre-operative pain. Unless a treatable cause for the production and growth of the epidural fibrosis[28,30] is apparent, such as pars inter-articularis fractures, pseud-arthrosis, segmental instability, or nerve root compression by mass effect, it is probably best not to attempt scar lysis.

None of these methods has been shown in a prospective clinical study to be effective. Although many of these factors have been shown to increase the epidural fibrosis when not handled properly, it does not follow that minimizing them will eliminate the fibrosis.

ADCON®-L TO PREVENT EPIDURAL FIBROSIS

Prevention of epidural fibrosis has been unsuccessful and unproven until the recent investigations with ADCON®-L[89–91]. ADCON®-L is a bioresorbable mechanical barrier to peridural scar. It is biologically active and blocks the ingrowth of fibroblasts from the surgically detached muscle. The gel is absorbed in about one month. The gel consistency allows it to achieve coverage of the neurological structures and remain in place. It is placed in the surgical wound covering all sides of the dura and accessible nerve root just prior to closing. The application of ADCON®-L typically takes only 2 to 3 minutes and is done only after immaculate hemostasis is achieved. The gel is composed of absorbable gelatin, USP; polyglycan ester; and buffered saline.

In Vitro stripe assay in cell culture (*Figure 1*) demonstrated that fibroblasts had not grown into the area where the test substance was placed at 24 and 72 h. A pre-clinical rat laminectomy model was conducted to study the effect of ADCON®-L at the operative site. It was noted that the surgical site with ADCON®-L was similar to an unoperated site, whereas the site without ADCON®-L had dense fibrotic tissue covering the dural and exiting nerve root (*Figure 2*)[92,93]. The proposed mechanism of action of ADCON®-L is to form a barrier to the migrating fibroblasts and prevent them from invading the epidural space, and hence producing epidural scarring (*Figure 3*).

The outcome after lumbar discectomy can potentially be improved by therapy on one of the mechanisms of failure. A hypothesis was made early in the development of ADCON®-L that epidural fibrosis was an important factor in patients with continued discomfort after lumbar disc surgery. The proposed clinical trials were prospective randomized studies comparing current best available care to the same with the addition of ADCON®-L over the dura and nerve root just before closing. In the study the patient and the examiners were masked as to treatment group. The surgeon was obviously not masked as to whether ADCON®-L was inserted into the surgical wound. The two groups had identical medical and surgical treatment except for the use of ADCON®-L. Any statistically significant differences in outcome between the two groups would be attributed to the use of ADCON®-L. An intent to treat type analysis was pre-specified for the statistical analysis of the data.

The treatment with ADCON®-L is a prophylactic regimen. It is not known pre-operatively which patients will develop extensive epidural fibrosis or which of these will be symptomatic. The regimen thus involves giving the treatment to all patients and then analyzing the outcomes to see which group did better on the average. Prophylactic treatment regimens are currently used in spinal surgery patients for infection and deep venous thrombosis. In these instance it is not known which patients will develop an infection or pulmonary embolus, so all patients are treated to decrease the incidence. Thus, the prophylactic treatment for epidural fibrosis is an extension of currently accepted medical logic to decrease the incidence of a poor outcome by a specific mechanism.

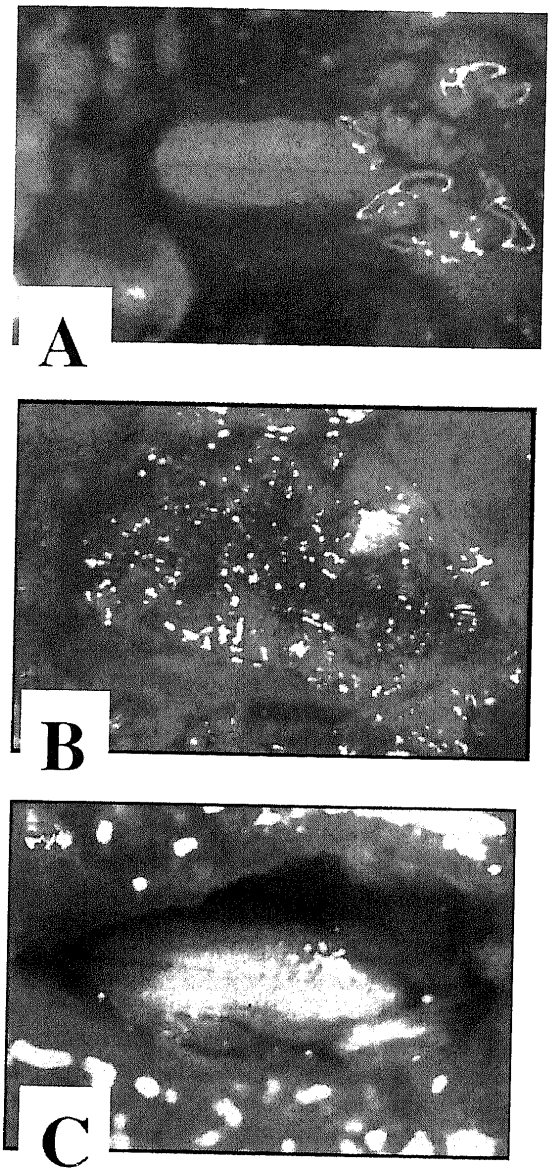


Figure 2: A preclinical rat laminectomy model demonstrates the effect of ADCON®-L at the operative site. **A:** Initial surgery. **B:** Two weeks post-operative the surgical site without ADCON®-L had dense fibrotic tissue covering the dural and exiting nerve root, whereas **C:** two weeks post-operative the surgical site with ADCON®-L was similar to an unoperated site

ADCON®-L has been studied in two large prospective randomized multicenter trials, one in Europe and the other in the United States. There are also a limited number of observations at re-operation to correlate with animal studies.

The clinical design of the studies was prospective, randomized, controlled, double-masked, and multi-center. The studies were planned with a committee of physicians (Drs Green, Grossman, Hardy, van Alphen, Yuan, Long, Robertson, Spencer, deTribolet, and Gratzl). Initial follow-up period was pre-planned to be six months and was later extended to 12 months because of a request from the USFDA. Maintenance of good clinical practice, review by the individual IRB/ethics committee and obtained patient informed consent were all done.

The pivotal study was conducted in nine European centers for six months and extended to include a post-study surveillance consisting of 12 month follow up. The second study was conducted at 16 spinal surgery centers in the United States, with a similar design to the European pivotal study. Interim data is available for analysis at this time. This second study was to confirm the results of the European pivotal study and provide additional clinical outcome information on patients after lumbar discectomies. The participating centers in these two studies are listed in *Tables 1* and *2* for Europe and the United States respectively.

The inclusion criteria were: first time lumbar surgery; herniated disc at L4/L5 or L5/S1; single level, unilateral (excluding far lateral) disc herniation; MRI consistent with the presenting clinical pattern; failure to resolve the clinical symptoms with conservative treatment, and requirement for immediate surgical decompression. The exclusion criteria were: previous lumbar surgery or chemonucleolysis; other significant spinal pathology; peridural steroids within four weeks prior to surgery, and the occurrence of an intra-operative dural rent.

A total of 298 patients between 17 and 60 years old were randomized in the pivotal study (147 randomized to ADCON®-L and 151 to best standard treatment–control). The patients were evaluated with clinical visits at 1, 3, and 6 months after surgery. Details of the patient demographic characteristics are listed in *Table 3*. No

Table 1: Clinical investigators in the European study

Nicholas de Tribolet, MD	Centre Hospitalier Universitaire Vaudois	Lausanne, Switzerland
François Porchet, MD	Centre Hospitalier Universitaire Vaudois	Lausanne, Switzerland
Thomas W. Lutz, MD	Kantonsspital Basel	Basel, Switzerland
Otmar Gratzl, MD	Kantonsspital Basel	Basel, Switzerland
Jacques Brotchi, MD	Hôpital Universitaire Erasme	Bruxelles, Belgium
H. August van Alphen, MD	Academisch Ziekenhuis Vrije Universiteit	Amsterdam, The Netherlands
Robert E. H. van Acker, MD	St. Lucas Ziekenhuis	Amsterdam, The Netherlands
Arnaldo Benini, MD	Kantonsspital St. Gallen	St. Gallen, Switzerland
Kevin N. Strommer, MD	Universitätsspital	Zürich, Switzerland
René L. Bernays, MD	Universitätsspital	Zürich, Switzerland
Jan Goffin, MD	Universitair Ziekenhuis Gasthuisberg	Leuven, Belgium
E. Augustus M. Beuls, MD	Academisch Ziekenhuis Maastricht	Maastricht, The Netherlands

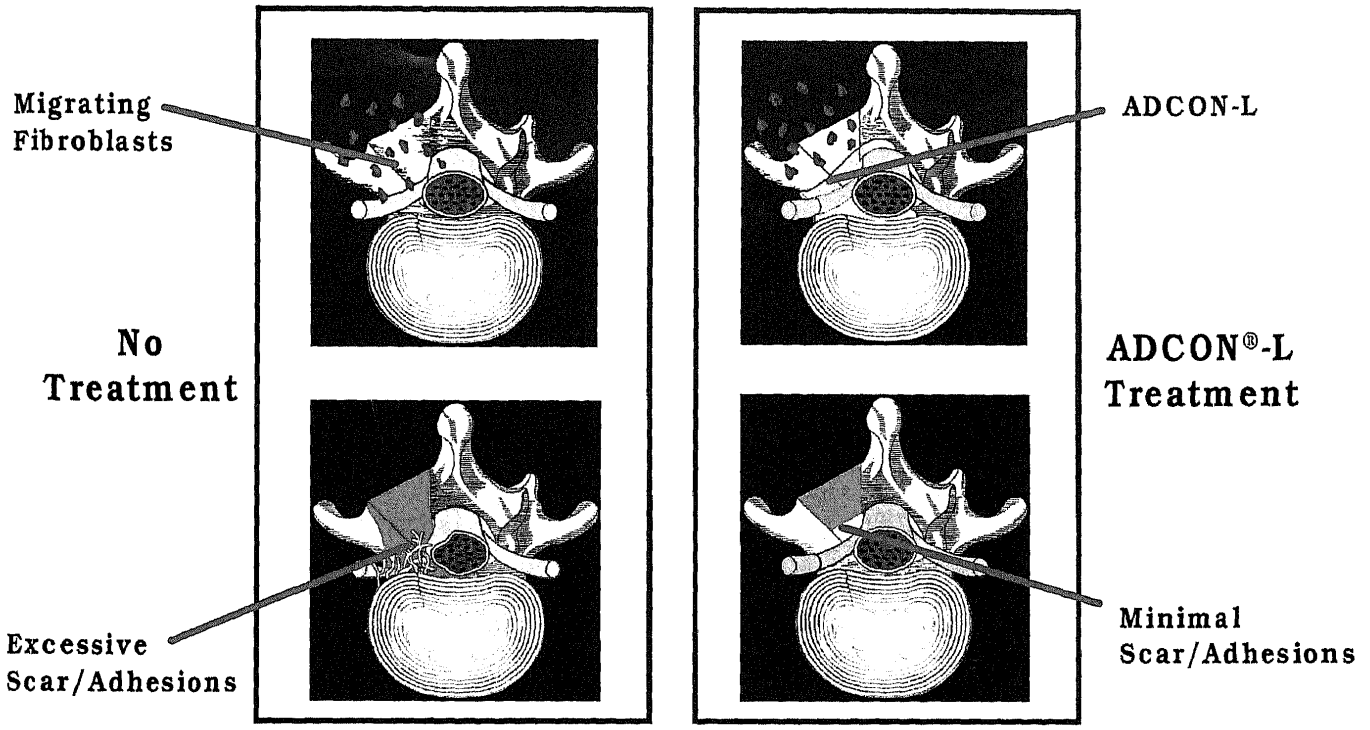


Figure 3: The proposed mechanism of action of ADCON®-L is to form a barrier to the migrating fibroblasts and prevent them from invading the epidural space, and hence producing epidural scarring

Table 2: Clinical investigators in the United States study

Edward Aulisi, MD	The Neurological Surgery Group	Rockville, MD
Stewart B. Dunsker, MD	Mayfield Neurological Institute	Cincinnati, OH
Jerry Engelberg, MD	University of Tennessee Health Sciences	Memphis, TN
Frederick Finger, MD	Presbyterian Hospital	Charlotte, NC
Fred H. Geisler, MD, PhD	Chicago Institute for Neurosurgery and Neuroresearch	Chicago, IL
Barth A. Green, MD	University of Miami	Miami, FL
Richard D. Guyer, MD	Institute for Spine and Biomedical Research	Plano, TX
Russell Hardy, MD	University Hospitals of Cleveland	Cleveland, OH
Donald Johnson, MD	Carolina Spine Institute	Mt. Pleasant, SC
Donlin M. Long, MD, PhD	Johns Hopkins Medical Institutions	Baltimore, MD
Joseph Maroon, MD	Allegheny General Hospital	Pittsburgh, PA
Joseph H. Miller, MD	University of Tennessee Health Sciences	Memphis, TN
Gerald Schell, MD	Field Neurosciences Institute	Saginaw, MI
David L. Spencer, MD	Lutheran General Spine Center	Park Ridge, IL
Robert Tiel, MD	LSU School of Medicine	New Orleans, LA
Hansen A. Yuan, MD	SUNY Health Sciences Center	Syracuse, NY

noteworthy difference between the two treatment groups was noticed in these baseline characteristics. The United States study had an interim analysis with 114 patients randomized to the ADCON®-L treatment group and 109 patients randomized to the control group.

MRI imaging at 6 months after the lumbar surgery in the pivotal study assessed the peridural post-operative scar. A single masked neuroradiologist scored the MRI scans using a standardized protocol. The MRI series consisted of five contiguous nonoverlapping 4 mm scans centered on the operated inter-vertebral space. Each of the three middle MRI slices was divided into four spatial quadrants centered on the thecal sac for a total of 12 quadrants. This protocol rated the amount of epidural fibrosis on a five-point ordinal scale in four quadrants as shown diagrammatically in *Figure 4*. *Figure 5* shows two examples of the scoring of two separate patients with scores of 1 and 4. The highest of these scores was used to represent the patient's overall epidural fibrosis parameter for statistical analysis. Thus, each patient only contributed one value to the analysis. If all four values for each patient were used in the statistical

Table 3: Patient characteristics (pivotal European study—evaluable patients)

Characteristic	Treatment group		p-value
	ADCON-L ($n=128$)	Control ($n=141$)	
Gender (Number (%))			1.0[a]
Male	79 (62%)	88 (62%)	
Female	49 (38%)	53 (38%)	
Age (years)			
Mean (standard deviation)	38.2 (10)	39.9 (9)	0.13[b]
Pre-operative clinical signs (Mean (SD))			
Radicular pain[c]	7.8 (2)	8.0 (2)	0.40[b]
Low back pain[c]	6.0 (3)	5.4 (3)	0.10[b]
SLR[d] angle (degrees)	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 (%))			0.95[a]
Laminectomy	2 (2%)	4 (3%)	
Laminotomy	22 (17%)	25 (18%)	
Hemilaminectomy	49 (38%)	53 (38%)	
Hemilaminotomy	55 (43%)	58 (41%)	
Other (Foraminotomy)	0 (0%)	1 (1%)	
Disc pathology (Number (%))			0.27[a]
Sequestration	57 (44%)	53 (38%)	
Extrusion	43 (34%)	61 (43%)	
Protrusion	28 (22%)	27 (19%)	

[a] Two-tailed test for comparison of distributions between treatment groups.
[b] Two-tailed *t*-test for comparison of means between treatment groups.
[c] Visual analogue scale (0–10 cm).
[d] Straight leg raise.

analysis, the number of samples would be higher by a factor of four. Standard statistical techniques require that each patient be represented only once, otherwise correlated samples rather than independent ones would be in the data set. If this had been done, the statistical inferences would not be correct. One global scar value or index has to be assigned to each patient before statistical analysis so that the statistical inferences in standard tests would be valid.

The scar was also evaluated at re-operation on both visual and tactile scores of four point ordinal scale. This was rated at several epidural locations.

The clinical assessment of outcome after lumbar discectomy was performed at six months post-operatively in the European and the United States studies. This assessment consisted of:

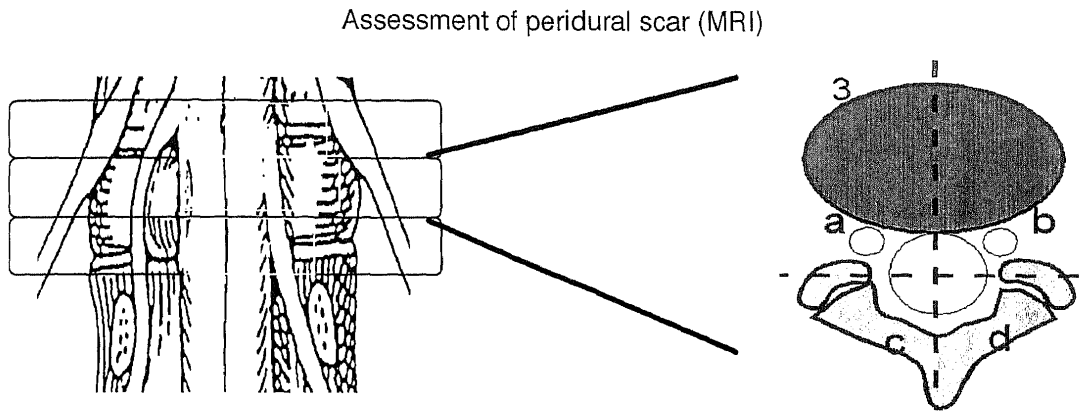
1. A visual analog pain scale on a 0 to 10 scale;
2. Johns Hopkins activity-related pain questionnaire;
3. The Roland Morris Disability Questionnaire.

Cataloging adverse events and monitoring re-operations comprised the safety assessment.

The therapeutic index of any drug or device is decided by comparing the risks to the benefits. The risks include adverse effects and potential problems with the device at insertion or absorption; effects of the presence of the device; and reaction to the absorption process or elimination of the breakdown products of the device. Details of the adverse events for the European pivotal study and United States study separated by treatment group are presented in *Table 4* and *Table 5* respectively. *Table 6* is a summary of the two studies and the post-study surveillance of the European study. Note that there are no noteworthy differences in the safety information or adverse events between ADCON®-L and control groups.

The surgical re-operation cases are listed in *Table 7* and *Table 8* for the European and United States study respectively. Note that there are no noteworthy differences between the treatment and control groups in either of the studies.

The pivotal European study had the five point MRI scar quality distribution assessed at 6 and 12 months post-operatively; the results are listed in *Table 9*. The treatment groups were compared using the Cochran–Mantel–Haenszel procedure stratified by center. Note the highly significant *p*-values ($p=0.010$) at both the 6 and 12 month follow up in the evaluable patients. This data was also examined with the scar qualified as non-extensive ($\leq 75\%$) and extensive ($>75\%$). The control group had 50% nonextensive and 50% extensive scar, whereas the ADCON®-L treatment group had 62%



Grade	Scar score	Percent of quadrant
Minimal	0	None/trace
	1	≤25%
Moderate	2	>25% and ≤50%
	3	>50% and ≤75%
Extensive	4	>75%

Figure 4: Assessment of peridural scar (MRI). Three MRI slices centered at the disc space were divided into four spatial quadrants centered on the thecal sac for a total of twelve quadrants. This protocol rated the amount of epidural fibrosis on a five-point ordinal scale in four quadrants

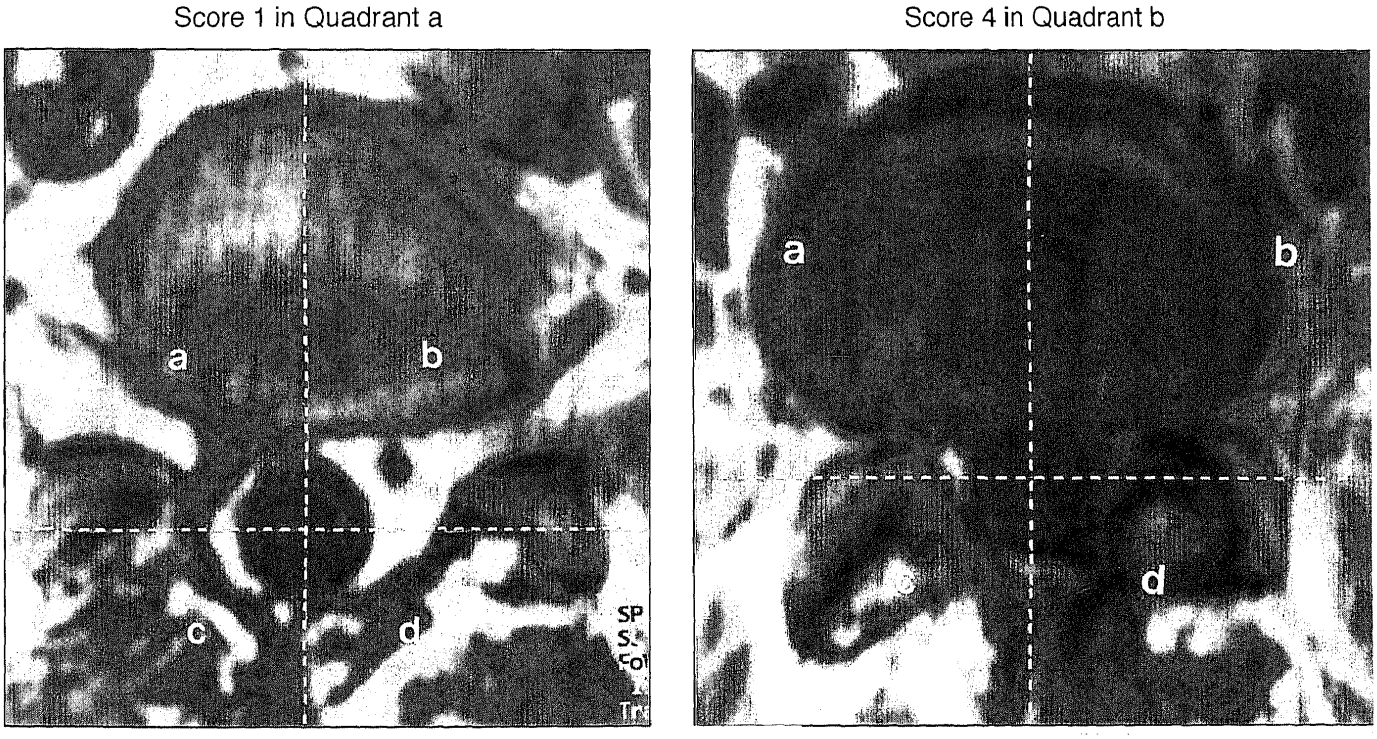


Figure 5: MRI scan slices for two examples of the scoring of two separate patients with scores of 1 and 4. The highest of these scores was used to represent the patient's overall epidural fibrosis parameter for statistical analysis

nonextensive and 38% extensive scar (*Figure 6*). The Cochran–Mantel–Haenszel procedure stratified by center analysis is also highly significant ($p=0.03$). A similar analysis for the 12 month data is presented in *Figure 7*. It is also highly statistically significant with $p=0.03$. The maximum scar may best correlate with the clinical symptoms.

The United States study had an interim analysis performed after 114 patients were randomized to the ADCON®-L treatment group and 109 patients rando-

Table 4: Adverse events (cumulative) experienced by *1% of either ADCON-L-treated or Control patients through 6 and 12 months—pivotal European clinical study

	6 Months			12 Months		
Event description	ADCON-L ($n=147$)	Control ($n=151$)	p-value*	ADCON-L ($n=147$)	Control ($n=151$)	p-value*
Redness	30 (20.4%)	39 (25.8%)	0.28	30 (20.4%)	39 (25.8%)	0.28
Swelling	23 (15.6%)	30 (19.9%)	0.37	23 (15.6%)	30 (19.9%)	0.37
Motor deficit	12 (8.2%)	12 (7.9%)	1.00	12 (8.2%)	13 (8.6%)	1.00
Tenderness	12 (8.2%)	11 (7.3%)	0.83	12 (8.2%)	11 (7.3%)	0.83
Sensory deficit	10 (6.8%)	16 (10.6%)	0.31	11 (7.5%)	17 (11.3%)	0.32
New or increased radiculitis	8 (5.4%)	10 (6.6%)	0.81	10 (6.8%)	12 (7.9%)	0.83
Back spasm	8 (5.4%)	8 (5.3%)	1.00	9 (6.1%)	9 (6.0%)	1.00
Headache	4 (2.7%)	1 (0.7%)	0.21	7 (4.8%)	3 (2.0%)	0.21
Temperature spike	1 (0.7%)	0 (0.0%)	0.49	2 (1.4%)	0 (0.0%)	0.24
Pseudo-meningocele	2 (1.4%)	0 (0.0%)	0.24	2 (1.4%)	0 (0.0%)	0.24
Wound infection	0 (0.0%)	2 (1.3%)	0.50	0 (0.0%)	2 (1.3%)	0.50
Skin rash	1 (0.7%)	1 (0.7%)	1.00	1 (0.7%)	2 (1.3%)	1.00
Deep thrombophlebitis	0 (0.0%)	2 (1.3%)	0.50	0 (0.0%)	2 (1.3%)	0.50

*Two-tailed Fisher's Exact Test
Adverse events experienced by less than 1% of the study group at 6 and 12 months included: (ADCON-L) bowel deficit, cauda equina syndrome, peridural hematoma, wound necrosis, transient alopecia, and (Control) septicemia, shock, disc space infection, wound necrosis, pulmonary embolism, wound keloid, and wound dehiscence.

Table 5: Adverse events (cumulative) experienced by *1% of either ADCON-L-treated or Control patients. US study at 6 months

Event description	ADCON-L ($n=114$)	Control ($n=109$)	p-value*
Sciatica	4 (3.5%)	4 (3.7%)	1.00
Spasm	3 (2.6%)	2 (1.8%)	1.00
Low back pain	3 (2.6%)	6 (5.5%)	0.32
Wound infection	2 (1.8%)	3 (2.8%)	0.68
Numbness	2 (1.8%)	1 (0.9%)	1.00
Cerebrospinal fluid leak	2 (1.8%)	0 (0.0%)	0.50
Urinary tract infection	1 (0.9%)	2 (1.8%)	0.62

*Two-tailed Fisher's Exact Test
Adverse events experienced by less than 1% of the study group at 6 months included: (ADCON-L) elevated temperature, headaches, urinary retention, wound pain, and (Control) allergic reaction, insomnia, lower extremity pain, numbness, urinary retention and weakness.

Table 6: Summary of the ADCON®-L safety data in the three clinical studies performed to date. Note that there are no significant differences between the treatment and control groups

	Incidence of adverse events by treatment group	
Clinical study	ADCON®-L	Control
Pivotal study (6 months)	35%	39%
US interim (6 months)	37%	40%
Post-study surveillance (12 months)	40%	44%

Table 7: Surgical reinterventions (pivotal European study)

Reason for re-operation	ADCON-L ($n=147$)	Control ($n=151$)	p-value*
Re-herniation at same level	7 (5%)	3 (2%)	0.21
Disc fragments	4 (3%)	1 (1%)	0.21
Other[a]	1 (1%)	4 (3%)	0.37
Total	12	8	0.36

*Two-tailed Fisher's Exact Test.
[a]ADCON-L: hip problem; Control: negative re-exploration for persistent, worsened pain (1), extreme fibrosis (1), spinal stenosis at a different level (1), herniation at a different level (1).

mized to the control group. The data for the United States interim analysis of the distribution of scarring by MRI criteria is presented in *Table 10.* A similar analysis as performed on the European data is highly significant, $p=0.03$, for the Cochran–Mantel–Haenszel procedure stratified by center. *Figure 8* shows the analysis separated by extensive *vs.* nonextensive scan on MRI. Again notice the highly significant $p=0.006$ for the Cochran–Mantel–Haenszel procedure stratified by center.

It is notable that the statistical analysis demonstrating decreased scar with ADCON®-L treatment is not dependent on:

1. The study;
2. The time of follow up;
3. Which of the two MRI scar score analysis scheme is used.

This uniformity in the statistical analysis of the data provides a high level of confidence in the results.

The scar density noted at re-operation was rated as no/minimal adhesions or firm adhesions and is shown in *Table 11.* The surgeons scored the scar on the nerve root and anterior to the dura sac. Typical epidural scarring both with and without ADCON®-L treatment is shown in *Figures 9* and *10* respectively. Note that with ADCON®-L treatment the epidural surgical planes are similar to the previously unoperated procedure. However, in cases without ADCON®-L treatment, dense epidural scarring is encountered. This requires a larger dissection to determine landmarks as well as sharp dissection, which potentially places the nerve root at greater risk of damage.

Table 8: Surgical reinterventions (US study)

Reason for re-operation	ADCON-L ($n=114$)	Control ($n=109$)	p-value*
Re-herniation at same level	3 (3%)	1 (1%)	0.62
Disc fragments	3 (3%)	2 (2%)	1.00
Total	6	3	0.32

*Two-tailed Fisher's Exact Test.

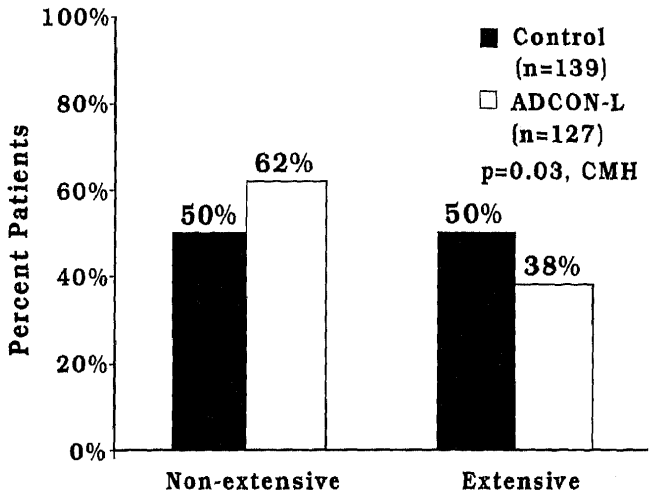


Figure 6: The pivotal European study assessed at 6 months post-operatively with the scar qualified as non-extensive ($\leq 75\%$) and extensive ($>75\%$). The control group had 50% nonextensive and 50% extensive scar, whereas the ADCON®-L treatment group had 62% nonextensive and 38% extensive scar. The Cochran–Mantel–Haenszel procedure stratified by center analysis is also highly significant ($p=0.03$)

Table 9: Distribution of scarring at 6 and 12 months (pivotal European study—evaluable patients)

Extent of scar[a]	None	0% to ≤25%	>25% to ≤50%	>50% to ≤75%	>75% to 100%	p-value[b]
6 months[c]						0.01
Control	1%	3%	17%	29%	50%	
ADCON-L	3%	10%	13%	36%	38%	
12 months[d]						0.01
Control	0%	9%	22%	28%	41%	
ADCON-L	4%	11%	26%	31%	28%	

[a] Most extensive scar on any of the 12 quadrants on the MRI scan.
[b] Two-tailed test for comparison of distributions between treatment groups using the Cochran–Mantel–Haenszel procedure stratified by center.
[c] There were 127 patients in the ADCON-L group, and 139 patients in the control group at 6 months.
[d] There were 116 patients in the ADCON-L group, and 130 patients in the control group at 12 months.

Table 10: Distribution of scarring at 6 months (US study—evaluable patients)

Extent of scar[a]	None	0% to ≤25%	>25% to ≤50%	>50% to ≤75%	>75% to 100%	p-value[b]
Control ($n=65$)	0%	3%	6%	14%	77%	0.03
ADCON-L ($n=76$)	0%	5%	11%	30%	54%	

[a] Most extensive scar on any of the twelve quadrants on the MRI scan.
[b] Two-tailed test for comparison of distributions between treatment groups using the Cochran–Mantel–Haenszel procedure stratified by center.

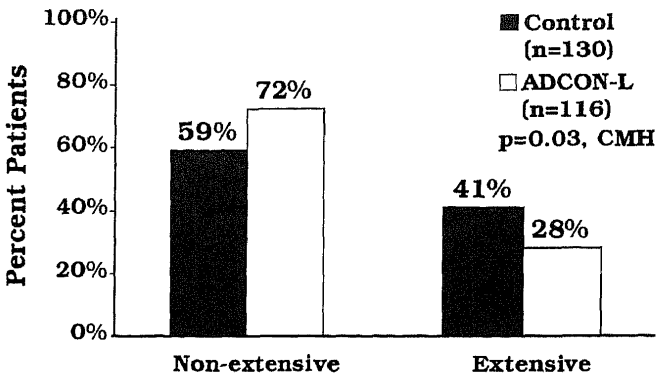


Figure 7: The pivotal European study assessed at 12 months post-operatively with the scar qualified as nonextensive ($\leq 75\%$) and extensive ($> 75\%$). The control group had 59% nonextensive and 41% extensive scar, whereas the ADCON®-L treatment group had 72% nonextensive and 28% extensive scar. The Cochran–Mantel–Haenszel procedure stratified by center analysis is also highly significant ($p = 0.03$)

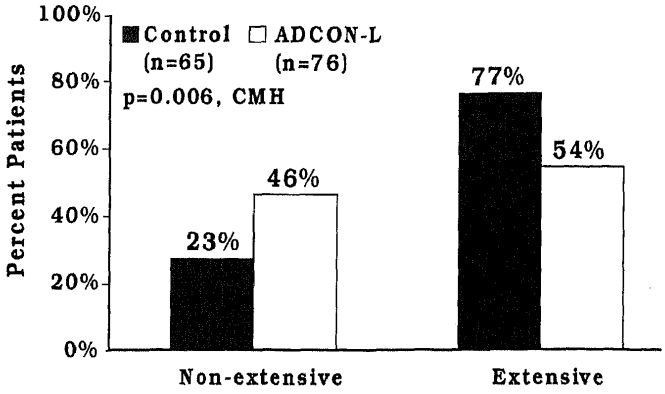


Figure 8: The United States study interim analysis assessed at 6 months post-operatively with the scar qualified as nonextensive ($\leq 75\%$) and extensive ($> 75\%$). The control group had 23% nonextensive and 77% extensive scar, whereas the ADCON®-L treatment group had 46% nonextensive and 54% extensive scar. The Cochran–Mantel–Haenszel procedure stratified by center analysis is also highly significant ($p = 0.006$)

Table 11: Scar observed at re-operation by the surgeon. The differences between no/minimal and firm adhesions are compared for the ADCON®-L and control groups at the nerve root and anterior to the dural sac

	No/minimal adhesions		Firm adhesions	
Scar location	Control	ADCON®-L	Control	ADCON®-L
Nerve root	33%	82%	33%	0%
Anterior	33%	73%	17%	9%

Table 12: Weighted activity-related pain scores[a] (pivotal European study at 6 months)

	ADCON-L	Control	*p*-value[b]
Pre-operative baseline mean score	2.49 ($n=128$)	2.52 ($n=141$)	0.74
Mean score after treatment	1.24 ($n=88$)[c]	1.58 ($n=84$)[c]	0.03
Percent of improvement from baseline[d]	50%	37%	

[a] Linear combinations based on National Low Back Pain Study (US) (BenDebba M, *et al.* A Simple Procedure for Assessing the Impact of Low Back Pain on Activities of Daily Living, 8th World Congress on Pain 58, 1996). Weighted sum of activities that caused an increase in pain. Maximum total score is 3.2. Activities included bending, riding/driving in a car, sitting *15 min, sitting >15 min, and lifting heavy objects >10 lbs.
[b] Two-tailed *t*-test for comparison of means between treatment groups.
[c] Excluding patients who did not have pain at 6 months.
[d] Percent of improvement from baseline equals (pre-operative baseline mean score minus mean score after treatment) divided by the pre-operative baseline score times 100.

The clinical outcome in the pivotal European study was assessed at 6 months with the weighted activity-related pain scores (*Table 12*). Note that the two groups had been equal at baseline but were now significantly different ($p = 0.03$) favoring better outcome in the ADCON®-L treatment group. Note also that there was an overall 50% improvement from baseline in the ADCON®-L treatment group and only a 37% change in the control group. The ADCON®-L treatment group had a benefit over the control group in five individual activities in the activity-related pain scale:

1. On riding in or driving a car ≥ 20 minutes by 44%;
2. Sitting ≤ 15 minutes by 44%;
3. Lifting objects > 10 pounds by 15%;
4. Sitting > 15 minutes by 13%;
5. Bending forward by 8%.

The United States interim analysis compared clinical outcome with the Roland–Morris score and is presented in *Table 13*. This is a disability questionnaire composed

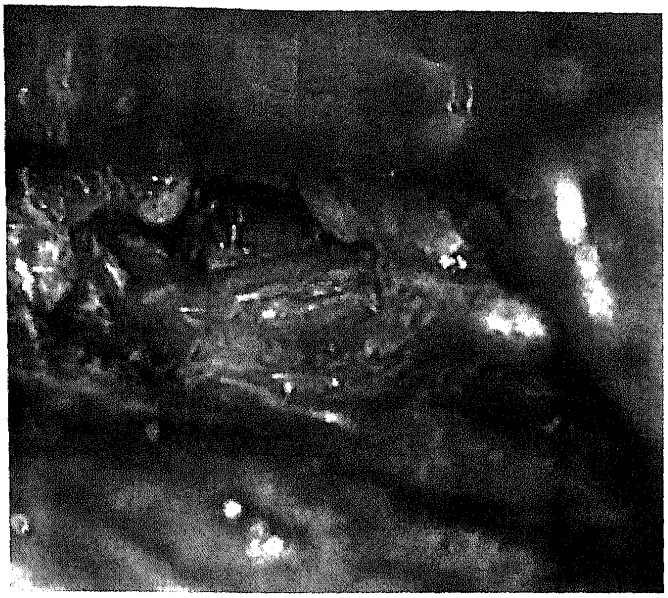


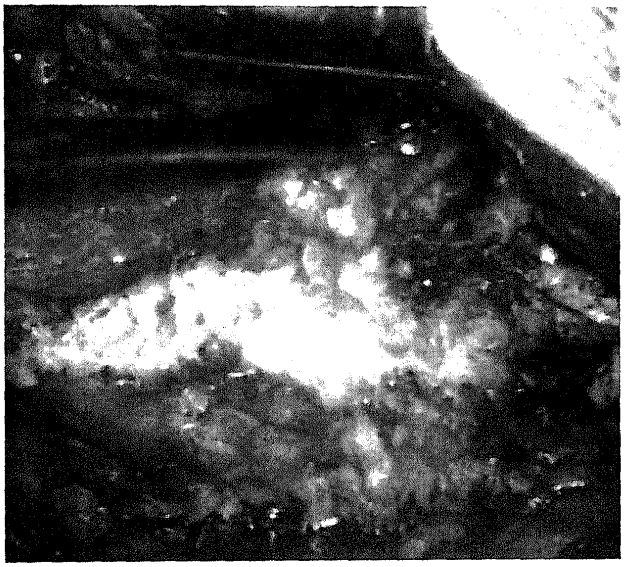
Figure 9: Typical epidural scarring at re-operation with ADCON®-L treatment at the first surgery. This 42-year-old male required a second discectomy 12 weeks after the first discectomy. At surgery no residual ADCON®-L was noticed and no adhesions to the nerve root or dura were noticed. Note the near normal tissue planes that are present with obvious position of the nerve root and dural sac. First operation: Right L5–S1 microdiscectomy with application of ADCON®-L; uneventful for 6 weeks; complaint of right recurrent sciatic pain; MRI shows recurrent disc hernia. Second operation: Twelve weeks post-discectomy; repeat microsurgery for recurrent disc hernia; no residual ADCON®-L; loose areolar connective tissue, non-adhesive to the nerve root and dura; right L5 nerve root easy to dissect

of 24 statements that describe typical ways in which symptoms may interfere with daily activities, work and recreation. An asymptomatic patient would have a score of 0 and a maximally affected patient would have a score of 24. The baseline score of the two groups are comparable but the mean score at 6 months follow up was significant ($p=0.03$) for an effect favoring ADCON®-L. This represented a 42% relative improvement in the ADCON®-L group *vs.* the control group. The ADCON®-L group had an 85% improvement from the baseline value.

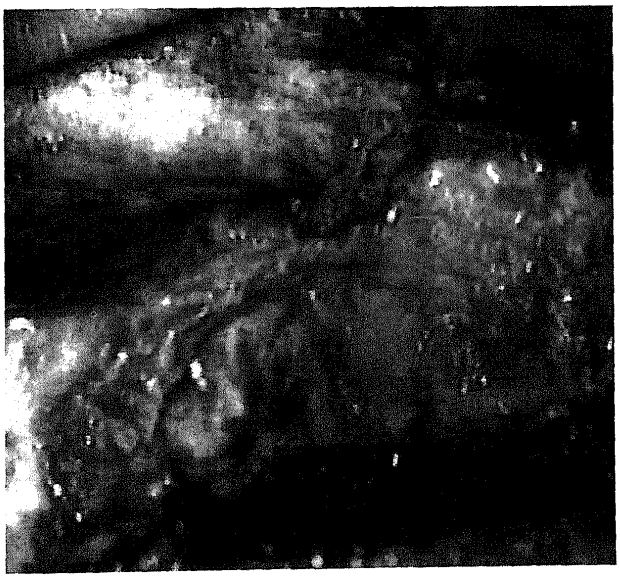
The European study monitored the percentage of patients with an improvement in the angle of the straight leg raising test. These results are presented in *Figure 11* for the 1, 3 and 6 month values for both treatment groups and for both the ipsilateral and contralateral sites from the operation. Note that the ADCON®-L group and the control group on the operative side both make a major improvement, but that the ADCON®-L group at all times had outcomes superior to the control group. At 6 months 94% of the ADCON®-L group has an improvement in the straight leg angle as compared to 87% in the control group. This difference is statistically significant with a $p=0.024$ favoring better outcome in the ADCON®-L group. This translates to a 54% drop in failures to improve in the straight leg raising for the ADCON®-L group compared with the control group. Statistical improvement was also noted in the non-operative side favoring the ADCON®-L group ($p=0.015$).

CONCLUSION

The two studies have demonstrated a significant association between clinical outcome and control of extensive peridural scar with ADCON®-L adhesion control gel. The studies demonstrated an excellent safety



A



B

Figure 10: Typical epidural scarring encountered at re-operation without ADCON®-L treatment at the previous surgery. **A:** Third re-operation in a 46-year-old female performed eight months after her last operation. A far lateral approach was necessary with disruption of the articulating facet joint to obtain reliable landmarks. **B:** Second operation five months after a lumbar discectomy. Dense fibrous scar was encountered over the dura and nerve root. Sharp dissection was required and the nerve root embedded in the scar was difficult to identify

Table 13: Total Roland–Morris score[a] at 6 months (US study—evaluable patients)

	Treatment group		
Total Roland–Morris score	ADCON-L	Control	*p*-value[b]
Pre-operative baseline mean score	14.7 (5.5 SD[d]) ($n=114$)	15.2 (4.9 SD[d]) ($n=109$)	0.46
Mean after treatment at 6 months	2.2 (4.3 SD[d]) ($n=86$)	3.8 (5.4 SD[d]) ($n=74$)	0.03
Percent of improvement from baseline[c]	85%	75%	

[a] Roland–Morris Disability Questionnaire is composed of a questionnaire containing 24 statements that describe typical ways in which symptoms may interfere with daily activities, work and recreation. A patient who has absolutely no radiculopathy-related impairment would have a score of 0, and a maximally-affected patient would have a score of 24.
[b] Two-tailed test for comparison of means between treatment group (analysis of variance with treatment group and center as factors).
[c] Percent of improvement from baseline equals (pre-operative baseline mean score minus mean score after treatment at 6 months) divided by the pre-operative baseline mean score times 100.
[d] Standard deviation.

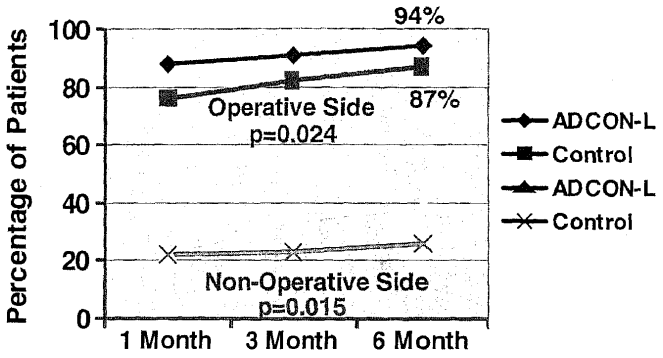


Figure 11: The pivotal European study monitored the percentage of patients with an improvement in the angle of the straight leg raising test for both treatment groups and for both the ipsilateral and contralateral sites from the operation. Note that the ADCON®-L group and the Control group on the operative side both make a major improvement, but that the ADCON®-L group at all times had outcomes superior to the Control group. At 6 months this difference is statistically significant with a $p=0.024$ favoring better outcome in the ADCON®-L group. Statistical improvement was also noted in the nonoperative side favoring the ADCON®-L group ($p=0.015$)

profile and significant improvement in outcome by both the reduction of scar imaged on MRI scan, and an enhanced function of the patient as assessed by the activity-related pain and the Roland–Morris scales. These results have been reproduced in two multi-center prospective randomized studies. With these results clinicians have, for the first time, a treatment for epidural fibrosis validated on a scientific basis. The results have also shown that epidural fibrosis is an important factor in those patients with less than excellent results after a lumbar discectomy.

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