Inhibition of epidural fibrosis with ADCON®-L: Effect on clinical outcome one year following re-operation for recurrent lumbar radiculopathy

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In a prospective multicenter study, 20 patients underwent re-operation for recurrent radiculopathy after lumbo–sacral discectomy, and were treated with ADCON®-L (Adhesion Control in a Barrier Gel) to inhibit epidural fibrosis following secondary surgery. Outcomes after re-operation were assessed at six and 12 months using: Visual Analog Scales to measure radicular and back pain, straight leg raising exams, and self-assessment of activity-related radicular pain. Each parameter was compared to baseline values, obtained immediately prior to the re-operation. The long term clinical results at 12 months after re-operation (summarized below) demonstrate a significant improvement of all clinical parameters, and correlated with the results seen at six months. Radicular pain, measured when most severe, was reduced from an average pre-operative score of 8.1–3.7 ($p < 0.005$). The straight leg raising angle increased from an average pre-operative value of 41°–67° ($p < 0.005$). Activity-related pain mean score was 4.6, vs. 17.0 pre-operatively ($p < 0.005$). Low back pain, measured when most severe, was reduced from an average pre-operative score of 6.1 to 3.1 ($p < 0.012$). These clinical findings compare very favorably with data reported in the literature. There were no adverse events or complications related to the use of ADCON®-L. [Neurol Res 1999; **21 Suppl 1**: S51–S60]

Keywords: Lumbar disc herniation; scar formation; Failed Back Surgery Syndrome; re-operation; recurrent disc herniation; outcome

INTRODUCTION

Recurrent radiculopathy is reported to occur in as many as 40% of patients who have undergone surgical treatment for primary lumbo–sacral disc herniation[1,2], and a diagnosis of Failed Back Surgery Syndrome (FBSS) is typically determined in these patients. When disabling sciatica and back pain recur after lumbar disc surgery, excessive epidural scar has been shown to play a key role in the etiopathogenesis of FBSS[2–13]. At present, conservative therapy has little to offer to these patients with FBSS[2,14], and the option of a secondary surgical procedure may be proposed to them. The incidence of re-operation following lumbo–sacral surgery is significant and ranges between 7% and 20%[14–17]. However, the prognosis after re-operation on patients diagnosed with FBSS is known to be less favorable than first-time surgery, particularly in same-side, same-level re-exposures, which represent approximately 50% of the cases[1,17]. In those patients where no clinical improvement has been obtained after repeat lumbar surgery, peridural scar or localized arachnoiditis are a typical finding[18]. By general consensus FBSS is, for this reason, considered to be a poor indication for repeat lumbo–sacral surgery.

The overall cost of disability inflicted by FBSS to society is immense; therefore, prevention of epidural scar formation (one of the factors causing FBSS) is a necessity[17,19]. ADCON®-L, Adhesion Control in a Barrier Gel, has been shown to inhibit epidural fibrosis in primary lumbar discectomy, resulting in improved post-operative outcome[20,21], and it has been proposed that ADCON®-L could afford a favorable outcome in re-operation patients.

The primary objective of this study was to evaluate the use of ADCON®-L gel in patients undergoing re-operation for recurrent radiculopathy following same-level lumbar disc surgery.

Moreover, the surgical outcome in those re-operated patients treated with ADCON®-L was compared with the post-operative results reported in patients not treated with ADCON®-L, as obtained through a meta-analysis of the literature. Finally, the correlation between clinical benefits obtained after using ADCON®-L at the time of the first surgery and the results of the re-operation series reported here are presented and discussed.

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Table 1: Investigational centers

Principal investigator	Institution	Location
I.K. Pople, FRCS	Frenchay Hospital	Bristol, UK
D. Lombardi, MD	Hôpital Cantonal Universitaire de Genève	Geneva, Switzerland
F. Porchet, MD	Centre Hospitalier Universitaire Vaudois	Lausanne, Switzerland
J. de Preux, MD	Hôpital Regional de Sion	Sion, Switzerland

Table 2: Patients' selection criteria

Inclusion	Exclusion
	Pre-operative
a. Same side, same level recurrent radiculopathy	a. Previous ADCON®-L application
b. Level: L4–L5 or L5–S1, unilateral	b. Spinal fusion, spinal instrumentation
c. Radicular pain > low back pain	c. Percutaneous nucleotomy, chemonucleolysis
d. SLR → radicular pain at ≤60°	d. Current or previous contra-lateral radiculopathy, if symptomatic within previous 12 months
e. Follow-up ≥6 months	e. Spondylolisthesis, instability, spondylitis, ankylosis, stenosis, rheumatoid arthritis, severe degenerative conditions
	f. Central neurologic condition, peripheral neuropathy
	g. Serious operative risk
	Intra-operative
	a. Incidental dural incision
	b. Discovery of spinal neoplasm, malformation, or infection
	c. Significant complication (e.g., anesthesia)

SLR = straight leg raising test

MATERIALS AND METHODS

Study population

This study was conducted at the neurosurgical departments of four investigational institutions, located in Switzerland and the UK (*Table 1*), according to the guidelines established by the local Ethics Committees. Patients experiencing recurrent radicular pain following a period of at least two months of relief after a lumbo–sacral discectomy procedure were screened at admission. Patients who required a surgical re-exploration at the same single level and side of the previously operated intervertebral space were considered for this trial, and subjected to careful selection criteria (*Table 2*). Standard pre-operative diagnostic studies were obtained to confirm one or more of the following suspected etiologies for the FBSS-related symptoms: true recurrent disc herniation, retained disc fragment, or moderate to severe epidural or periradicular fibrosis. All selected patients provided an informed consent.

Pre-operative evaluation

Prior to re-operation, all patients underwent a baseline evaluation, which included a self-assessment of their radicular and low back pain on 0–10 cm Visual Analog Pain Scales (VAPS), where '0' represents absence of pain, and '10' represents the most excruciating pain[22], each one in three degrees of intensity ('most severe', 'average', and 'least severe'); a straight leg raising (SLR) exam on the symptomatic leg (the angle at which radicular pain was produced was measured with a goniometer); and the administration of a Roland Morris Disability Questionnaire (RMDQ)[23] modified for self-assessment of activity-related radicular pain, which consists of 24 questions; one point was assigned to each question checked as 'yes', for a maximum score of 24 (*Table 3*).

Surgical procedures

Through a standard midline approach, a re-exposure of the operative site was performed under magnification, the degree of adherence of scar tissue to the dura, and its anatomical location were recorded. Other intra-operative findings pertaining to presence of a re-

Table 3: Modified Roland Morris disability questionnaire

1. I stay home most of the time because of my sciatica.
2. I change position frequently to try and get comfortable with my sciatica.
3. I walk more slowly than usual because of my sciatica.
4. Because of my sciatica, I am not doing any of the jobs that I usually do around the house.
5. Because of my sciatica, I use a handrail to get upstairs.
6. Because of my sciatica, I lie down to rest more often.
7. Because of my sciatica, I have to hold on to something to get out of an easy chair.
8. Because of my sciatica, I try to get other people to do things for me.
9. I get dressed more slowly than usual because of my sciatica.
10. I only stand up for short periods of time because of my sciatica.
11. Because of my sciatica, I try not to bend or kneel down.
12. I find it difficult to get out of a chair because of my sciatica.
13. My sciatica is bothersome almost all of the time.
14. I find it difficult to turn over in bed because of my sciatica.
15. My appetite is not very good because of my sciatica.
16. I have trouble putting on my socks (or hose) because of my sciatica.
17. I only walk short distances because of my sciatica.
18. I sleep less well because of my sciatica.
19. Because of my sciatica, I get dressed with help from someone else.
20. I sit down most of the day because of my sciatica.
21. I avoid heavy jobs around the house because of my sciatica.
22. Because of my sciatica, I am more irritable and bad tempered with people than usual.
23. Because of my sciatica, I go upstairs more slowly than usual.
24. I stay in bed most of the time because of my sciatica.

Table 4: Patients' general information before re-operation

	No. of cases	Mean	Range
Total patients	20		
Male	10		
Female	10		
Age (years)		38.1	28–47
Physical activity			
Heavy	6		
Moderate	5		
Light	3		
Sedentary lifestyle	6		
Level			
L4–L5	10		
L5–S1	10		
Time interval after			
Previous surgery		33 ± 16 months	2 months–27 years
Onset of symptomatology		6 ± 1 month	6 days–22 months

Table 5: Surgical data

	No. of cases	Mean	Range
Type of procedure			
Hemilaminectomy	5*		
Hemilaminotomy	5*		
Laminotomy	5		
Foraminotomy	4		
Facetectomy	1		
Intra-operative findings			
Extrusion contained by annulus fibrosus	10**		
Extrusion through annulus fibrosus	6		
Protrusion	2		
Free disc fragment	2		
Duration of re-exploration		97 ± 11 min	25–230 min

* In two cases, concurrent foraminotomy and/or facetectomy were performed.
** In one patient, a free disc fragment was also found under the posterior longitudinal ligament and removed. For intra-operative assessment of epidural scar, see text.

herniated disc, disc fragments, and/or only fibrosis at the site, were also noted. At the completion of surgery, hemostasis was attained and no other agent to prevent adhesions (e.g., fat grafts, steroids, fibrin glue, Vicryl™ mesh, or other materials) was permitted. ADCON®-L was applied in all the patients around the dura mater, nerve root, but not within the disc space, and the surgical wound was closed in a routine fashion.

Follow-up

All the subjects received standard care after re-operation; follow-up evaluations were conducted by a physician at six months and one year post-operatively. Each evaluation included: a standard neurological examination, with assessment of wound healing; a careful inquiry about any adverse events; an SLR exam; the VAPS rating of radicular and low back pain; and a modified self-assessment of activity-related radicular pain (RMDQ).

Statistical analysis

Parameters of clinical outcome following re-operation were statistically compared to the respective pre-operative baseline values using the paired Student's *t*-test, with a Type I error rate of 0.05.

RESULTS

General information

Patients' characteristics, types of surgical procedures performed, and findings at re-operation are summarized in *Tables 4* and *5*. The right side was involved in 11 patients and the left in nine. None of the study patients had received previous application of ADCON®-L at any time during their past surgical experience.

Intra-operative scar assessment

The description of epidural scar was available from 19 patients, showing that scar tissue was moderate to severe

Table 6: Mean visual analog scale scores for radicular pain

		Post-operative VAPS scores	
Intensity of pain	Pre-operative VAPS score	6 months	12 months
Least severe	4.9 ± 0.6 (20)	2.0 ± 0.5 (20) $p < 0.001$	2.2 ± 0.6 (16) $p < 0.005$
Average	6.7 ± 0.4 (19)	2.9 ± 0.5 (20) $p < 0.001$	2.9 ± 0.6 (16) $p < 0.001$
Most severe	8.1 ± 0.3 (20)	3.8 ± 0.6 (20) $p < 0.001$	3.7 ± 0.8 (16) $p < 0.001$

VAPS = visual analog pain scale. Values are expressed as mean ± standard error of the mean; number of evaluable patients is in parentheses. p values are obtained by comparing the results at follow-up with the pre-operative findings (Student's t-test).

Table 7: Radicular pain relief during post-operative outcome

	Post-operative time	
Pain intensity	6 months	12 months
Least	15/20 (75%)	11/16 (69%)
Average	17/19 (89%)	14/15 (93%)
Worst	17/20 (85%)	13/16 (81%)

Values express the number (or percentage) of patients who had improved visual analog pain scale scores.

Table 8: Straight leg raising exam mean values

	Post-operative (°)	
Pre-operative (°)	6 months	12 months
41.3 ± 2.7 (20)	65.2 ± 3.4 (20) $p < 0.001$	66.9 ± 4.3 (16) $p < 0.001$

Mean angles are expressed in degrees.

in 14 patients, within the dorsal region; in the lateral region, the dural sac appeared more or less adherent to the periosteum in 14 patients; in the anterior region, the adhesion between dural sac and posterior longitudinal ligament was moderate to firm in 16 patients; finally, scar tissue surrounding the emerging nerve root was found moderate to severe in 10 patients.

Measurement of outcome

Radicular pain

The mean VAPS score for radicular pain, when most severe, was significantly decreased by 4.3 points at six months, and by 4.4 points at one year ($p < 0.005$, for both time intervals; *Tables 6* and *7*).

SLR exam

On average, the results of SLR tests showed significant improvements both at the six-month assessment (by 23.9°), and at 12 months (by 25.6°), when compared to pre-operative baseline measurements ($p < 0.001$ for both time intervals; *Table 8*).

Table 9: Activity-related radicular pain mean scores

	Post-operative RMDQ scores	
Pre-operative RMDQ score	6 months	12 months
17.0 ± 0.8 (20)	5.5 ± 1.5 (19) $p < 0.001$	4.6 ± 1.9 (14) $p < 0.001$

Mean values are obtained from a modified Roland Morris Disability Questionnaire (RMDQ), where 24 daily activities are listed.

Activity-related radicular pain

The mean modified RMDQ scoring was significantly reduced by 11.5 points at six months, and by 12.4 points at one year ($p < 0.001$ for both time intervals; *Table 9*). The one-year results were available from 14 patients.

Low back pain

The mean VAPS score for low back pain, when most severe, was significantly decreased by 1.9 points at six months ($p < 0.05$), and by 2.8 points at one year ($p = 0.05$), as shown in *Table 10*.

Complications

Two patients had complications during their clinical course following re-operation. The first patient manifested signs of a recurrent right L4–L5 disc herniation and lumbar instability, which required a re-operation five-and-a-half months after the previous surgery. Remarkably, at the time of this re-exposure of the surgical site, no peridural scar was found with the exception of thin and filmy attachments in the ventral region. The dural sac was easily separated from the surrounding extra-dural tissues, and a free disc fragment which was found outside the PLL, had migrated caudally. The fragment was removed, and an intersomatic fusion at L4–L5 was performed; during the procedure, a cerebro spinal fluid leak occurred and was corrected. The post-operative course was uneventful, and the patient showed a significant functional improvement.

Table 10: Mean visual analog scale scores for low back pain

Intensity of pain	Pre-operative VAPS score	Post-operative VAPS scores	
		6 months	12 months
Least severe	3.8 ± 0.5 (20)	2.0 ± 0.5 (20) $p < 0.01$	2.0 ± 0.6 (16) $p < 0.05$
Average	5.0 ± 0.5 (19)	3.0 ± 0.5 (20) $p = 0.05$	2.4 ± 0.6 (16) $p = 0.05$
Most severe	6.1 ± 0.5 (20)	4.2 ± 0.7 (20) $p < 0.05$	3.1 ± 0.8 (16) $p = 0.05$

VAPS, visual analog pain scale. *p* values are obtained by comparing the results at follow-up with the pre-operative findings (Student's *t*-test).

Table 11: Average relief of radicular pain following lumbo–sacral disc re-operation: Meta-analysis

Authors	Year	N	Use of ADCON®-L	% of patients improved	
				6 months	12 months
North *et al.*[2]	1991	102	No	47%*	N/A
Silvers *et al.*[17]	1994	82	No	N/A	27%**
Present series	1998	20	Yes	89%	93%

N, Total number of patients. *Number of patients was not provided. **Actual mean follow-up time was 11 months; 'improvement' is defined by leg pain relief (excellent and good outcomes).

The second patient had a favorable recovery until 10 months after re-operation, when a sudden recurrence of radicular and back pain resulted from physical strain; the patient was re-admitted to the hospital, and diagnosed with recurrent right L4–L5 disc herniation (radiculography and CT scan). The patient refused the option of another surgical procedure.

Final overall assessment of clinical outcome

From this series, only three patients failed to show improvement in their radicular pain at the 12-month follow-up. In one of these patients, who also developed cervical pain, the lack of improvement was attributed to psycho–social factors. In a second case, the painful symptoms were not consistent with the objective neurological status which was normal, without neurological deficits or signs of irritative radiculopathy. In a third case, described above, radicular pain was the result of a recurrent disc herniation (the patient refused further surgery).

Outcome after lumbo-sacral re-operation without ADCON®-L

To determine the benefit afforded by ADCON®-L to patients re-operated for lumbo-sacral disc pathology, the results obtained from this study were compared with other similar clinical series where ADCON®-L was not used. From a meta-analysis of the relevant literature, few published reports were found to describe the clinical outcome following lumbo-sacral disc re-operation in sufficient detail, to be comparable with the present study. Two reported series[2,17], however, cover clinical data congruous with the results of this study, and are summarized in *Table 11* and *Figure 1*.

Comparison of present series with patients treated for primary lumbo-sacral discectomy

The post-operative results obtained in this series were compared with the one-year outcome observed in a large, prospective, controlled and randomized trial where 128 patients were treated with ADCON®-L at the time of primary lumbo-sacral discectomy[20].

If the post-operative outcome following application of the gel during primary discectomy is compared to the results obtained after re-operation, several common elements surface. The results from the SLR test are similar. A significant return of the test to normal values is observed at six months and maintained at one year following primary discectomy for both the primary surgery and re-operation clinical series.

As expected, the overall clinical improvement following re-operation, although significant, was not as positive as the outcome following primary discectomy (*Figure 2*). A similar finding is observed with the assessment of radicular pain (*Figure 3*).

The scores obtained from the modified RMDQ are also similar. The results observed six months post-operatively in this study are similar to those obtained in 88 patients treated with ADCON®-L at the time of their primary lumbo-sacral discectomy, from another controlled clinical trial[21] (*Figure 4*).

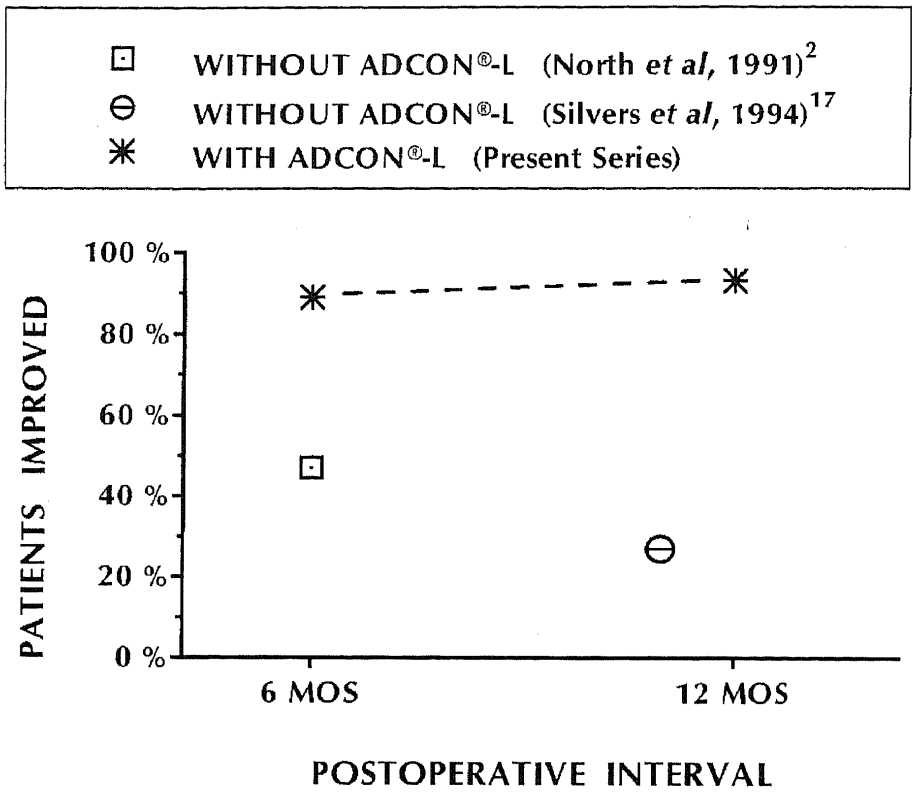

Figure 1: Radicular pain following lumbo–sacral disc re-operation: Outcome with and without ADCON®-L. The average post-operative follow-up in the series reported by Silvers *et al.* was 11 months

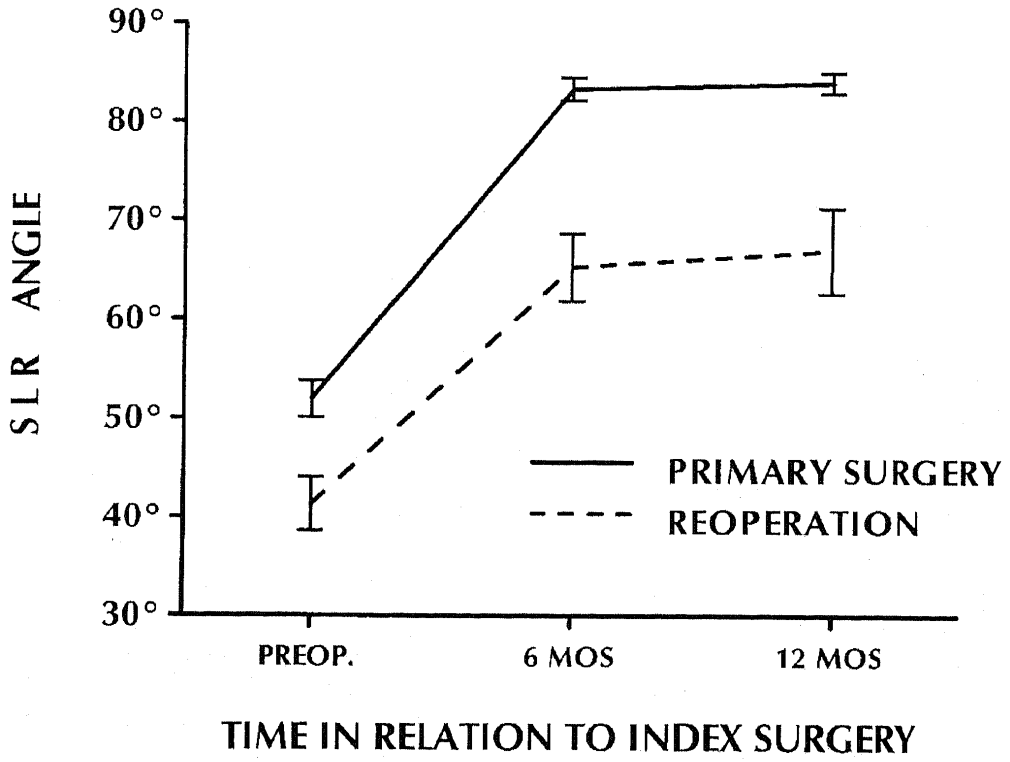

Figure 2: Outcome of Straight Leg Raising Exam after primary lumbo–sacral disc surgery *vs.* re-operation, with ADCON®-L. Primary surgery results are obtained from 128 patients treated with ADCON®-L (European Study; see text for details). Values are expressed as mean angle in degrees ± standard error of the mean

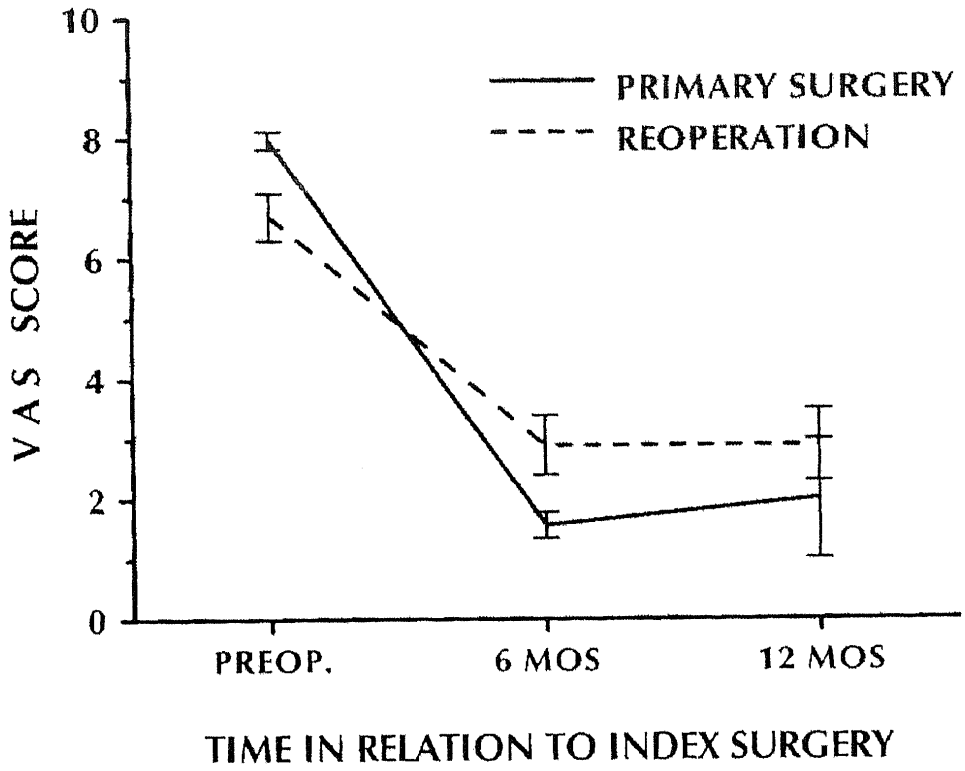

Figure 3: Outcome of radicular pain after primary lumbo-sacral disc surgery (European Study) *vs.* re-operation, with ADCON®-L. Radicular pain is assessed when 'most severe'. Values are expressed as mean score ± standard error of the mean

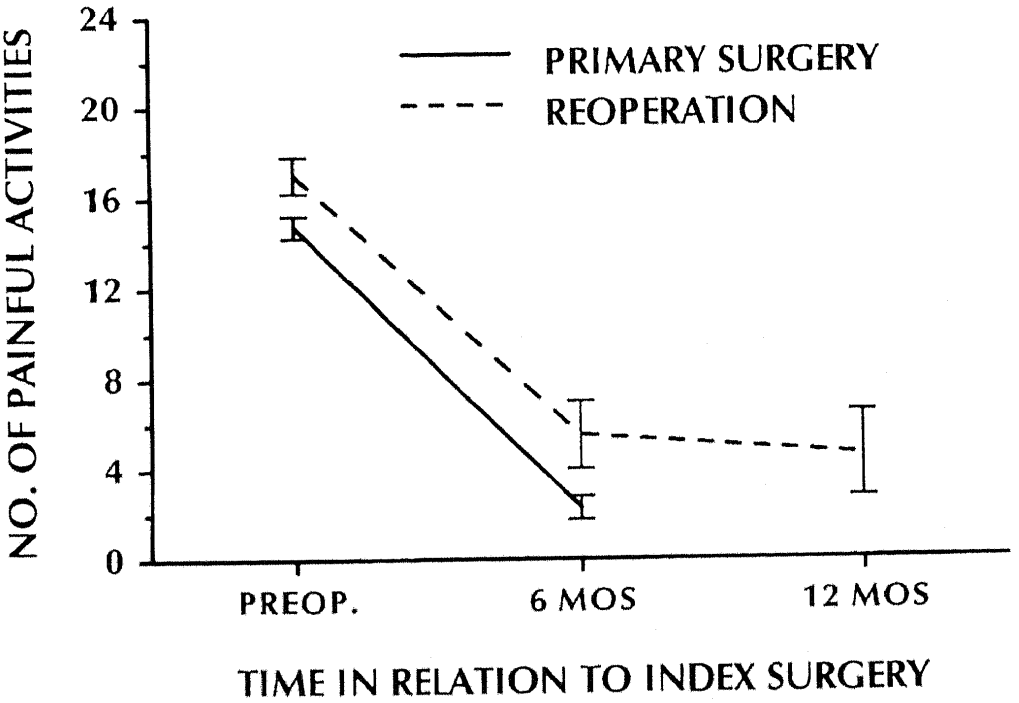

Figure 4: Outcome of activity-related radicular pain after primary lumbo-sacral disc surgery (USA Study; see text for details) *vs.* re-operation, with ADCON®-L. Twenty-four activities of daily living were investigated and assessed (modified Roland Morris Disability Questionnaire). Values are expressed as mean score ± standard error of the mean

DISCUSSION

Failed Back Surgery Syndrome is a severely disabling and chronic clinical condition, with epidural fibrosis recognized as one of its most frequent etiopathogenetic factors[24–28]. From a series of 40 lumbar disc patients examined five years after surgery for disabling sciatica, 18 cases had an unfavorable outcome, and the increased amount of scar tissue was shown to correlate significantly with the poor clinical result ($p = 0.008$)[8].

In a prospective series of 93 patients who required a secondary lumbar surgery following discectomy or decompression for spinal stenosis, epidural fibrosis was demonstrated in 35 cases (38%) at their first re-operation, and in five of the eight patients who underwent a third operation[28]. In general agreement with the medical community, those same authors do not recommend re-operation when fibrosis is suspected to be the only cause for FBSS. It has been reported that less than one third of the patients re-operated after lumbar disc surgery show persistent improvement of their symptoms[2], and the odds of a long term surgical success after re-operation are considerably diminished in those cases where epidural fibrosis is the main cause of FBSS[6,8,15,28,29]; overall, the failure rate is reported to reach a staggering 62%–83%[1].

While the results after repeated surgery for recurrent disc herniations are sometimes comparable to those after the first intervention, repeated surgery for epidural fibrosis is not only significantly less successful, but also involves significant surgical hazards[1,26,28,30-33]. When attempts are made to remove epidural fibrosis at re-operation, these additional risks of post-operative morbidity are imposed on the already compromised patient's health[17]. Moreover, the presence of epidural fibrosis prolongs the operating time, increases the risk for dural tears[17], and may delay healing as well[34]. Furthermore, epidural fibrosis typically tends to recur[35] and, therefore, the benefits of scar resection are often transient.

On the other hand, direct evidence has demonstrated that post-operative clinical success is positively associated with absence of peridural scar[2]. Since fibrotic scarring within the epidural region is secondary to a migration of fibroblasts into the laminectomy site from the erector spinae muscles, various attempts have been made to create and maintain a separation between the dura mater and the surrounding soft tissues. No single agent or technique, however, has obtained widespread acceptance mainly because of limited effectiveness or safety concerns. A variety of different treatment and surgical strategies have been attempted to prevent post-operative fibrosis without providing consistent long-term results[24,36–39]. Dense and solid fibrous scar surrounding devices or biological implants used to prevent epidural fibrosis following laminectomy procedures, or severe adverse events in relation to their use, have been reported[9,40–42]. Thus, the search for a safe and effective device to protect lumbar disc patients from detrimental peridural fibrosis has long been the subject of considerable research.

ADCON®-L is a biocompatible and resorbable barrier gel used during lumbar laminectomy and laminotomy procedures, where it inhibits the peridural fibrotic scar and adhesions, and their clinical sequelae[20,43], thereby reducing the incidence of FBSS. The characteristics of this barrier gel are unique in several respects: the safety profile of ADCON®-L is excellent, its formulation conforms naturally to irregular surfaces, and due to processes of natural resorption, surgical removal is not required.

The effectiveness of ADCON®-L as an anti-fibrotic barrier at the time of primary lumbar disc surgery has been clinically proven in two major trials: one was conducted at nine surgical centers in three European countries between 1992 and 1995[20]; and the second is an ongoing study being conducted at 14 surgical centers in the USA[21]. The conclusions from the present study demonstrate that ADCON®-L is also useful when applied at the time of lumbar re-operation for recurrent radicular signs and symptoms following previous lumbar disc surgery at the same level due to recurrent disc herniation, or retained disc fragment. The significant improvement in both radicular and low back pain, performance of daily activities, and SLR test observed six months post-operatively was maintained at 12 months, indicating that the long lasting clinical effects outlive the physical presence of the barrier gel at the surgical site, since ADCON®-L is completely resorbed within approximately four weeks from its application[20].

Radicular pain, the symptom which warranted the index re-operation in all our cases, was improved in less than half of the patients reported by North *et al.* at the six-month follow-up[2]. It has been reported by other investigators that, one year after re-operation, only one patient of four shows improved radicular pain[17]. Since the three individual clinical series presented in *Figure 1* are sufficiently homogeneous, the results presented in this paper suggest that the application of ADCON®-L at the time of re-operation clearly provides a more favorable outcome than the post-operative results in patients not treated with ADCON®-L, even considering the relative limited size of the population presented in this series. The benefit shown in re-operated patients treated with ADCON®-L further emphasizes the role of epidural fibrosis in the etiology of FBSS following repeat lumbo-sacral surgery. Moreover, patients diagnosed with FBSS who undergo re-operations typically experience only a transient post-operative improvement, followed by a decline. Since this deterioration is often attributed to the progressive recurrence of fibrosis within three to six months post-operative, the use of ADCON®-L was expected to enable a longer symptom-free post-operative course in a larger proportion of these patients. This hypothesis was tested and proven correct with the 12-month results.

There were no adverse events attributed to the use of ADCON®-L. Conversely, though this was not designed as a controlled study, the clinical course subsequent to the lumbar re-operation compares favorably to the outcome observed in similar patients not treated with ADCON®-L.

Although the events which may affect the outcome after primary and secondary lumbar surgery may be dissimilar, it is hypothesized that both of them have one common denominator relevant to clinical success, namely, presence or absence of epidural scar. By protecting the dura and the lumbar roots from epidural scar and adhesions, ADCON®-L provides a favorable post-operative outcome in both primary and secondary back surgery.

The finding that the clinical outcome at one year after lumbo-sacral re-operation was substantially predicted at six months is another element in common with the results observed following primary discectomy[20]. From these earlier investigations, magnetic resonance imaging has shown that the extent of epidural fibrosis within the anterior and posterior regions were substantially unchanged between six months and one year following surgery[44].

CONCLUSIONS

In this prospective multicenter study the safety and effectiveness of ADCON®-L applied in patients undergoing lumbar disc re-operation were demonstrated. The re-operated patients included in this series showed an improvement lasting throughout the 12 months of post-operative evaluation. This favorable effect is significantly different from the typical results reported in comparable patients not treated with ADCON®-L.

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