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Reduction of Radiculopathy and Pain With Oxiplex/SP Gel After Laminectomy, Laminotomy, and Discectomy

A Pilot Clinical Study

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Study Design. Safety using Oxiplex/SP Gel during single-level discectomy for reduction of symptoms associated with unilateral herniation of the lumbar disc was investigated by self-assessment questionnaire and magnetic resonance imaging.

Objective. To evaluate the safety and assess the efficacy parameters of Oxiplex/SP Gel.

Summary of Background Data. Animal studies demonstrated that Oxiplex/SP Gel (CMC/PEO) reduced epidural fibrosis after lumbar surgery.

Methods. Surgeons examined spine and lower extremities of patients scheduled for discectomy to assess neurologic function and pain. Treated patients received sufficient Oxiplex/SP Gel (1–3 mL) to coat the nerve root and fill the epidural space. The control condition was surgery alone. At baseline, then 30 days, 90 days, and 6 months after surgery, patients completed self-assessment questionnaires concerning leg pain, lower extremity weakness, functional disability, daily living activities, symptoms, and radiculopathy. Magnetic resonance imaging was performed at baseline and 90 days after surgery. At 30 and 90 days after surgery, patients underwent physical examination, wound inspection, and laboratory tests.

Results. The surgical procedures were well tolerated by the 23 patients treated with Oxiplex/SP Gel and the 11 control patients. There were no unanticipated adverse events, no clinically significant laboratory results, and no significant differences detected by magnetic resonance imaging. Treated patients had greater reduction in outcome measures at 30 days. The differences in scores were attenuated at 90 days and 6 months. A subgroup, the patients with significant leg pain and weakness at baseline (11 patients treated with Oxiplex/SP Gel and 7 control patients), had greater reduction in outcome measures than the control patients throughout the study.

Conclusions. Oxiplex/SP Gel was easy to use and safe for patients undergoing unilateral discectomy. Greater benefit in clinical outcome measures was seen in gel-treated patients, especially those with severe leg pain and weakness at baseline. [Key words: discectomy, failed back, laminectomy, laminotomy, Oxiplex/SP Gel, surgery] **Spine 2003;28:1080–1088**

Postoperative fibrosis is a frequent consequence of surgical procedures in the epidural space. Compression or tethering of the nerve root often causes recurrent radicular pain and physical impairment.[1,2] An epidural scar occurs after lumbar discectomy by replacement of normal epidural fat with fibrotic tissue. Spinal nerve roots and dorsal root ganglions are particularly sensitive to mechanical deformation caused by epidural fibrosis.[3] Ross *et al*[4] reported that patients with an extensive epidural scar were 3.2 times more likely to experience recurrent radicular pain than patients with less extensive scarring. When Hurme *et al*[5] examined 40 patients 5 years after primary surgery for herniated lumbar disc, 18 were found to have an increased amount of scar tissue, which correlated with poor results. Thus, extensive epidural fibrosis occurring after lumbar surgery contributes to failed back surgery syndrome (FBSS), characterized by recurrent radicular or lower back and leg pain.[3,6,7]

Acquisition of meticulous hemostasis is an effective surgical technique for reducing epidural fibrosis.[8] In addition to good surgical technique,[9] many materials have been implanted on the dura in an effort to prevent or reduce scar formation after surgery in the epidural space.[10–15] Results from preclinical studies have demonstrated reduction of epidural fibrosis with a variety of implanted devices.[16–18] One such formulation, Adcon-L (Gliatech, Cleveland, OH), has received FDA approval for scar reduction after lumbar surgery.[19] Widespread use of Adcon-L was limited by reports of late-onset headaches and associated leakage of CSF from dural injuries potentially related to delayed healing and foreign body reaction.[20–24]

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Oxiplex/SP Gel is composed of polyethylene oxide (PEO) and sodium carboxymethylcellulose (CMC). Calcium chloride is added to induce ionic cross-linking. Both CMC and PEO are known to reduce adhesions and fibrotic scarring that form after surgery.[25,26] Because CMC is rapidly resorbed, calcium chloride is added to the formulation to create stronger interaction between the components, thereby prolonging residence in the body.[26,27] Studies of rabbit laminotomies have demonstrated by gross morphology and histology that Oxiplex/SP Gel is cleared from the epidural space within 30 days and effectively reduces epidural scar.[29] Furthermore, Oxiplex/SP Gel did not affect dural repair and was not associated with chronic inflammation or foreign body response. This article reports results from a pilot clinical trial of Oxiplex/SP Gel performed in accordance with the FDA, which demonstrated reduction of postoperative pain and radiculopathy in patients after discectomy *via* laminectomy or laminotomy.

■ Materials and Methods

Study Design. This randomized, single-blind, multicenter, pilot clinical trial study evaluated the safety of Oxiplex/SP Gel in reducing postoperative epidural fibrosis and related symptoms after surgery for herniated lumbar disc at L4–L5 or L5–S1. Patients underwent presurgical eligibility evaluations, including examination by a neurosurgeon or orthopedic spine surgeon, and magnetic resonance imaging (MRI) of the spine.

A self-assessment questionnaire (Lumbar Spine Outcomes Questionnaire [LSOQ]) related to patients' pain, symptoms, and activities of daily living was completed before surgery and at scheduled postoperative intervals (30 days, 90 days, 6 months).[30,31] A computer-generated paradigm randomized patients to a treatment (Oxiplex/SP Gel) or control (no Oxiplex/SP Gel) group with balanced assignment across the study and per center. Randomization occurred immediately before wound closure. The study patients were not informed as to their group assignment until after data analysis.

Both patient groups underwent follow-up MRI evaluations 90 days after surgery, with and without gadolinium contrast. All the MRIs were reviewed by two masked neuroradiologists. At 30 and 90 days after surgery, all the patients were assessed by physical examination, lower extremity neurologic function, wound inspection, self-assessment LSOQ, and laboratory tests including CBC, chemistry panel, and urinalysis.

Maintaining the Study Blinding. The following procedures were used to maintain blinding for all ratings and assessments. The investigator, site study coordinator, and other applicable site personnel agreed not to discuss the treatment assignments during the course of the study, or to provide any documents to the patient that may have revealed the assignment (*e.g.*, an operative report). The patients completed the self-assessment questionnaires before meeting with the physician or study coordinator.

Randomization. Randomization was assigned when the patient's surgical procedure was completed to the point at which hemostasis was assured and the surgeon was ready to close the operative site. At that time, the sponsor was called for patient assignment: to receive Oxiplex/SP Gel or not to receive any additional adhesion prevention treatment (control condition). Any hemostatic agents used during surgery were removed before closure of the surgical site. All the patients underwent closure in the surgeon's routine fashion. The test patients received sufficient Oxiplex/SP Gel to coat the nerve roots and fill the operative site (approximately 3 mL).

Table 1. Oxiplex/SP Gel Pilot Study Demographics

	All Subjects	Oxiplex/SP Gel	Control
No. enrolled	35	23	12
	24 (68%)	17 (74%)	7 (58%)
	11 (31%)	6 (26%)	5 (42%)
	28	28	28
	65	65	63
	42	42	43.5
	43.5	43.5	43.6
	31 (89%)	21 (91%)	10 (83%)
	2 (6%)	2 (9%)	0
	1 (3%)	0	1 (8%)
	1 (3%)	0	1 (8%)

Inclusion Criteria. The patients were adults scheduled to undergo their first surgery for removal of a unilateral, herniated, lumbar, intervertebral disc associated with radiculopathy. Specific inclusion criteria required signs and symptoms of lumbar or lumbosacral radiculopathy affecting one predominant nerve root level, radiologic evidence of nerve root compression, and/or confirmed existence of an extruded or sequestered disc fragment at L4–L5 or L5–S1 compatible with clinical signs and symptoms. Preoperative laboratory test results needed to be within normal limits or deemed not to be of clinical significance by the investigator.

The patients included in the study underwent at least 2 weeks of nonoperative treatment without resolution of pain, which the surgeon could waive if the patient was experiencing intractable pain or progressive loss of neurologic function. During the 2-week nonoperative period, the physician treated the patient as necessary with physical therapy, narcotics, or any other nondisqualifying treatments that would alleviate the patient's discomfort. No patient had epidural steroid treatment withheld to qualify for the study.

Exclusion Criteria. Patients were excluded if they had undergone previous spinal surgery, had been treated with epidural steroids within 4 weeks or oral steroids within 10 days of the proposed surgery, and/or had received aspirin or other nonsteroidal antiinflammatory drugs within 7 days of the proposed surgery. Patients who had received myelograms or lumbar punctures within 24 hours before surgery also were excluded. Other exclusion criteria specified any concurrent disease that, in the surgeon's opinion, could influence the outcome of the proposed surgery, any postoperative involvement in a current or anticipated worker's compensation claim, or any involvement in a current or anticipated personal injury litigation. Patients were excluded intraoperatively for dural entry, discovery of intraspinal tumor, the need to involve more than one level, exploration of the contralateral side, placement of an epidural fat pad, or retention of a hemostat.

Table 2. Oxiplex/SP Gel Pilot Study: All Patients

Variable	N	Oxiplex Mean	(SD)	N	Control Mean	(SD)	P
Leg pain							
Baseline	23	57.8	(18.4)	12	65.8	(16.7)	0.215
30 days							
Actual value	23	13.2	(18.8)	12	25.0	(28.2)	0.147
Changes from baseline	23	44.6	(29.7)	12	40.8	(30.0)	0.725
Relative change from baseline	23	72.9	(41.3)	12	61.3	(40.6)	0.435
90 days							
Actual value	23	22.0	(26.5)	11	21.3	(25.4)	0.940
Changes from baseline	23	35.8	(34.3)	11	43.5	(30.0)	0.526
Relative change from baseline	23	56.8	(57.2)	11	66.8	(42.1)	0.608
6 months							
Actual value	22	15.8	(16.0)	11	20.6	(29.4)	0.540
Changes from baseline	22	40.9	(27.8)	11	44.2	(32.5)	0.762
Relative change from baseline	22	67.5	(37.6)	11	68.2	(49.2)	0.963
Symptoms							
Baseline	23	46.9	(21.3)	12	52.3	(22.7)	0.496
30 days							
Actual value	23	19.7	(20.5)	12	32.8	(22.2)	0.090
Changes from baseline	23	27.2	(26.0)	12	19.4	(25.2)	0.406
Relative change from baseline	23	53.3	(50.1)	12	17.4	(68.7)	0.086
90 days							
Actual value	23	22.4	(27.5)	11	23.5	(25.9)	0.915
Changes from baseline	23	24.5	(28.3)	11	26.3	(30.0)	0.870
Relative change from baseline	23	52.4	(52.6)	11	38.0	(92.1)	0.565
6 months							
Actual value	22	17.6	(19.8)	11	19.4	(23.3)	0.818
Changes from baseline	22	28.1	(21.7)	11	30.4	(25.8)	0.793
Relative change from baseline	22	34.5	(34.5)	11	56.9	(57.4)	0.647
Activity related pain							
Baseline	23	2.10	(0.97)	12	2.27	(0.90)	
30 days							
Actual value	23	1.21	(1.27)	12	1.43	(1.19)	0.628
Changes from baseline	23	0.89	(1.31)	12	0.83	(1.13)	0.901
Relative change from baseline	21	39.8	(53.2)	12	36.9	(51.4)	0.880
90 days							
Actual value	23	1.34	(1.21)	11	1.24	(1.32)	0.816
Changes from baseline	23	0.76	(1.24)	11	0.99	(1.71)	0.660
Relative change from baseline	21	33.0	(57.9)	11	23.7	(116.7)	0.764
6 months							
Actual value	22	1.15	(1.15)	10	1.42	(1.35)	0.570
Changes from baseline	22	0.92	(1.10)	10	0.76	(1.04)	0.692
Relative change from baseline	20	49.9	(49.9)	10	46.1	(53.0)	0.928
Functional disability							
Baseline	23	50.7	(24.5)	12	51.1	(26.9)	
30 days							
Actual value	23	37.9	(18.3)	12	39.9	(19.4)	0.765
Changes from baseline	23	12.8	(29.2)	12	11.2	(19.5)	0.864
Relative change from baseline	22	13.1	(53.3)	12	−5.7	(79.3)	0.415
90 days							
Actual value	23	26.4	(16.8)	11	25.6	(18.5)	0.906
Changes from baseline	23	24.4	(26.6)	11	22.9	(20.5)	0.879
Relative change from baseline	22	40.7	(38.8)	11	15.7	(115.0)	0.359
6 months							
Actual value	22	24.1	(16.8)	11	25.1	(16.1)	0.877
Changes from baseline	22	25.5	(23.0)	11	23.5	(21.3)	0.811
Relative change from baseline	21	49.0	(26.1)	11	14.3	(115.5)	0.192
Weakness in lower extremity							
Baseline	23	2.25	(1.16)	12	2.75	(1.06)	0.574
30 days							
Actual value	23	1.57	(0.95)	12	2.25	(0.97)	0.052
Changes from baseline	23	0.96	(1.55)	12	0.50	(1.09)	0.371
Relative change from baseline	23	20.3	(58.0)	12	4.2	(68.2)	0.467
90 days							
Actual value	23	1.70	(0.93)	11	1.82	(1.08)	0.734
Changes from baseline	23	0.83	(1.37)	11	0.82	(1.25)	0.987
Relative change from baseline	23	19.2	(48.7)	11	25.0	(37.1)	0.730
6 months							
Actual value	22	1.55	(0.86)	11	1.91	(1.14)	0.311
Changes from baseline	22	0.91	(1.41)	11	0.73	(1.27)	0.721
Relative change from baseline	22	20.5	(60.3)	11	21.2	(41.7)	0.970

(Table continues)

Table 2. Continued

Variable	N	Oxiplex Mean	(SD)	N	Control Mean	(SD)	P
Radiculopathy score							
Baseline	23	52.7	(15.3)	12	59.2	(17.8)	0.271
30 days							
Actual value	23	16.7	(18.1)	12	29.3	(23.8)	0.091
Changes from baseline	23	36.0	(18.9)	12	29.9	(23.2)	0.475
Relative change from baseline	23	66.8	(24.6)	12	48.4	(37.3)	0.184
90 days							
Actual value	23	22.4	(24.7)	11	22.5	(23.5)	0.991
Changes from baseline	23	30.3	(23.2)	11	34.8	(26.8)	0.658
Relative change from baseline	23	56.4	(34.0)	11	56.4	(45.8)	0.998
6 months							
Actual value	22	16.4	(16.4)	11	20.1	(25.2)	0.655
Changes from baseline	22	19.5	(19.5)	11	37.3	(26.7)	0.757
Relative change from baseline	22	31.2	(31.2)	11	64.3	(45.0)	0.793

Treatment Response Assessments. Self-assessment of the clinical outcome was performed by use of the Lumbar Spine Outcome Questionnaire (LSOQ).[31,32] Five composite scores were derived from the patients' responses to the LSOQ. Higher scores were indicative of more severe pain.

Leg Pain Severity Measure. Severity of leg pain was assessed on a 6-point adjective rating scale indicating the severity of leg or buttock pain: 1 (hurts the most), 2 (hurts the least), 3 (average pain), 4 (pain at the end of an active day), 5 (pain on awakening), and 6 (pain at the moment of response to the questionnaire). The responses were converted to numerical values ranging from 0 (no pain) to 5 (excruciating pain). Six scores were thus obtained for each patient at each evaluation. These scores were combined and rescaled to yield composite leg pain severity scores in the range of 0 to 100.

Physical Symptoms and Radiculopathy Score. On a 4-point scale (never, occasionally, frequently, and always), patients indicated how often they had experienced the following symptoms during the preceding 7 days: numbness or tingling in the lower extremities, weakness in the lower extremities, bowel or bladder dysfunction, and trouble falling asleep or being awakened from sleep because of pain. The responses were converted to numerical values ranging from 0 (never) to 3 (always), then combined and rescaled to yield physical symptoms scores ranging from 0 to 100. A radiculopathy score was obtained by summing the leg pain severity scores and the symptoms scores, then dividing by 2.

Functional Disability and Activity-Related Pain Scores. On a 4-point scale (all, most, some, and none), the patients indicated how many of their daily activities they could perform, the number of days they could not perform work-related activities, the number of hours they spent during the day resting, and the activities on a provided list that exacerbated their pain.[32] The eight scores were combined and rescaled to yield composite functional disability scores in the range of 0 to 10. The patients indicated, from a list of 12 activities of daily living, whether each activity increased, decreased, or left unchanged their pain. Their responses were converted to numerical values and rescaled, as previously described.[32]

Outcome Measures and Statistical Analysis. Changes from baseline laboratory values were analyzed using the paired *t* test or the Wilcoxon matched-pairs signed-rank test. For each of the five composite measures, analyses of variance (ANOVA) were used to evaluate changes from baseline and to compare the two groups (Oxiplex/SP Gel and control groups). Changes in lower extremity weakness were evaluated using Fisher's exact test.

For each patient, an absolute and a relative change were computed. The absolute change scores were computed from the differences between the values reported at the 30-day, 90-day, and 6-month follow-up assessments and the corresponding baseline values. Relative change scores, expressed as percentages, were computed by subtracting the posttreatment value from the baseline value, then dividing by the baseline value. For all analyses, P values less than 0.05 were considered significant.

MRI Evaluation. Although evaluation of MRI images generally has not predicted the clinical response to surgery, it has provided a useful safety assessment of postsurgical repair.[33–38] Magnetic resonance imaging was performed at 90 days (12–14 weeks) with and without gadolinium contrast. Epidural abnormality was defined as a low T1 signal of epidural material. Enhanced and nonenhanced quadrant scores were recorded on the MRI case report form (CRF). The amount of abnormality was graded on a scale of 0 to 6 for each quadrant: 0 (none), 1 (0–5%), 2 (6–25%), 3 (26–50%), 4 (51–75%), 5 (76–95%), and 6 (96–100%) of epidural space.

Statistical analysis of MRI quadrants for each of the five 2-mm slices was performed using a categorical variable analysis. The reliability of MRI scores was assessed using weighted kappa coefficients for ordinal data.

■ Results

All the patients (23 in the Oxiplex/SP Gel group and 12 in the control group) tolerated the surgical procedures well and had good postoperative recovery Table 1). There were no device-related adverse events. As determined by the principal investigator, the adverse events that did occur were consistent with typical postoperative recovery. There were no clinically significant changes in laboratory values. The MRI analysis, including observations of enhancing and nonenhancing abnormalities, did not show significantly different results between the con-

Table 3. Oxiplex/SP Gel Pilot Study: Patients With Baseline Leg Pain Score ≥40 and Lower Extremity Weakness >2

Variable	N	Oxiplex Mean	(SD)	N	Control Mean	(SD)	P
Leg pain							
Baseline	11	64.5	(18.6)	7	66.3	(9.5)	0.813
30 days							
Actual value	11	11.5	(18.9)	7	37.6	(30.4)	0.038
Changes from baseline	11	52.9	(29.0)	7	28.7	(28.0)	0.100
Relative change from baseline	11	80.3	(31.8)	7	44.4	(43.9)	0.060
90 days							
Actual value	11	21.2	(27.0)	6	31.2	(29.7)	0.492
Changes from baseline	11	43.3	(30.6)	6	33.3	(31.5)	0.536
Relative change from baseline	11	67.6	(37.9)	6	50.4	(49.8)	0.435
6 months							
Actual value	10	16.7	(16.1)	6	31.2	(34.3)	0.267
Changes from baseline	10	45.9	(30.0)	6	33.3	(37.2)	0.470
Relative change from baseline	10	68.5	(32.7)	6	49.4	(59.8)	0.419
Symptoms							
Baseline	11	61.7	(16.0)	7	61.0	(17.0)	0.928
30 days							
Actual value	11	16.5	(14.6)	7	41.9	(25.1)	0.015
Changes from baseline	11	45.3	(18.0)	7	19.1	(23.6)	0.017
Relative change from baseline	11	73.0	(22.4)	7	29.0	(40.7)	0.009
90 days							
Actual value	11	22.5	(23.7)	6	31.8	(30.5)	0.491
Changes from baseline	11	39.3	(22.9)	6	26.0	(29.1)	0.315
Relative change from baseline	11	65.8	(33.7)	6	45.1	(51.1)	0.328
6 months							
Actual value	10	19.9	(20.7)	6	25.5	(25.2)	0.636
Changes from baseline	10	40.7	(22.3)	6	32.3	(26.1)	0.506
Relative change from baseline	10	67.5	(27.7)	6	56.5	(49.1)	0.572
Activity related pain							
Baseline	11	2.18	(0.84)	7	2.37	(0.83)	0.645
30 days							
Actual value	11	0.90	(1.19)	7	1.71	(1.28)	0.191
Changes from baseline	11	1.28	(1.31)	7	0.67	(1.19)	0.330
Relative change from baseline	11	55.8	(50.2)	7	33.4	(47.6)	0.362
90 days							
Actual value	11	1.05	(1.13)	6	1.48	(1.40)	0.502
Changes from baseline	11	1.13	(1.42)	6	0.83	(1.56)	0.700
Relative change from baseline	11	45.3	(67.0)	6	36.7	(66.1)	0.805
6 months							
Actual value	10	1.20	(1.17)	5	1.56	(1.00)	0.568
Changes from baseline	10	0.93	(1.01)	5	0.68	(0.93)	0.651
Relative change from baseline	10	46.7	(51.5)	5	35.8	(49.3)	0.702
Functional disability							
Baseline	11	60.7	(25.2)	7	66.7	(18.2)	0.595
30 days							
Actual value	11	34.2	(14.7)	7	44.6	(22.8)	0.255
Changes from baseline	11	26.5	(28.5)	7	22.1	(16.0)	0.716
Relative change from baseline	11	28.1	(53.4)	7	35.1	(26.1)	0.752
90 days							
Actual value	11	25.0	(11.4)	6	32.8	(23.3)	0.360
Changes from baseline	11	35.7	(28.4)	6	31.8	(18.0)	0.767
Relative change from baseline	11	46.1	(40.2)	6	51.8	(28.2)	0.766
6 months							
Actual value	10	24.0	(15.6)	6	29.8	(20.1)	0.525
Changes from baseline	10	35.3	(25.6)	6	34.8	(14.3)	0.968
Relative change from baseline	10	53.4	(26.7)	6	55.9	(20.1)	0.841
Weakness in lower extremity							
Baseline	11	3.55	(0.52)	7	3.43	(0.53)	0.653
30 days							
Actual value	11	1.36	(0.67)	7	2.43	(1.13)	0.023
Changes from baseline	11	2.18	(1.08)	7	1.00	(0.82)	0.025
Relative change from baseline	11	59.1	(25.4)	7	31.0	(24.4)	0.034
90 days							
Actual value	11	1.64	(0.67)	6	1.83	(0.98)	0.631
Changes from baseline	11	1.91	(0.94)	6	1.50	(1.22)	0.453
Relative change from baseline	11	52.3	(21.1)	6	43.1	(34.3)	0.500
6 months							
Actual value	10	1.40	(0.70)	6	2.33	(1.21)	0.068
Changes from baseline	10	2.10	(0.99)	6	1.00	(1.41)	0.088
Relative change from baseline	10	58.3	(24.5)	6	27.8	(40.7)	0.079

Table 3. Continued

Variable	N	Oxiplex Mean	(SD)	N	Control Mean	(SD)	*P*
Radiculopathy score							
Baseline	11	63.5	(12.2)	7	63.9	(12.5)	0.947
30 days							
Actual value	11	14.3	(15.3)	7	40.0	(26.0)	0.017
Changes from baseline	11	49.2	(18.9)	7	23.9	(21.7)	0.019
Relative change from baseline	11	77.0	(24.6)	7	38.8	(35.6)	0.016
90 days							
Actual value	11	22.1	(24.7)	6	31.7	(28.1)	0.477
Changes from baseline	11	41.4	(23.2)	6	29.7	(27.7)	0.367
Relative change from baseline	11	66.6	(34.0)	6	48.4	(48.7)	0.377
6 months							
Actual value	10	18.5	(16.4)	6	28.5	(29.0)	0.368
Changes from baseline	10	43.5	(19.6)	6	32.8	(30.8)	0.408
Relative change from baseline	10	69.5	(25.6)	6	52.5	(54.6)	0.406

trol and treated patients. The median scores, determined from all four quadrants of five slices for the control patients (n = 10) and the treated patients (n = 23), were 1.755 and 1.550 for the enhanced scores and 0.125 and 0.100 for the nonenhanced scores, respectively. There were no significant differences in MRI values between the two evaluators (kappa coefficient, 0.654). The results from the Lumbar Spine Outcomes Questionnaire (LSOQ) 30 days, 90 days, and 6 months after surgery for all the patients are shown in Table 2.

In this small pilot study, there were no statistically significant differences between the treated patients and the control patients on the five composite scores and the single-item score derived from the LSOQ questionnaire. Overall, the symptoms were reduced in the Oxiplex/SP Gel–treated patients in all the time points. Weakness in the lower extremity was reduced in the Oxiplex/SP Gel–treated patients, as compared with the control patients, at the 30-day time point ($P = 0.052$). The radiculopathy score also was reduced in the Oxiplex/SP Gel–treated patients at the 30-day time point ($P = 0.091$). In general, the patients who received Oxiplex/SP Gel had lower LSOQ scores than the control patients 30 days after surgery (Table 2). These differences in scores at 30 days were attenuated or not present at 90 days and 6 months.

Analysis of preoperative scores showed a subgroup of patients (11 patients treated with Oxiplex/SP Gel and 7 control patients) who had substantial leg pain (score, ≥40) and weakness in the lower extremity (score, >2) at baseline (Table 3). Evaluation of LSOQ scores in this subgroup demonstrated differences in treatment response in all categories 30 days, 90 days, and 6 months after surgery. Reduction in leg pain scores ($P = 0.038$), symptoms ($P = 0.015$), weakness in the lower extremity ($P = 0.023$), and radiculopathy score ($P = 0.017$) at 30 days for the Oxiplex/SP Gel–treated patients all were statistically lower than for the control patients. All change from baseline scores at 30 days, 90 days, and 6 months showed reductions in the Oxiplex/SP Gel–treated patients, as compared with the control patients. The relative change from baseline in LSOQ scores was greater for most categories at 6 months in the Oxiplex/SP Gel–treated group than in the control group (Figure 1).

■ Discussion

Focal limitation of epidural scar formation, while maintaining healing of the surgical site, necessitates understanding the natural history of epidural fibrosis.[23,39,40] Fibrosis can form between spinal dura mater and interposing structures as a result of hematoma or residual necrotic tissues, including fat.[41] Inflammatory reaction to foreign substances also enhances fibrogenesis.[42] It is reported that fewer than one third of the patients who undergo reoperation after lumbar disc surgery show persistent improvement of their symptoms. The chance of long-term surgical success after reoperation is considerably diminished in cases wherein epidural fibrosis is prevalent.[43–45] Repeated surgery for epidural fibrosis not only is less successful, but also involves prolonged operating time and increased risks for adhesive arachnoiditis and dural tears resulting from scarification by fibrosis at the surgical site.[14,43,44,46,47]

Pain scales are a common method for assessing patient outcome after back surgery. At least 22 scales exist in the literature.[30,48] However, the presence of pain alone is a narrow definition of outcome that correlates poorly with physical function.[49] Recording disability in daily tasks may reduce subjective differences in evaluation of symptoms and provides a measure with less potential bias. Waddell and Main[50] stated that in evaluating clinical outcome of surgery for low back pain, three components require consideration: pain, physical impairment, and disability. As a result, many contemporary studies use multiple questionnaires to assess treatment outcomes.[30] BenDebba *et al*[31,32] developed a comprehensive, disease-specific questionnaire for assessing reports of low back pain and evaluating the outcomes of treatments for these reports. This instrument, the Lumbar Spine Outcome Questionnaire (LSOQ), was used to evaluate the response of 2539 patients undergoing treatment for low back pain. The questionnaire was shown to have high test–retest reliability, good content and construct validity, and responsiveness to change after treatment. It was

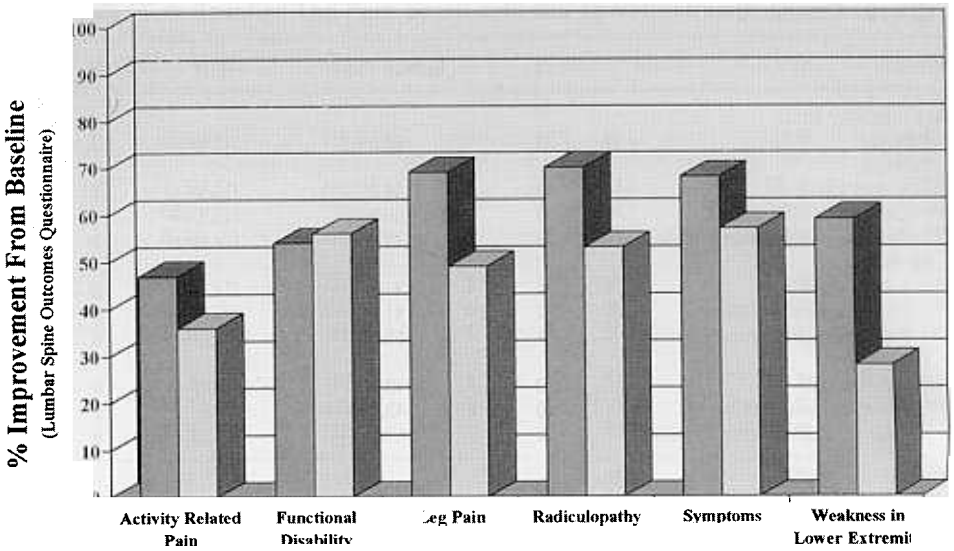

Figure 1. The percentage of improvement from baseline score for each of the six composite measures of the Lumbar Spine Outcome Questionnaire 6 months after surgery for patients who had significant pain and symptoms before unilateral discectomy for a single-level herniated disc at L4–L5 or L5–S1 (Oxiplex/SP Gel = dark bars; surgery only control = light bars).

reported to be acceptable to patients and easy to administer. The LSOQ was used in this study as an instrument designed specifically to measure clinical outcomes after lumbar discectomy for herniated discs in patients with pain and radiculopathy.

Interpretation of clinical data from FDA-monitored safety studies is limited beyond general safety consideration because the number of patients was small. Unlike pivotal studies, which often contain more than 250 patients, safety studies, which precede pivotal studies in the United States, typically have only 20 to 30 patient exposures to the device. In this study, the number of patients treated with Oxiplex/SP Gel was 23. The utility of the clinical trial data is dependent on the comparability of data at baseline. In this study, interpretation of the outcomes measure was limited by differences in baseline values. The difference in baseline values for the leg pain category was particularly problematic. When the relatively low-scoring patients were removed from consideration, the baseline values for leg pain became similar (64.5 *vs* 66.3, Table 3), and a difference in treatment response became apparent (leg pain, 67% *vs* 50%, relative change). When this group of patients was analyzed, a clear separation in clinical outcome measures between the Oxiplex/SP Gel–treated patients and the control patients was evident (Table 3), which continued through the 6-month study interval (Figure 1). Although subgroup analysis is notoriously misguided, in this case identification of this subgroup (patients with leg pain scores, ≥40; lower extremity weakness, >2) assisted in the design of the pivotal study.

In conclusion, patients treated with Oxiplex/SP Gel had safety profiles similar to those of the surgery-only control patients. In the patients with significant leg pain and lower extremity weakness at baseline, the patients who received Oxiplex/SP Gel had a general improvement in outcome, as compared with the control patients. Confirmation of these observations awaits a larger clin trial.

■ Key Points

- Change in pain score after lumbar discectomy was demonstrated by self-assessment questionnaire: the Lumbar Spine Outcomes Questionnaire.
- Patients with a herniated disc, significant pain, and lower extremity weakness reported clinical benefit with the use of Oxiplex/SP Gel.
- The safety profiles of the Oxiplex/SP Gel–treated patients and the surgical controls were the same after lumbar discectomy.

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