

Reduction in leg pain and lower-extremity weakness with Oxiplex/SP Gel for 1 year after laminectomy, laminotomy, and discectomy

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Object. Although good surgical technique is effective in reducing postoperative epidural fibrosis, compression or tethering of the nerve root may cause recurrent radicular pain and physical impairment. The implantation of a bioresorbable gel on the dura may further decrease the amount of scar formation after surgery and thus improve the patient's ability to perform activities of daily living (ADL). This study is a 12-month evaluation of the safety and effectiveness of Oxiplex/SP Gel (FzioMed, Inc., San Luis Obispo, CA) in the reduction of pain and radiculopathy after lumbar discectomy.

Methods. A pilot randomized single-blind multicenter clinical trial was conducted to evaluate the performance of Oxiplex/SP Gel in patients who underwent surgery for unilateral herniation of the lumbar disc at L4–5 or L5–S1. Eighteen patients with severe leg pain and lower-extremity weakness (11 women and seven men) were randomly assigned intraoperatively to receive the gel at the conclusion of surgery (treatment group) or to undergo surgery alone (control group). Self-assessment questionnaires (Lumbar Spine Outcomes Questionnaire) to assess pain, symptoms, and ADL were completed preoperatively and at scheduled postoperative intervals (30 days, 90 days, 6 months, and 12 months).

The authors examined the spine and lower extremities of patients scheduled for discectomy to assess neurological function and pain. Treated patients received sufficient Oxiplex/SP Gel (1–3 ml) to coat the nerve root and fill the epidural space. Postoperative clinical evaluations were performed at 30 and 90 days. Patients completed the self-assessment questionnaires at baseline and were contacted by telephone or mail for the completion of the postoperative self-assessment questionnaires.

Surgical procedures were well tolerated; no device-related adverse events and no clinically significant laboratory results were reported. The 11 patients with severe leg pain and lower-extremity weakness who were treated with Oxiplex/SP Gel had a reduction in those symptoms at 30 days, 90 days, 6 months, and 12 months after discectomy, compared with the seven control patients who underwent surgery only.

Conclusions. Oxiplex/SP Gel was easy to use and safe in patients who underwent unilateral discectomy. A greater benefit in clinical outcome measures was seen over the 12-month follow-up period in gel-treated patients.

KEY WORDS • herniated disc • laminectomy • lumbar discectomy • failed-back surgery • Oxiplex/SP Gel • Lumbar Spine Outcomes Questionnaire

Epidural fibrosis occurring after lumbar surgery may contribute to failed-back surgery syndrome, which is characterized by recurrent radiculopathy with symptoms including weakness and pain in the lower extremity.^{17,20,27} Compression or tethering of spinal nerve roots and dorsal root ganglia often causes recurrent radicular pain and

physical impairment.^{2,23,27,31} In addition to the application of good surgical techniques,¹³ many kinds of materials have been implanted in the epidural space in an effort to reduce scar formation.^{1,8,14,28} One formulation, ADCON-L (Gliatech, Cleveland, OH), received FDA approval for scar reduction following lumbar surgery.^{28,31} Nevertheless, widespread use of ADCON-L was limited by reports of late-onset headaches and associated leakage of cerebrospinal fluid from dural injuries; these adverse events were potentially related to delayed healing and foreign body reaction.^{16,22}

Abbreviations used in this paper: ADL = activities of daily living; CMC = carboxymethylcellulose; FDA = Food and Drug Administration; LSOQ = Lumbar Spine Outcomes Questionnaire; MR = magnetic resonance; PEO = polyethylene oxide.

Oxiplex/SP Gel is composed of PEO and CMC, to which CaCl is added to stabilize the gel.²⁴ Both CMC and PEO are known to reduce adhesion formation, and fibrotic scars that form after surgery.^{21,30} CMC was shown in pre-clinical studies to prevent tissue adherence, whereas PEO interacts with proteins that when organized contribute to fibrosis.²⁴ Because CMC is rapidly resorbed, CaCl is added to the formulation to create a stronger interaction between the components, thereby prolonging retention in the body. In studies of laminotomies in rabbits it has been demonstrated by gross morphology findings and histological studies that Oxiplex/SP Gel is cleared from the epidural space within 30 days and is effective in reducing epidural adhesions.²⁹ Furthermore, Oxiplex/SP Gel did not affect dural repair and was not associated with chronic inflammation or foreign body response. Previously, we reported results from a pilot clinical trial of Oxiplex/SP Gel performed in accordance with FDA guidelines. In this earlier study we demonstrated reduced postoperative leg pain and lower-extremity weakness over a 6-month follow-up period in patients in whom discectomy had been performed through a laminectomy or laminotomy.¹⁹ In this paper, we extend the results to the final 12-month end point of the study.

CLINICAL MATERIAL AND METHODS

Study Design

In this randomized single-blind multicenter, pilot clinical study we evaluated the safety of Oxiplex/SP Gel (FzioMed, Inc., San Luis Obispo, CA) when it was used to reduce postoperative epidural fibrosis and related symptoms after surgery for herniation of the lumbar disc at L4–5 or L5–S1. All patients underwent presurgical eligibility evaluations, including examination by a neurosurgeon or orthopedic spine surgeon, and MR imaging of the spine. All MR images were reviewed by two neuroradiologists in a blinded fashion.

A self-assessment questionnaire, the LSOQ, which posed questions related to patients' pain, symptoms, and ADL was completed preoperatively and at scheduled postoperative intervals (30 days, 90 days, 6 months, and 12 months).⁴⁶ A computer-generated paradigm was used to randomize patients to treatment or control groups (Oxiplex/SP Gel [11 patients] or surgery only [seven patients], respectively) and balanced assignments were made across the study and per center. Randomization (2:1, treated/control) was performed immediately before wound closure. Patients enrolled in the study were not informed of their group assignment until the data analysis was completed. At 30 and 90 days postoperatively, all patients were assessed using an array of methods including physical examination, lower-extremity neurological function tests, wound inspection, self-assessment LSOQ, and laboratory tests including complete blood count, 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 and not to provide any documents to the patient that might reveal the assignment (for example, an operative report). Patients completed the self-assessment questionnaires before meeting with the physician or study coordinator.

Randomization of Patients

Randomization assignments were made when the patient's procedure was completed to the point at which hemostasis was assured and the surgeon was ready to close the surgical site. At that time, the FzioMed clinical affairs section was called for patient assignment: either to the group receiving Oxiplex/SP Gel or to the control group (in which patients did not receive additional adhesion prevention treatment). Any hemostatic agents used during surgery were removed before gel was applied and the surgical site was closed (drains were not used). All patients underwent wound closure in the surgeon's routine fashion. Patients in the treatment group received enough Oxiplex/SP Gel to coat the nerve roots and fill the operative site (~3 ml).

Inclusion Criteria

Patients were adults who were scheduled to undergo their first surgery for removal of a unilateral herniated, lumbar intervertebral disc associated with radiculopathy. Specific inclusion criteria included signs and symptoms of lumbar or lumbosacral radiculopathy affecting one nerve root level predominantly, radiological evidence of nerve root compression, and/or confirmation of an extruded or sequestered disc fragment at the L4–5 or L5–S1 level compatible with clinical signs and symptoms. Preoperative laboratory test results were within normal limits or were deemed not to be of clinical significance by the investigator. Patients had undergone at least a 2-week period of medical treatment without resolution of pain.

Exclusion Criteria

Patients were excluded if they had previously undergone spinal surgery, had been treated with epidural steroid drugs within 4 weeks of the proposed surgery or with oral steroid agents within 10 days before, and/or if they had received aspirin or other nonsteroidal antiinflammatory drugs within 7 days before the proposed surgery. Patients who had undergone myelography or lumbar puncture within 24 hours prior to surgery were also excluded. Other exclusion criteria included any concurrent disease that, in the surgeon's opinion could influence the outcome of the proposed surgery or postoperative period, involvement in a current or anticipated Workers' Compensation claim, and/or status as a party to current or anticipated personal injury litigation. Patients were excluded intraoperatively if 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 hemostatic agent occurred.

Treatment Response Assessments

The self-assessment measure of clinical outcome was obtained using the LSOQ.¹⁹ Five composite scores were

derived from the patients' responses to the LSOQ. All patients had evidence of substantial leg pain (score ≥ 40) and/or lower-extremity weakness (score > 2) at baseline. Higher scores were indicative of more severe pain.

Leg Pain Severity Measure. Patients used a six-point adjective rating scale to indicate the severity of leg/buttock pain: 1) when it hurts the most; 2) when it hurts the least; 3) on average; 4) at end of an active day; 5) on awakening; and 6) at the moment of responding to the questionnaire. The responses were converted to numerical values ranging from 1 (no pain) to 6 (excruciating pain). Six values were thus obtained for each patient at each evaluation, and these values 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 four-point scale (never, occasionally, frequently, and always) patients indicated how often they had experienced the following symptoms during the last 7 days: 1) numbness or tingling in the lower extremities; 2) weakness in the lower extremities; 3) bowel or bladder dysfunction; and 4) trouble falling asleep or being awakened from sleep by pain. Responses were converted to numerical values ranging from 1 (never) to 4 (always), and then combined and rescaled to yield physical symptoms scores from 0 to 100. A radiculopathy score was obtained by summing the leg pain severity scores and the symptoms scores, and then dividing by 2.

Functional Disability and Activity-Related Pain Scores. Patients rated on a four-point scale (all, most, some, none) the degree to which they were still able to perform each of five common ADL, yielding five scores. They reported the number of days each month during which they could not perform any of their usual work-related activities and the number of hours they spent during an average 24-hour day reclining, lying down, or sleeping, which yielded two additional scores. From a list we provided they identified ADL that exacerbated their pain, yielding another score. The eight scores thus obtained from each patient at each evaluation were combined and rescaled to yield a composite functional disability score in the range of 0 to 100 and an activity-related pain score in the range of 0 to 3.2.

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 were used to evaluate changes from baseline and to compare the two groups (Oxiplex/SP Gel and control). Changes in lower-extremity weakness were evaluated using the Fisher exact test.

An absolute and a relative change score were computed for each patient. The absolute change scores were computed by subtracting the values reported at the 30-day, 90-day, 6-month, and 12-month follow-up visits from the corresponding baseline values. Relative change scores, expressed as percentages, were computed by subtracting the posttreatment from the baseline value, and then dividing by the baseline value. For all analyses, probability values of less than 0.05 were considered significant.

RESULTS

All patients tolerated the surgical procedures well and had uneventful postoperative recoveries; there were no device-related adverse events. There were no clinically significant changes in laboratory values. The analysis of MR images, including observations of enhancing and nonenhancing abnormalities, did not reveal significantly different results between the control and treated patients.

Results of the LSOQ for all patients at each follow-up interval after surgery are shown in Tables 1 through 6. Differences in treatment responses between treated and control patients were seen in all categories at 30 days, 90 days, 6 months, and 12 months postsurgery. Reduction in leg pain ($p = 0.038$), symptoms ($p = 0.015$), weakness in the lower extremity ($p = 0.023$), and radiculopathy scores ($p = 0.017$) at 30 days in Oxiplex/SP Gel-treated patients were all statistically significantly lower compared with controls. The relative change from baseline in LSOQ scores was greater for most categories at 6 and 12 months in the Oxiplex/SP Gel-treated group compared with the control group. At 12 months, the Oxiplex/SP Gel-treated patients maintained a clinically significant difference in the reduction of leg pain (73% compared with 55%; Fig. 1 upper) and lower-extremity weakness (50% compared with 37%; Fig. 1 lower) when measured against controls.

DISCUSSION

Due to the relatively small number of patients, interpretation of clinical data from FDA-monitored safety studies is limited beyond general safety considerations. Unlike pivotal studies, which often contain in excess of 250 patients, safety studies, which precede pivotal studies in the US, typically limit patients' exposure to a device. In our

TABLE 1
Leg pain in 18 patients after discectomy with or without Oxiplex/SP Gel treatment*

Variable	Treatment Group		Control Group		p Value
	No. of Patients	Mean \pm SD	No. of Patients	Mean \pm SD	
baseline	11	64.5 \pm 18.6	7	66.3 \pm 9.5	0.813
30 days					
actual value	11	11.5 \pm 18.9	7	37.6 \pm 30.4	0.038
Δ from baseline	11	52.9 \pm 29.0	7	28.7 \pm 28.0	0.100
relative Δ from baseline	11	80.3 \pm 31.8	7	44.4 \pm 43.9	0.060
90 days					
actual value	11	21.2 \pm 27.0	6	31.2 \pm 29.7	0.492
Δ from baseline	11	43.3 \pm 30.6	6	33.3 \pm 31.5	0.536
relative Δ from baseline	11	67.6 \pm 37.9	6	50.4 \pm 49.8	0.435
6 mos					
actual value	10	16.7 \pm 16.1	6	31.2 \pm 34.3	0.267
Δ from baseline	10	45.9 \pm 30.0	6	33.3 \pm 37.2	0.470
relative Δ from baseline	10	68.5 \pm 32.7	6	49.4 \pm 59.8	0.419
12 mos					
actual value	11	20.0 \pm 25.6	6	27.2 \pm 24.3	0.583
Δ from baseline	11	44.5 \pm 19.5	6	37.3 \pm 28.6	0.550
relative Δ from baseline	11	73.4 \pm 31.1	6	55.7 \pm 42.4	0.339

* Relative change scores are expressed as percentages. Abbreviation: Δ = change.

TABLE 2

Lower-extremity weakness in 18 patients after discectomy with or without Oxiplex/SP Gel treatment

Variable	Treatment Group		Control Group		p Value
	No. of Patients	Mean \pm SD	No. of Patients	Mean \pm SD	
baseline	11	3.55 \pm 0.52		3.43 \pm 0.53	0.653
30 days					
actual value	11	1.36 \pm 0.67	7	2.43 \pm 1.13	0.023
Δ from baseline	11	2.18 \pm 1.08	7	1.00 \pm 0.82	0.025
relative Δ from baseline	11	59.1 \pm 25.4	7	31.0 \pm 24.4	0.034
90 days					
actual value	11	1.64 \pm 0.67	6	1.83 \pm 0.98	0.631
Δ from baseline	11	1.91 \pm 0.94	6	1.50 \pm 1.22	0.453
relative Δ from baseline	11	52.3 \pm 21.1	6	43.1 \pm 34.3	0.500
6 mos					
actual value	10	1.40 \pm 0.70	6	2.33 \pm 1.21	0.068
Δ from baseline	10	2.10 \pm 0.99	6	1.00 \pm 1.41	0.088
relative Δ from baseline	10	58.3 \pm 24.5	6	27.8 \pm 40.7	0.079
12 mos					
actual value	11	1.73 \pm 0.90	6	2.00 \pm 1.26	0.612
Δ from baseline	11	1.82 \pm 1.08	6	1.33 \pm 1.51	0.452
relative Δ from baseline	11	50.0 \pm 27.1	6	37.5 \pm 44.0	0.476

study, 11 patients with severe leg pain and weakness of the lower extremity were treated with Oxiplex/SP Gel. When this group of patients was analyzed, a difference in clinical outcome measures between the Oxiplex/SP Gel–treated and control patients was evident (Table 1). The Oxiplex/SP Gel–treated patients continued to show an improvement relative to the controls throughout the 12-month study interval (Fig. 1). No device-related safety issue arose during the 12-month study, although a larger clinical trial is required to confirm these findings.

It was reported that fewer than one third of patients who undergo a repeated operation after lumbar disc surgery

TABLE 3

Radiculopathy score in 18 patients after discectomy with or without Oxiplex/SP Gel treatment

Variable	Treatment Group		Control Group		p Value
	No. of Patients	Mean \pm SD	No. of Patients	Mean \pm SD	
baseline	11	63.5 \pm 12.2		63.9 \pm 12.5	0.947
30 days					
actual value	11	14.3 \pm 15.3	7	40.0 \pm 26.0	0.017
Δ from baseline	11	49.2 \pm 18.9	7	23.9 \pm 21.7	0.019
relative Δ from baseline	11	77.0 \pm 24.6	7	38.8 \pm 35.6	0.016
90 days					
actual value	11	22.1 \pm 24.7	6	31.7 \pm 28.1	0.477
Δ from baseline	11	41.4 \pm 23.2	6	29.7 \pm 27.7	0.367
relative Δ from baseline	11	66.6 \pm 34.0	6	48.4 \pm 48.7	0.377
6 mos					
actual value	10	18.5 \pm 16.4	6	28.5 \pm 29.0	0.368
Δ from baseline	10	43.5 \pm 19.6	6	32.8 \pm 30.8	0.408
relative Δ from baseline	10	69.5 \pm 25.6	6	52.5 \pm 54.6	0.406
12 mos					
actual value	11	22.0 \pm 24.7	6	23.8 \pm 25.0	0.886
Δ from baseline	11	41.5 \pm 18.2	6	37.5 \pm 27.5	0.725
relative Δ from baseline	11	68.5 \pm 31.5	6	60.4 \pm 43.7	0.664

TABLE 4

Symptoms in 18 patients after discectomy with or without Oxiplex/SP Gel treatment

Variable	Treatment Group		Control Group		p Value
	No. of Patients	Mean \pm SD	No. of Patients	Mean \pm SD	
baseline	11	61.7 \pm 16.0		61.0 \pm 17.0	0.928
30 days					
actual value	11	16.5 \pm 14.6	7	41.9 \pm 25.1	0.015
Δ from baseline	11	45.3 \pm 18.0	7	19.1 \pm 23.6	0.017
relative Δ from baseline	11	73.0 \pm 22.4	7	29.0 \pm 40.7	0.009
90 days					
actual value	11	22.5 \pm 23.7	6	31.8 \pm 30.5	0.491
Δ from baseline	11	39.3 \pm 22.9	6	26.0 \pm 29.1	0.315
relative Δ from baseline	11	65.8 \pm 33.7	6	45.1 \pm 51.1	0.328
6 mos					
actual value	10	19.9 \pm 20.7	6	25.5 \pm 25.2	0.636
Δ from baseline	10	40.7 \pm 22.3	6	32.3 \pm 26.1	0.506
relative Δ from baseline	10	67.5 \pm 27.7	6	56.5 \pm 49.1	0.572
12 mos					
actual value	11	23.6 \pm 25.7	6	20.0 \pm 30.3	0.797
Δ from baseline	11	38.1 \pm 24.4	6	37.8 \pm 32.0	0.985
relative Δ from baseline	11	63.7 \pm 35.8	6	66.2 \pm 49.7	0.907

ery show persistent improvement of their symptoms; the chance of long-term surgical success after a repeated operation may be diminished in cases in which epidural fibrosis is prevalent.^{7,10,11} Fibrosis can form between spinal dura mater and interposing structures as a result of hematoma or residual necrotic tissues, including fat.^{18,26,32} Repeated surgery for epidural fibrosis is often less successful and may require a prolonged operating time and increased risks of adhesive arachnoiditis and dural tears because of scarification by fibrosis at the surgical site.^{12,15,25}

Pain scales are a common method for assessing patient outcome after back surgery. BenDebba and coworkers^{5,6}

TABLE 5

*Activity-related pain in 18 patients after discectomy with or without Oxiplex/SP Gel treatment**

Variable	Treatment Group		Control Group		p Value
	No. of Patients	Mean \pm SD	No. of Patients	Mean \pm SD	
baseline	11	2.18 \pm 0.84	7	2.37 \pm 0.83	0.645
30 days					
actual value	11	0.90 \pm 1.19	7	1.71 \pm 1.28	0.191
Δ from baseline	11	1.28 \pm 1.31	7	0.67 \pm 1.19	0.330
relative Δ from baseline	11	55.8 \pm 50.2	7	33.4 \pm 47.6	0.362
90 days					
actual value	11	1.05 \pm 1.13	6	1.48 \pm 1.40	0.502
Δ from baseline	11	1.13 \pm 1.42	6	0.83 \pm 1.56	0.700
relative Δ from baseline	11	45.3 \pm 67.0	6	36.7 \pm 66.1	0.805
6 mos					
actual value	10	1.20 \pm 1.17	5	1.56 \pm 1.00	0.568
Δ from baseline	10	0.93 \pm 1.01	5	0.68 \pm 0.93	0.651
relative Δ from baseline	10	46.7 \pm 51.5	5	35.8 \pm 49.3	0.702
12 mos					
actual value	11	1.21 \pm 1.05	6	1.31 \pm 1.09	0.854
Δ from baseline	11	0.97 \pm 1.06	6	1.01 \pm 1.02	0.949
relative Δ from baseline	11	44.9 \pm 44.5	6	49.0 \pm 41.3	0.855

Reduction in leg pain and weakness with Oxiplex/SP Gel

TABLE 6
Functional disability in 18 patients after discectomy with or without Oxiplex/SP Gel treatment*

Variable	Treatment Group		Control Group		p Value
	No. of Patients	Mean \pm SD	No. of Patients	Mean \pm SD	
baseline	11	60.7 \pm 25.2		66.7 \pm 18.2	0.595
30 days					
actual value	11	34.2 \pm 14.7	7	44.6 \pm 22.8	0.255
Δ from baseline	11	26.5 \pm 28.5	7	22.1 \pm 16.0	0.716
relative Δ from baseline	11	28.1 \pm 53.4	7	35.1 \pm 26.1	0.752
90 days					
actual value	11	25.0 \pm 11.4	6	32.8 \pm 23.3	0.360
Δ from baseline	11	35.7 \pm 28.4	6	31.8 \pm 18.0	0.767
relative Δ from baseline	11	46.1 \pm 40.2	6	51.8 \pm 28.2	0.766
6 mos					
actual value	10	24.0 \pm 15.6	6	29.8 \pm 20.1	0.525
Δ from baseline	10	35.3 \pm 25.6	6	34.8 \pm 14.3	0.968
relative Δ from baseline	10	53.4 \pm 26.7	6	55.9 \pm 20.1	0.841
12 mos					
actual value	11	30.2 \pm 19.0	6	29.5 \pm 21.5	0.947
Δ from baseline	11	30.5 \pm 30.2	6	35.2 \pm 25.6	0.756
relative Δ from baseline	11	38.1 \pm 51.2	6	52.6 \pm 36.5	0.552

developed a comprehensive disease-specific questionnaire for assessing complaints of low-back pain and evaluating the outcomes of treatments for these complaints. According to their findings, this instrument, the LSOQ, was shown to have high test-retest reliability, good content and construct validity, and it was responsive to change following treatment. It was reported to be acceptable to patients and easy to administer. The LSOQ was used in our study as an instrument designed specifically to measure clinical outcomes after lumbar discectomy for herniated discs in patients presenting with pain and radiculopathy.

As shown in our study, evaluation of outcomes data at 6 months seems predictive of long-term follow-up findings after lumbar discectomy. Previously, BenDebba, et al.,⁵ reported that, based on a composite scoring system, outcomes improved over the first 6 months after surgery in patients with low-back pain undergoing discectomy. Thereafter, pain and function scores remained relatively constant over the 2-year duration of the study. Danielsen, et al.,⁹ demonstrated that changes in visual analog scale scores as well as the Roland-Morris Disability Index were similar at 6 and 12 months after discectomy. In a landmark study that has now extended to 5 years after decompression laminectomy for lumbar spinal stenosis, Atlas, et al.,³ showed that modified Roland scores that were reduced during the initial 6 months postoperatively remained relatively constant over the next 54 months, with data collected at 12, 24, 36, 48, and 60 months. Woertgen, et al.,³³ found similar results in 98 patients who were followed for 2 years after lumbar disc surgery for relief of radicular pain. The Low-Back Outcome Score improved through 3 months after surgery to reach the maximal benefit, which persisted during the 12- and 24-month measures.

CONCLUSIONS

In patients treated with Oxiplex/SP Gel the safety pro-

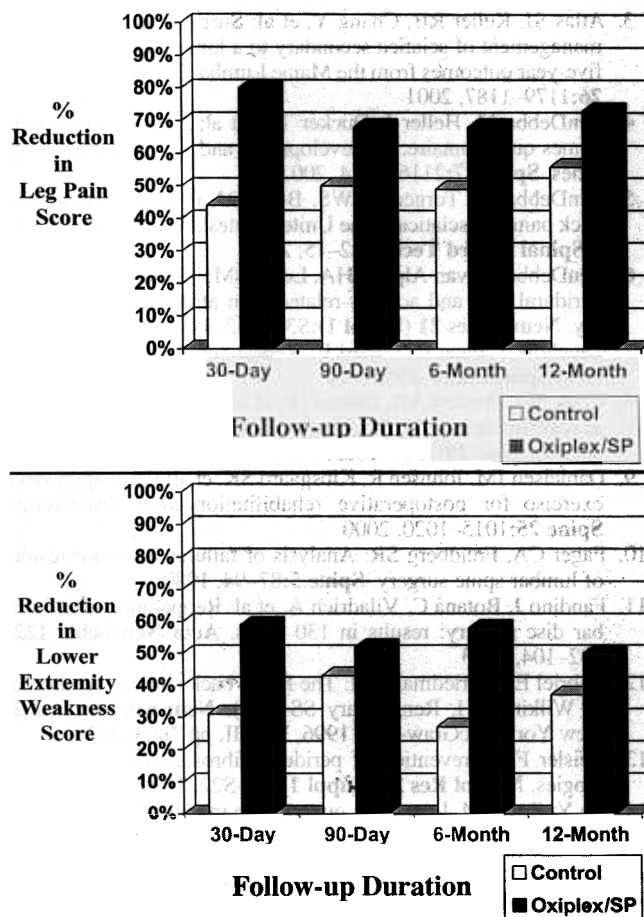


Fig. 1. Bar graphs showing follow-up scores in patients who received Oxiplex /SP Gel (11 patients) or who served as surgical controls (seven patients) after lumbar discectomy for severe leg pain and lower-extremity weakness. Upper: Improvements in leg pain scores. Lower: Improvements in scores for lower-extremity weakness.

files were similar to those of the surgery-only control patients. In patients with substantial leg pain and lower-extremity weakness at baseline, those who received Oxiplex/SP Gel attained a general improvement in outcome compared with control patients; this improvement continued over the 1-year duration of the study. Confirmation of these observations awaits a larger clinical trial.

Acknowledgment

We thank Trish Lyons for her editorial assistance in the preparation of this article.

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Manuscript received March 22, 2004.

Accepted in final form June 21, 2004.

Support for this study was provided in part by FzioMed, Inc., San Luis Obispo, California.

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