Spine

SPINE Volume 37, Number 8, pp 631–641


RANDOMIZED TRIAL

# Oxiplex Reduces Leg Pain, Back Pain, and Associated Symptoms After Lumbar Discectomy

Alfred L. Rhyne, MD,* Scott L. Blumenthal, MD,† Edmund H. Frank, MD,‡ Ken Y. Hsu, MD,§ Kee D. Kim, MD,‖ Jim A. Youssef, MD,¶ Jeffrey C. Wang, MD,# Paul Arnold, MD,** Mohammed BenDebba, PhD,†† Kathleen M. Block, MA, BSN,‡‡ Thomas G. Juarez,§§ Richard P. Chiacchierini, PhD,‡‡ Ronald J. Ehmsen, ScD,‡‡ John S. Krelle, MBA,‡‡ Gere S. diZerega, MD,‖‖ and the Oxiplex Clinical Study Group

**Study Design.** Prospective, randomized, blinded clinical trial.

**Objective.** To evaluate effectiveness of Oxiplex gel for reduction of pain and associated symptoms after lumbar discectomy.

**Summary of Background Data.** Oxiplex gel (carboxymethylcellulose, polyethylene oxide, and calcium) is used during discectomy to coat the surgical site for reduction of pain and symptoms after lumbar discectomy.

**Methods.** Patients undergoing single-level lumbar discectomy performed by laminectomy or laminotomy and randomized to receive either surgery plus Oxiplex gel (treatment group) or surgery alone (control group) were assessed 6 months after surgery using (1) a quality of life questionnaire (Lumbar Spine Outcomes Questionnaire [LSOQ]) and (2) clinical evaluations.

**Results.** There were no statistically significant differences in baseline demographics, surgical procedures, LSOQ scores, and clinical evaluations between treatment (N = 177) and control (N = 175) groups. More gel-treated patients were satisfied with outcome of their surgical treatment than control patients ($P = 0.05$). The gel-treated group showed greater reductions in pain and symptoms from baseline compared with surgery-only controls. Additional benefits of gel were consistently shown in reduction of leg and back pain at 6 months in the patient population having substantial back pain at baseline (greater than or equal to the median LSOQ pain score of 63). In that population, there was a statistically significant reduction of leg pain and back pain ($P < 0.01$) in the treatment group compared with controls. Fewer patients in the treatment group had abnormal musculoskeletal physical examinations at 6 months compared with controls. There were no cases of cerebrospinal fluid leaks and no differences in laboratory values or vital signs. Patients in the treatment group had less hypoesthesia, paraesthesia, sensory loss, and fewer reoperations during the 6-month follow-up than controls (1 *vs*. 6).

**Conclusion.** These data demonstrate improvements in clinical outcomes resulting from the use of Oxiplex gel in discectomy procedures for treatment of lumbar disc herniation.

**Key words:** back pain, discectomy, herniated disc, laminectomy, laminotomy, leg pain, Lumbar Spine Outcomes Questionnaire, Oxiplex. **Spine 2012;37:631–641**

More than 700,000 patients undergo lumbar spine surgery in the United States each year. Development of postoperative inflammation, infiltration of neurotoxins, and formation of fibrosis in the epidural space can lead to postoperative leg and back pain.[1–7] A significant number of patients require reoperation within 5 years of surgery for herniated disc due to persistent or recurrent pain.[4,5] Keskimaki *et al*[6] reported that 12.3% of 25,359 patients with herniated lumbar discs underwent subsequent lumbar operations in a 9-year follow-up (cumulative risk of 18.9%). The reoperation rates within 5 years of decompression were found by Martin *et al*[8] to be 19.2% in a cohort of 22,537 patients. Thus, one of the largest unmet needs in spinal surgery is a treatment to reduce leg and back pain as well as subsequent surgical intervention after lumbar disc surgery.[9,10]

Oxiplex intraoperative gel (FzioMed, Inc., San Luis Obispo, CA) was developed in response to this need. This gel is used at the end of the surgical procedure, just prior to closure, to coat the tissues in the surgical field. Oxiplex works as a mechanical barrier by coating the nerve root, annulus fibrosus and associated neural structures in the epidural space to reduce their interaction with pain mediators and to reduce fibrosis after surgery.[10,11] This study reports

From the *OrthoCarolina Spine Center, Charlotte, NC; †Texas Back Institute, Plano, TX; ‡Oregon Health Science University, Dept. of Neurosurgery, Portland, OR; §St. Mary's Spine Center, San Francisco, CA; ‖University of California Davis School of Medicine, Department of Neurological Surgery, Sacramento, CA; ¶Durango Orthopedic Associates, Durango, CO; #University of California at Los Angeles Department of Orthopaedic Surgery, Santa Monica, CA; **Department of Surgery, University of Kansas Medical Center, Kansas City, KS; ††Department of Neurosurgery, Johns Hopkins School of Medicine, Baltimore, MD; ‡‡FzioMed, Inc., San Luis Obispo, CA; §§R.P. Chiacchierini & Associates, LLC, Rockville, MD; and ‖‖Keck-USC School of Medicine, Los Angeles, CA.

Acknowledgment date: August 20, 2010. First revision date: March 8, 2011. Acceptance date: July 14, 2011.

The device(s)/drug(s) that is/are the subject of this manuscript is/are not intended for human use.

Corporate/Industry funds were received to support this work. One or more of the author(s) has/have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript: e.g., honoraria, gifts, consultancies, royalties, stocks, stock options, decision making position.

Address correspondence and reprint requests to Gere S. diZerega, MD, Keck-USC School of Medicine, 1321 N. Mission Road, Los Angeles, CA, 90033; E-mail: dizerega@usc.edu

DOI: 10.1097/BRS.0b013e3182309af7

results from a FDA-monitored clinical trial, which evaluated the safety and efficacy of the gel in patients undergoing a single-level lumbar laminectomy for removal of a herniated disc.

## MATERIALS AND METHODS

The study was a randomized, third-party blinded (study subject, postoperative clinical evaluator, postoperative Lumbar Spine Outcomes Questionnaire [LSOQ] interviewer), multicenter, pivotal clinical trial to evaluate the safety and effectiveness of the gel to reduce postoperative leg and back pain as well as related symptoms after surgery for removal of a herniated lumbar disc at L4–L5 or L5–S1. The clinical protocol was approved by the US Food and Drug Administration under an Investigational Device Exemption, and the study was conducted at 31 different clinical trial sites with approval of the institutional review board at each site. All of the clinical investigators (n = 61) were independent of the sponsor. All subjects signed an informed consent approved by the respective institutional review boards. The informed consent was typically presented to the potential study subject by the site's study coordinator and signed by the subject prior to baseline Quality of Life questionnaire evaluation. Subjects were screened for eligibility in 3 stages. Initial preoperative eligibility assessment included a medical evaluation by an orthopedic spine surgeon or neurosurgeon. Assessments of the lower extremity were grouped for analytical purposes as "musculoskeletal exams" (sitting and standing assessments of pain, spasms, range of motion, straight leg reflex, and gait) and "neurological exams" (L4–S1 sensory examinations, deep tendon reflexes, motor examinations, as well as bladder and sexual function). The second stage was completion of the baseline LSOQ. The LSOQ is a validated, multi-item, self-report questionnaire designed to assess a number of factors that are considered relevant in evaluating treatment outcomes in lumbar spinal disorders. This quality-of-life measure was used to assess the subjects' overall reduction in leg and back pain after lumbar surgery, satisfaction with the overall therapy, and subsequent disability.[12] Subjects with significant pain and symptoms as measured by the LSOQ, who met all intraoperative screening criteria, were randomized to either surgery plus gel (treatment) or surgery only (control). Randomization occurred after the discectomy procedure was complete to the point that the surgeon was ready to close the operative site. Subjects were randomized (1:1) to treatment or control according to a computer-generated paradigm, with balanced assignment across the study and on a per center basis. Study subjects were not informed as to group assignment until all data were analyzed.

Postoperative LSOQ assessments were completed by study personnel at an independent, contracted vendor (*via* telephone or written contact) 6 months after surgery. All subjects received clinical follow-up evaluations at 6-months postoperatively including physical examination, assessment of lower extremity weakness, testing of neurological function, and laboratory tests. A qualified clinical evaluator performed the postoperative examinations. The clinical evaluator was a medically trained professional who was blinded to the subject's treatment assignment.

## INCLUSION/EXCLUSION CRITERIA

Subjects eligible for this study were adults (18–70 years of age) who were scheduled to undergo their first surgical intervention to treat unilateral herniation of their lumbar intervertebral disc. All study subjects had sciatic pain on the same side of their body as the disc herniation. Subjects had radiological evidence (magnetic resonance image study or computed tomography/myelogram) of nerve root compression, and/or confirmed existence of an extruded or sequestered disc fragment compatible with clinical signs and symptoms at the L4–L5 or L5–S1 level. Subjects entering the study underwent at least 2 weeks of nonoperative treatment without resolution of pain, unless the surgeon decided the subject was experiencing intractable pain or there was progressive loss of neurological function. All subjects had measurable pain and symptoms as determined by the LSOQ. Subjects who received steroids within 4 weeks prior to surgery, a lumbar puncture within 24 hours prior to surgery, or were diagnosed with foraminal stenosis were excluded. Subjects of a current or anticipated worker's compensation claim or party to a current or anticipated personal injury litigation were also excluded. Subjects who experienced any of the following intraoperative criteria were excluded from the study during surgery: dural entry; spinal fusion; multilevel herniation or the need to involve more than 1 level; exploration of contralateral side; or epidural fat placement.

## RANDOMIZATION/BLINDING

Randomization, provided by an independent statistician, was site-specific and computer-generated in blocks of 4 and 2. Randomization assignment of each subject was determined after intraoperative eligibility criteria were satisfied. Sequentially numbered sealed boxes (with a subject identification number) contained either gel (treatment) or an empty, nonsterile syringe (control). The boxes used for the control group mimicked the appearance, weight, and feel of the boxes containing the treatment gel.

Subjects were contacted by study personnel *via* telephone or mail to complete their self-assessment questionnaires. Both the subject and study personnel were blinded to the treatment assignment throughout the study period. All clinical evaluations were performed by a blinded clinical evaluator. At the time of study completion, the subject signed a document (Study Blind Documentation/Subject Declaration worksheet) confirming maintenance of the subject blind. The surgeons who applied the gel did not participate in collection of LSOQ or clinical outcomes data.

## GEL APPLICATION

Subjects in the treatment and control groups underwent standard surgical therapy. Subjects in the treatment group had their annulus fibrosus, dura, and exiting nerve root coated with gel along both the dorsal and ventral surfaces. The gel was applied into the laminectomy/laminotomy site to fill the

surgical site to the ventral surface of the vertebral lamina. The wound was then closed in routine fashion.

## EFFICACY AND SAFETY MEASUREMENTS

Efficacy was determined at 6 months after surgery by quantitating the following LSOQ parameters: leg pain, back pain, patient satisfaction, and disability days. In addition, a clinical evaluation of neurological and motor function was performed 6 months after surgery. Assessments of adverse events and concomitant therapies were conducted at 1 month, 3 months, and 6 months postoperatively.

## STATISTICAL ANALYSIS

The final data analysis was performed by an independent contracted statistician. Primary efficacy outcome was measured as the change in LSOQ score from baseline for leg pain, back pain, number of disability days, as well as overall subject satisfaction determined at study end. LSOQ scores were calculated using the method described by BenDebba *et al*.[12] Additional measures of efficacy included clinical outcome based on changes in neurological evaluation and clinical examination. The study was powered at 80% to show a difference in leg pain at the *P* value 0.05 or more level based on results from a previous feasibility study.[13,14] The analysis populations were: (1) intention-to-treat population, defined as all randomized subjects and (2) the evaluable population, defined as all randomized subjects who completed the 6-month LSOQ. The analysis of safety was conducted on the intention-to-treat population. The efficacy analyses were conducted on the evaluable population. For safety analyses, Fisher's exact test was used except where otherwise specified to assess statistical significance and a 2-sided *P* value less than 0.05 was considered to be significant. The posttreatment change from baseline in LSOQ scores was determined by general estimating equations analysis with supportive subgroup analysis performed by *t*-test.

An interim analysis was performed by an independent data management safety board after approximately 75% of the subjects were treated to determine safety and if any adjustments in sample size were required due to the results of the control population. There were no safety issues noted and no changes in the study were made. The study was continued until full enrollment was completed.

## RESULTS

A total of 2967 patients were preliminarily screened for eligibility; 1836 patients did not meet all of the initial baseline criteria. The study was discussed with 1131 patients, 333 patients refused consent and 11 patients were deemed ineligible after signing the informed consent due to lab abnormalities or multilevel involvement on radiological examination. The second stage of eligibility assessment, baseline LSOQ, was completed by 787 patients. Of the 420 patients who met the baseline LSOQ criteria (367 were screen failures), 19 patients withdrew consent or did not have surgery and 49 patients were found to be ineligible during surgery.

Postoperative follow-up, data collection, and analysis were performed on enrolled subjects only. Subjects were enrolled at the end of surgery after all eligibility criteria had been verified. The number of subjects enrolled was 352: 177 subjects treated with gel and 175 subjects in the surgery-only control group. One control subject dropped out due to reasons unrelated to the study. The number of subjects reported here is 351 (intention-to-treat: treatment, n = 177; control, n = 174). The number of subjects who completed the 6-month LSOQ was 339. The evaluable population at 6 months consisted of: treatment, n = 171; control, n = 168. Demographic variables (Table 1), preoperative neurological examinations (Table 2), and LSOQ scores (Table 3) were well balanced at baseline.

## SAFETY

No subjects were discontinued from the study due to an adverse event. All adverse events were based on completed clinical evaluations of the subjects and were recorded on the case report forms. No significant differences were found in adverse events (Table 4) or concomitant therapies (data not shown) between treatment and control groups. No findings related to clinical chemistries and hematology were found to be clinically significant. None of the serious adverse events were determined by the investigators to be due to the use of the gel (Figure 1).

### Leg Pain

The subjects with back pain scores less than the median level of 63 at baseline (gel, n = 67, 43 ± 23; control, n = 63, 48 ± 20) had similar reductions in leg pain at 6 months ($P = 0.14$). However, subjects with median or higher baseline LSOQ back pain scores (median = 63) had significantly greater reductions in leg pain in the treatment group (n = 78, 62 ± 20) compared with the control group (n = 78, 52 ± 27) at 6 months (18% relative change, $P = 0.01$, Figure 1).

### Back Pain

The subjects were subgrouped on the basis of the severity of back pain at baseline. An LSOQ score of 63 or more (approximately 55% of the subjects) identified their back pain to be "severe" back pain and is consistent with a subject declaration of pain as "distressing" or "incapacitating." Subjects with LSOQ back pain scores lower than 63 at baseline (gel, n = 67, 24 ± 25; control, n = 63, 25 ± 22) had similar reductions in back pain at 6 months ($P = 0.69$). However, subjects with median or higher LSOQ back pain scores (*i.e.*, ≥ 63) at baseline had significantly greater reductions in back pain in the treatment group (n = 78, 55 ± 21) compared with the control group (n = 78, 46 ± 24) at 6 months (19% relative change, $P = 0.01$, Figure 1).

### Satisfaction

Subjects' satisfaction with their surgical treatment was directly assessed by the LSOQ at the end of the study (month 6) using a 5-point scale shown in Figure 2 (ranging from 1: extreme satisfaction to 5: extreme dissatisfaction). Subjects with LSOQ back pain scores of 63 or more at baseline had significantly greater overall satisfaction in the treatment group (n = 89, 2 ± 1.4) compared with the control group (n = 98, 2.5 ± 1.6) at 6 months ($P = 0.04$). Subjects with back pain

**TABLE 1. Demographic Variables**

| Characteristic | Control | Oxiplex | |
|---|---|---|---|
| **Continuous Measures** | **Mean (SD) N (Min, Max)** | **Mean (SD) N (Min, Max)** | ***P* Value*** |
| Age | 41.71 (10.66) 175 | 41.81 (10.53) 177 | 0.93 |
| | (22.0, 67.0) | (21.0, 72.0) | |
| Height | 1.72 (0.10) 175 | 1.73 (0.10) 177 | 0.63 |
| | (1.52, 1.98) | (1.52, 2.03) | |
| Weight | 83.13 (20.43) 174 | 85.30 (19.10) 177 | 0.26 |
| | (38.79, 137.3) | (51.8, 147.2) | |
| BMI | 27.75 (5.55) 174 | 28.45 (5.84) 177 | 0.43 |
| | (11.9, 42.9) | (18.2, 48.4) | |
| Pulse | 75.48 (10.63) 168 | 74.21 (9.84) 175 | 0.26 |
| | (52.0, 105.0) | (50.0, 107.0) | |
| Blood pressure | | | |
| Systolic | 124.60 (15.82) 169 | 125.88 (16.86) 176 | 0.46 |
| | (90.0, 186.0) | (90.0, 173.0) | |
| Diastolic | 77.76 (9.70) 169 | 78.53 (10.75) 176 | 0.31 |
| | (56.0, 110.0) | (40.0, 115.0) | |
| Respiration | 16.51 (2.73) 167 | 16.61 (2.45) 167 | 0.90 |
| | (12.0, 24.0) | (12.0, 24.0) | |
| **Categorical Measures** | n/N (%) | n/N (%) | *P* Value† |
| Sex (male) | 98/175 (56.00) | 87/177 (49.15) | 0.20 |
| Race | | | |
| Caucasian | 153/175 (87.43) | 152/177 (85.88) | 1.00 |
| African American | 4/175 (2.29) | 9/177 (5.08) | |
| Hispanic | 11/175 (6.29) | 8/177 (4.52) | |
| Asian | 3/175 (1.71) | 2/177 (1.13) | |
| Other | 4/175 (2.29) | 6/177 (3.39) | |

**Two-sided two-sample Wilcoxon rank sum test.*
*†Two-sided Fisher's exact test.*
*BMI indicates body mass index; max, maximum; min, minimum.*

scores less than 63 at baseline (treatment group, n = 82, 2.2 ± 1.3; control group, n = 70, 1.9 ± 1.9) had similar levels of satisfaction (lower the number, the greater the satisfaction) at 6 months ($P = 0.12$). More subjects in the control group reported self-care and performance of housework scores that were worse at 6 months compared with subjects in the treatment group (Figure 3).

## Disability

The number of disability days during the 6-month study was significantly greater in the control group (n = 141) compared with the treatment group (n = 145) (mean difference of control group: treatment group results = 2.07 days, 95% CI = 0.003–4.14, $P = 0.05$).

## Reoperation

Seven subjects underwent a reoperation within 3 months after surgery (Figure 4). Of the 7, 1 subject (0.6%) was from the treatment group and 6 subjects (3.4%) were from the control group ($P = 0.07$).

## Clinical Evaluations

Clinical evaluations performed on the lower extremity at 6 months after surgery were similar between study groups

**TABLE 2. Neurological Examination**

| Characteristic | Control | | Oxiplex | | |
|---|---|---|---|---|---|
| **Clinical presentation** | **n/N (%)** | **Not Assessed** | **n/N (%)** | **Not Assessed** | ***P* Value*** |
| Pain radiating beyond knee with neurological signs | 137/175 (78.29) | 0 | 143/176 (81.25) | 1 | 0.60 |
| Pain radiating beyond knee with w/o neurological signs | 31/175 (17.71) | | 29/176 (16.48) | | |
| Pain radiating to the knee w/o neurological signs | 7/175 (4.00) | | 4/176 (2.27) | | |
| Deep tendon reflexes | | | | | |
| Right patella present | 164/175 (93.71) | 0 | 164/176 (93.18) | 1 | 1.00 |
| Right Achilles present | 139/175 (79.43) | 0 | 143/176 (81.25) | 1 | 0.69 |
| Left patella present | 157/174 (90.23) | 1 | 161/176 (91.48) | 1 | 0.71 |
| Left Achilles present | 124/174 (71.26) | 1 | 136/176 (77.27) | 1 | 0.22 |
| Sensory examination | | | | | |
| L4 right reduced | 7/175 (4.00) | 0 | 5/176 (2.84) | 1 | 0.57 |
| L4 left reduced | 15/174 (8.62) | 1 | 13/177 (7.34) | 0 | 0.70 |
| L5 right reduced | 35/175 (20.00) | 0 | 22/177 (12.43) | 0 | 0.06 |
| L5 left reduced | 37/175 (21.26) | 0 | 51/177 (28.81) | 0 | 0.11 |
| S1 right reduced | 33/175 (18.86) | 0 | 26/177 (14.69) | 0 | 0.32 |
| S1 left reduced | 35/174 (20.11) | 1 | 42/177 (23.73) | 0 | 0.44 |
| Straight leg raise | | | | | |
| Negative | 45/175 (19.53) | 0 | 38/177 (21.47) | 0 | 0.60 |
| Positive bilateral | 16/175 (9.14) | | 15/177 (8.47) | | |
| Positive unilateral | 114/175 (65.14) | | 124/177 (70.06) | | |

**Two-sided Fisher's exact test.*

**TABLE 3. Baseline Lumbar Spine Outcomes Questionnaire Composite Results**

| Characteristic | Control | Oxiplex | |
|---|---|---|---|
| **Composite Measures** | **Mean (SD) N<br>Median (Min, Max)** | **Mean (SD) N<br>Median (Min, Max)** | ***P* Value*** |
| Leg pain | 67.74 (14.14) 174 | 67.54 (15.17) 177 | 0.96 |
| | 70.0 (40.0, 100.0) | 70.0 (33.0, 100.0) | |
| Back pain | 59.44 (21.77) 174 | 59.16 (20.87) 177 | 0.66 |
| | 65.0 (0.0, 100.0) | 63.0 (0.0, 100.0) | |
| Symptoms | 62.18 (16.41) 174 | 64.56 (16.70) 177 | 0.17 |
| | 60.0 (27.0, 93.0) | 67.0 (20.0, 100.0) | |
| Disability days | 1.33 (1.17) 174 | 1.52 (1.13) 177 | 0.12 |
| | 1.0 (0.0, 3.0) | 2.0 (0.0, 3.0) | |

**Activity index required the sum over a number of questions and was incomplete for 6 control and 11 treated patients.*
*Max indicates maximum; min, minimum.*

**TABLE 4. Incidence of AEs Occurring in ≥ 5%**

| | Oxiplex | % | Control | % | Total Subjects | % |
|---|---|---|---|---|---|---|
| Subjects randomized | N = 177 | | N = 175 | | N = 352 | |
| Subjects reporting any AEs | n = 163 | | n = 153 | | n = 316 | |
| System organ class | | | | | | |
| Preferred term | | | | | | |
| Gastrointestinal disorders | | | | | | |
| Constipation | 12 | 6.8 | 6 | 3.4 | 18 | 5.1 |
| Nausea | 35 | 19.8 | 36 | 20.6 | 71 | 20.2 |
| Vomiting | 10 | 5.6 | 9 | 5.1 | 19 | 5.4 |
| General disorders and administrative site conditions | | | | | | |
| Chills | 8 | 4.5 | 8 | 4.6 | 16 | 4.5 |
| Pyrexia | 8 | 4.5 | 11 | 6.3 | 19 | 5.4 |
| Injury, poisoning, procedural complications | | | | | | |
| Incision site complication | 57 | 32.2 | 69 | 39.4 | 126 | 35.8 |
| Procedural pain | 56 | 31.6 | 54 | 30.9 | 110 | 31.3 |
| Musculoskeletal, connective tissue disorders | | | | | | |
| Arthralgia | 12 | 6.8 | 12 | 6.9 | 24 | 6.8 |
| Back Pain | 44 | 24.9 | 39 | 22.3 | 83 | 23.6 |
| Buttock pain | 12 | 6.8 | 13 | 7.4 | 25 | 7.1 |
| Intervertebral disc protrusion | 4 | 2.3 | 9 | 5.1 | 13 | 3.7 |
| Muscle spasm | 25 | 14.1 | 31 | 17.7 | 56 | 15.9 |
| Muscular weakness | 9 | 5.1 | 9 | 5.1 | 18 | 5.1 |
| Musculoskeletal stiffness | 9 | 5.1 | 5 | 2.9 | 14 | 4.0 |
| Myalgia | 6 | 3.4 | 13 | 7.4 | 19 | 5.4 |
| Pain in extremity | 26 | 14.7 | 38 | 21.7 | 64 | 18.2 |
| Nervous system disorder | | | | | | |
| Dizziness | 10 | 5.6 | 8 | 4.6 | 18 | 5.1 |
| Headache | 14 | 7.9 | 12 | 6.9 | 26 | 7.4 |
| Hypoaesthesia | 18 | 10.2 | 26 | 14.9 | 44 | 12.5 |
| Hyporeflexia | 9 | 5.1 | 4 | 2.3 | 13 | 3.7 |
| Sensory loss | 4 | 2.3 | 8 | 4.6 | 12 | 3.4 |
| Psychiatric disorders | | | | | | |
| Insomnia | 12 | 6.8 | 7 | 4.0 | 19 | 5.4 |
| Skin and subcutaneous tissue disorders | | | | | | |
| Pruritis | 8 | 4.5 | 6 | 3.4 | 14 | 4.0 |

*AEs indicates adverse events.*

except for the musculoskeletal examination (Table 5). Subjects in the control group had more abnormalities in musculoskeletal examination (24%) than subjects in the treatment group (16%).

### Sensory Abnormalities

Subjects in the treatment group reported fewer abnormalities in lower extremity including pain, hypoaesthesia, and myalgia (n = 53) than subjects in the control group (n = 84).

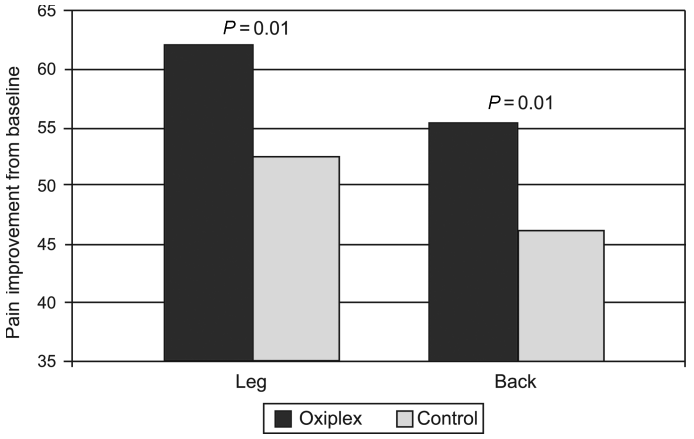


**Figure 1.** Improvement in leg and back pain by treatment using Lumbar Spine Outcomes Questionnaire (LSOQ) evaluations. When baseline back pain was severe (LSOQ score ≥ 63), the differences in leg and back pain improvements in the Oxiplex gel-treated group (n = 78) compared with the control group (n = 78) were statistically significant ($P = 0.01$ and $P = 0.01$, respectively).

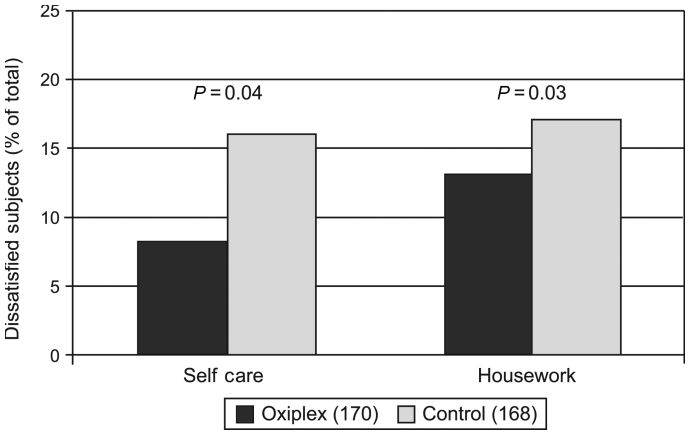


**Figure 3.** Improvement in daily activities by treatment. Significantly more subjects in the surgery-only control group reported dissatisfaction with their self-care and ability to perform housework compared with subjects in the Oxiplex gel-treated group.

Subjects in the treatment group (n = 4) reported fewer sensory abnormalities in the lower extremities than those in the control group (n = 10).

## DISCUSSION

The effectiveness of the gel for the reduction of leg and back pain as well as associated symptoms after single-level lumbar discectomy was determined using quality-of-life measures and clinical evaluations. As the study collected data through 6 months after surgery, the condition of the subjects could be determined at a time point that is generally considered predictive of long-term outcome.[12,15] The safety results showed no difference between groups. For all effectiveness measures, subjects in the treatment group did better than subjects in the surgery-only group. Physical examinations of subjects in the treatment group at 6 months identified fewer sensory abnormalities in the lower extremity than subjects in the control group. In the challenging group with severe back pain at baseline, subjects in the treatment group experienced significantly greater reductions in leg and back pain. Only 1 subject in the treatment group underwent reoperation during the 6-month study. In contrast, 6 subjects in the control group underwent reoperation. Overall, subjects in the treatment group were significantly more satisfied with their treatment and experienced significantly less disability than subjects in the control group.

The gel-treated group had no cases of cerebrospinal fluid (CSF) leaks or related abnormalities. Rodgers *et al*[11] showed in a rabbit model of lumbar laminectomy that application of the gel over the dura and through the laminectomy/laminectomy site prevented dural adherence to adjacent structures. Furthermore, when the dura was surgically entered, there were no differences in dural repair or healing in rabbits treated with gel compared with surgery-only controls. The absence of CSF leaks in the pivotal clinical study is consistent with preclinical studies. In addition, there have been no reports of CSF leaks

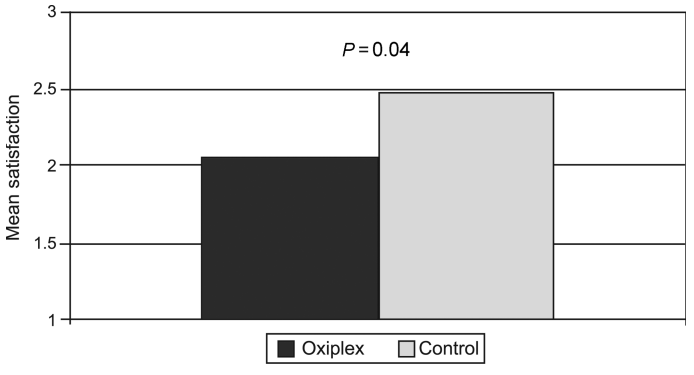


**Figure 2.** Improvement in overall patient satisfaction by treatment. When baseline back pain was severe (Lumbar Spine Outcomes Questionnaire score ≥ 63), the improvement in satisfaction exhibited in the Oxiplex gel-treated group (n = 89) compared with the control group (n = 98) was statistically significant ($P = 0.04$) (the lower the number, the greater the satisfaction).

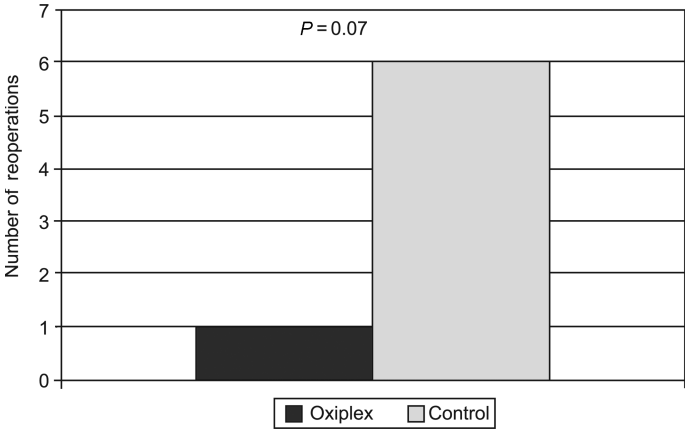


**Figure 4.** Reoperations. During the course of the study, 7 subjects underwent reoperations (Oxiplex gel-treated group, n = 1; control group, n = 6). All of these reoperations occurred within 3 months of the initial operation and occurred at the same lumbar level.

**TABLE 5. Abnormal Physical Examination at 6 Months Postoperatively**

| Body System* | Oxiplex N (%) | Control N (%) | Total Subjects N (%) | *P* Value† |
|---|---|---|---|---|
| Subjects randomized | 177 | 175 | 352 | |
| Subjects with physical examination at 6 mo | 140 | 144 | 284 | |
| General appearance | 7 (5.0) | 7 (4.9) | 14 (4.9) | 1.00 |
| Ears, eyes, nose, throat | 6 (4.3) | 10 (6.9) | 16 (5.6) | 0.44 |
| Head, neck, thyroid | 2 (1.4) | 3 (2.1) | 5 (1.8) | 1.00 |
| Lungs | 0 (0.0) | 2 (1.4) | 2 (0.7) | 0.50 |
| Chest, including breasts | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |
| Heart/cardiovascular | 1 (0.7) | 5 (3.5) | 6 (2.1) | 0.21 |
| Lymph nodes | 0 (0.0) | 1 (0.7) | 1 (0.4) | 1.00 |
| Abdomen | 6 (4.3) | 4 (2.8) | 10 (3.5) | 0.54 |
| Genitalia | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |
| Anorectal | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |
| Musculoskeletal | 22 (15.7) | 35 (24.3) | 57 (20.1) | 0.08 |
| Neurological (nonlower spine) | 44 (31.4) | 38 (26.4) | 82 (28.9) | 0.36 |
| Skin | 11 (7.9) | 8 (5.6) | 19 (6.7) | 0.48 |
| Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |

**Body systems are not mutually exclusive.*
*†P value is for Oxiplex* versus *Control at 6 months and is from Fisher's exact test.*
*N/A indicates not applicable.*

related to gel use since the product was introduced outside the United States in early 2002.

### Mechanism(s) of Action

Patients with sciatica and severe lumbar back pain comprise a clinically challenging subgroup of patients with disc herniation. Decompression surgery typically improves sciatica more than lumbar back pain.[9,10,17,18] The sensory nerve fibers predominate on the surface of the annulus fibrosis and along annular tears.[19,20] Patients with a herniated lumbar disc often have a greater density of sensory nerves in the annulus fibrosus and epidural space than patients with less severe lumbar back pain.[10,20–23] The wide variety of pain mediators that come in contact with these sensory nerves during and after disc surgery can sensitize neural tissue to postoperative pain and neurological symptoms.[23–25] In addition, exposed nuclear material can irritate the sensory nerves of the epidural space.[10,25] Increase in sensory nerve excitability that can occur after decompression surgery often prolongs sensory nerve sensitization resulting in pain and hyperalgesia long after the surgical procedure.[26–28]

The proposed mechanism of action of the gel is coating the sensory nerves of the epidural space, including the annulus fibrosus, dura, and nerve root, thereby providing a barrier to cellular and biochemical pain mediators that would otherwise lead to postsurgical pain. The polyethylene oxide component of the gel reduces protein deposition[29] on the surface of covered tissues. The carboxymethylcellulose component allows for gel adherence to tissues,[30] thereby placing both materials adjacent to tissue surfaces. Coverage of sensory nerves with gel after disc surgery would serve as a barrier to reduce their exposure to and contact with biochemical and cellular pain mediators while preventing adjacent structures from adhering to one another.[10]

Fibrosis has received considerable attention as a contributor to sciatica and lumbar back pain after decompression surgery. Kuslich *et al*[31] and Jou *et al*[32] found that spinal nerve roots encased in perineural fibrosis were sensitive to external stimulation in patients with prior laminectomies undergoing repeat procedures under minimal anesthesia. Other investigators have published data derived from a preclinical laminectomy model that resulted in a heightened sensitivity to pain.[33,34] Pain reduction occurred as a result of polysaccharide coverage of sensory nerves in the epidural space after laminectomy and disc injury. Similar findings were reported by Kato *et al*.[35]

Epidural fibrosis and subsequent tethering of the nerve root to the disc or pedicle (and thereby compression), may also contribute to postsurgical sciatica and lumbar back pain. However, results of clinical outcome studies attempting to correlate adhesion formation with pain have not been consistent, as most patients with epidural fibrosis do not develop symptomatic complaints.[36–38] The pain is thought to result from entrapment of the nerve root by fibrosis resulting in enhanced

sensitization. Support for this hypothesis was recently provided by Kobayashi *et al*,[39] who reported a correlation with sciatic pain, perineural fibrosis, and altered nerve root action potential in patients undergoing lumbar discectomy. Fransen[40] evaluated the extent of epidural fibrosis in a group of 396 patients after single-level disc herniation and presenting with sciatica often associated with lumbar back pain. All subjects were operated upon by the same surgeon in the same institution. Upon completion of a conventional microdiscectomy, the decompressed nerve root and epidural space including the annulus fibrosus were systematically covered with gel. Five patients needed reoperations for recurrent herniation, 2 after less than a week, 1 after 1 month, and 2 within the first year after surgery. During the reoperations, there was little or no epidural fibrosis noted that facilitated dissection and separation of the nerve root from surrounding tissues.

### Quality of Life Measures

Clinical evaluation of agents to reduce the incidence and severity of pain and related symptoms after lumbar surgery for discectomy is challenged by utilization of a clinically relevant measure with a metric amenable to rigorous review. Although magnetic resonance imaging of postlaminectomy patients readily identifies fibrosis at the surgical site, consistent correlation between fibrosis and postsurgical pain is largely unproven.[31,37,38,41–49] Pain scales are a common method for assessing patient outcome after back surgery; at least 22 scales have been previously developed.[50] Quantifying clinical results with these instruments is confounded by background "noise" inherent in pain analysis. The most widely used statistics are based on simple pre- and posttreatment score comparisons.[50–56] However, use of a single global statistic does not guarantee that the instrument performs well in all subsets of subjects.[50–55] The presence of pain alone is a narrow definition of outcome that correlates poorly with physical function.[50,52–54]

The LSOQ is a multi-item, self-report questionnaire designed to assess a number of factors that are relevant in evaluating treatment outcomes for patients with lumbar spinal disorders. The LSOQ was used in this pivotal study, with the approval of the Food and Drug Administration, as a valid measure of clinical outcomes after lumbar discectomy for herniated discs. LSOQ measures in this study from subjects at 6 months with relatively low back pain at baseline did not show a significant difference between study groups. In contrast, in subjects with severe back pain at baseline, there was a clear difference in measurable leg and back pain at 6 months between study groups, with gel subjects showing statistically significant improvements compared with controls. Sensitivity to detect changes toward the lower end of quality-of-life scales is typically less. The changes in scores and the minimal clinically important change for patients with low initial scores are smaller than for the average patient with these types of outcome measures.[51,55,57]

### Summary of European Publications on Oxiplex Gel

Multiple clinical studies from European investigators have been presented that confirm and extend the results reported here. Gill *et al*[58] found that gel-treated patients (N = 20) had a significant reduction in postoperative pain compared with randomized controls (N = 20) after decompressive spinal surgery. Simons[59] performed a large (N = 270 patients), randomized, controlled study of patients undergoing lumbar surgery for radiculopathy. The incidence of postoperative pain was reduced 50% in gel-treated patients compared with controls (16% *vs.* 8%). The need for postsurgical therapy was reduced to 3% for the gel-treated patients compared with surgery-only controls (8%). Fransen[40] compared the results of gel-treated patients (N = 184) to those who received Adcon-L (N = 62) after spinal surgery. Both were found to significantly reduce pain after surgery. Guizzardi *et al*[60] and Assietti *et al*[61] obtained similar results showing additional benefit from gel compared with surgery alone. In all of these studies, no significant adverse events were reported that were attributed to gel.

In summary, in this large pivotal study, Oxiplex gel was found to be safe when applied to the laminectomy/laminotomy site after discectomy. There were no CSF leaks in the gel-treated group. There was a general improvement in clinical outcomes (abnormal musculoskeletal examinations; neurological abnormalities) and subject satisfaction in the gel-treated subjects compared with surgery-only controls. Subjects in the treatment group had fewer abnormalities of sensory function as determined by physical examination and fewer reoperations. Although subjects in the treatment group had consistently better outcomes than subjects in the control group, the ability of the LSOQ to measure those differences was limited to subjects with leg pain as well as severe back pain at baseline. Taken together, these data demonstrate multiple improvements in clinical outcome compared with that achieved by surgery alone due to the addition of Oxiplex gel to discectomy for treatment of lumbar herniation.

## ➢ Key Points

- ❑ In a subgroup of patients with substantial back pain at baseline, Oxiplex reduced the severity of leg and back pain at 6 months after single-level lumbar discectomy compared with surgery alone.
- ❑ Oxiplex-treated subjects had fewer reoperations and neurological abnormalities at 6 months after removal of herniated discs compared with surgery-only patients.
- ❑ There were no safety issues or spinal fluid leaks in the 177 patients who received Oxiplex.
- ❑ Oxiplex was easy to apply to the surgical site.

### Acknowledgments

The authors thank the Oxiplex Clinical Study Group doctors: Anthony Asher, MD, Carolina Neurosurgery & Spine Associates, Charlotte, NC; Darrel Brodke, University of Utah, Salt Lake City, UT; Timothy Burd, Michael Longley, Eric Phillips, and John McClellan, Nebraska Foundation for Spinal Research, Omaha, NE; Thomas Chappell, UCI

Department of Neurosurgery, Orange, CA; Dennis Crandall, Sonoran Spine Center, Phoenix, AZ; Michael Daubs, Donald McKay, Orthopaedic Specialists of Nevada, Las Vegas, NV; John Delashaw, Alexander West, Oregon Health & Science University, Portland, OR; John Demakas, Deaconess Medical Center, Spokane, WA; Jeffrey Fischgrund, William Beaumont Hospital Orthopedic Research, Royal Oak, MI; Jeff Garr, Swedish Research Center, Seattle, WA; Matthew Hannibal, James Zucherman, St. Mary's Spine Center, San Francisco, CA; Jonathan Horne, Robert Horne, William Muir, Physicians' Research Options, Sandy, UT; Michael Janssen, DO, Center for Spinal Disorders, Thornton, CO; Donald Johnson, Southeastern Spine Institute, Mount Pleasant, SC; Eric Laxer, Bruce Darden, and Leon Dickerson, OrthoCarolina Spine Center, Charlotte, NC; Leon Liem, Neurological Institute, The Queen's Medical Center Neurological Institute, Honolulu, HI; Harry Lockstadt, Bluegrass Musculoskeletal Research, Lexington, KY; Robert Masson, Richard Smith, Stephen Goll, and Reginald Tall, Southeastern Clinical Research Consultants, Orlando, FL; Anthony Matan, SUNY Upstate Medical University, Syracuse, NY; Paul McCormick, Columbia University, The Neurological Institute Spine Center, New York, NY; Jan Muizelaar, Rolando Roberto, and Rudolph Schrot, UC Davis School of Medicine, Department of Neurological Surgery, Sacramento, CA; Daniel Robertson, John Dusseau, Bijan Bakhtian, Lee Neurosurgery, Fort Meyers, FL; Barton Sachs, Texas Back Institute, Plano, TX; Srinath Samudrala, Michael Wang, USC University Hospital, Los Angeles, CA; Arya Shamie, Langston Holly, and Larry Khoo, Santa Monica UCLA Medical Center, Santa Monica, CA; John Sledge, Richard Ozuna, Sports Medicine North Orthopaedics Surgery Inc., Peabody, MA; Michael Swank, Cincinnati Orthopedic Research Institute, Cincinnati, OH; John S. Thalgott, Center for Disease and Surgery of the Spine, Las Vegas, NV; Antoine Tohmeh, Orthopaedic Specialty Clinic of Spokane, PLLC, Spokane, WA; Alex Vaccaro, Rothman Institute, Philadelphia, PA; and William Welch, Joseph Maroon, and Peter Gerszten, UPMC Presbyterian University Hospital, Pittsburgh, PA.

## References

1. Slipman CW, Shin CH, Patel RK, et al. Etiologies of failed back surgery syndrome. *Pain Med* 2002;3:200–14.
2. Yamashita K, Ohzono K, Hiroshima K. Patient satisfaction as an outcome measure after surgical treatment for lumbar spinal stenosis: testing the validity and discriminative ability in terms of symptoms and functional status. *Spine* 2006;31:2602–8.
3. Papadopoulos EC, Girardi FP, Sandu HS, et al. Outcome of revision discectomies following recurrent lumbar disc herniation. *Spine* 2006;31:1473–6.
4. Skaf G, Bouclaous C, Alaraj A, et al. Clinical outcome of surgical treatment of failed back surgery syndrome. *Surg Neurol* 2005;64:483–9.
5. Skaf G, Long DM, Filtzer DL, et al. Clinical features of the failed-back syndrome. *J Neurosurg* 1988;69:61–71.
6. Keskimaki I, Seitsalo S, Osterman H, et al. Reoperations after lumbar disc surgery: a population-based study of regional and interspecialty variations. *Spine* 2000;25:1500–8.
7. Bosscher HA, Heavner JE. Incidence and severity of epidural fibrosis after back surgery: an endoscopic study. *Pain Pract* 2010;10:18–24.
8. Martin BI, Mirza SK, Comstock BA, et al. Reoperation rates following lumbar spine surgery and the influence of spinal fusion procedures. *Spine* 2007;32:382–7.
9. Kleinstück FS, Fekete T, Jeszenszky D, et al. The outcome of discectomy for lumbar herniated disc is influenced by the severity of concomitant pre-operative low back pain. *Eur Spne J* 2011;20:1166–73.
10. diZerega GS, Traylor MM, Alphonso LS, et al. Use of temporary implantable biomaterials to reduce leg pain and back pain in patients with sciatica and lumbar disc herniation. *Materials* 2010;3:3331–68.
11. Rodgers KE, Robertson JT, Espinoza T, et al. Reduction of epidural fibrosis in lumbar surgery with Oxiplex adhesion barriers of carboxymethylcellulose and polyethylene oxide. *Spine J* 2003;3:277–84.
12. BenDebba M, diZerega GS, Long DM. The Lumbar Spine Outcomes Questionnaire: its development and psychometric properties. *Spine J* 2007;7:118–32.
13. Kim KD, Wang JC, Robertson DP, et al. Reduction of radiculopathy and pain with Oxiplex/SP gel after laminectomy, laminotomy, and discectomy: a pilot clinical study. *Spine* 2003;28:1080–8.
14. Kim KD, Wang JC, Robertson DP, et al. Reduction in leg pain and lower-extremity weakness with Oxiplex/SP Gel for 1 year following laminectomy, laminotomy and discectomy. *Neurosurg Focus* 2004;17:ECP1.
15. Atlas SJ, Keller RB, Chang Y, et al. Surgical and nonsurgical management to a lumbar disc herniation: five year outcomes from the Maine Lumbar Spine Study. *Spine* 2001;26:1179–87.
16. Katz JN, Lipson SJ, Chang LC, et al. Seven to 10-year outcome of decompressive surgery for degenerative lumbar spinal stenosis. *Spine* 1996;21:92–8
17. Pearson AM, Blood EA, Frymoyer JW, et al. SPORT lumbar intervertebral disk herniation and back pain. *Spine* 2008;4:428–35.
18. Toyone T, Tanaka T, Kato D, et al. Low-back pain following surgery for lumbar disc herniation. A prospective study. *J Bone Joint Surg Am* 2004;86-A:893–6.
19. Palmgren T, Grönblad M, Virri J, et al. An immunohistochemical study of nerve structures in the anulus fibrosus of human normal lumbar intervertebral discs. *Spine* 1999;24:2075–9.
20. Freemont AJ. The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain. *Rheumatol (Oxford)* 2009;48:5–10.
21. Kobayashi S, Yoshizawa H, Yamada S. Pathology of lumbar nerve root compression. Part 1: Intraradicular inflammatory changes induced by mechanical compression. *J Orthop Res* 2004;22:170–9.
22. Takahashi K, Aoki Y, Ohtori S. Resolving discogenic pain. *Eur Spine J* 2008;17:428–31.
23. Aoki Y, Rydevik B, Kikuchi S, et al. Local application of disc-related cytokines on spinal nerve roots. *Spine* 2002;27:1614–7.
24. Burke JG, Watson RWG, McCormack D, et al. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. *J Bone Joint Surg Br* 2002;84:196–201.
25. Olmarker K, Myers RR, Kikuchi S, et al. Pathophysiology of nerve root pain in disc herniation and spinal stenosis. In: Herkowitz HN, Dvorak J, Bell GR, et al., eds. *The Lumbar Spine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:11–30.
26. Zimmermann M. Pathobiology of neuropathic pain. *Eur J Pharmacol* 2001;429:23–37.
27. Koshi T, Ohtori S, Inoue G, et al. Lumbar posterolateral fusion inhibits sensory nerve ingrowth into punctured lumbar intervertebral discs and upregulation of CGRP immunoreactive DRG neuron innervating punctured discs in rats. *Eur Spine J* 2010;19:593–600.
28. Bahari S, El-Dahab M, Cleary M, et al. Efficacy of triamcinolone acetonide and bupivacaine for pain after lumbar discectomy. *Eur Spine J* 2010;19:1099–103.
29. Lee JH, Kopecek J, Andrade JD. Protein-resistant surfaces prepared by PEO-containing block copolymer surfactants. *J Biomed Mater Res* 1989;23:351–68.
30. Madsen F, Eberth K, Smart JD. A rheological examination of the mucoadhesive/mucus interaction: the effect of mucoadhesive type and concentration. *J Control Release* 1998;50:167–78.

31. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica. *Orthop Clin North Am* 1991;22:181–7.
32. Jou IM, Tai TW, Tsai TM, et al. Spinal somatosensory evoked potential to evaluate neurophysiologic changes associated with postlaminotomy fibrosis: an experimental study. *Spine* 2007;32:2111–8.
33. Schimizzi AL, Massie JB, Murphy M, et al. High-molecular-weight hyaluran inhibits macrophage proliferation and cytokine release in the early wound of a preclinical postlaminectomy rat model. *Spine J* 2006;6:550–6.
34. Akeson WH, Massie JB, Huang B, et al. Topical high-molecular-weight hyaluronan and a roofing barrier sheet equally inhibit postlaminectomy fibrosis. *Spine J* 2005;5:180–90.
35. Kato T, Haro H, Komori H, et al. Evaluation of hyaluronic acid sheet for the prevention of postlaminectomy adhesions. *Spine J* 2005;5: 479–88.
36. North RB, Campbell JN, James CS, et al. Failed back surgery syndrome: 5-year follow-up in 102 patients undergoing repeated operation. *Neurosurgery* 1991;28:685–90.
37. Ido K, Urushidani H. Fibrous adhesive entrapment of lumbosacral nerve roots as a cause of sciatica. *Spinal Cord* 2001;39: 269–73.
38. Coskun E, Suzer T, Topuz O, et al. Relationships between epidural fibrosis, pain, disability, and psychological factors after lumbar disc surgery. *Eur Spine J* 2000;9:218–23.
39. Kobayashi S, Takeno K, Yayama T, et al. Pathomechanisms of sciatica in lumbar disc herniation: effect of periradicular adhesive tissue on electrophysiological values by an intraoperative straight leg raising test. *Spine* 2010;35:2004–14.
40. Fransen P. Safety of carboxymethylcellulose/polyethylene oxide for the prevention of adhesions in lumbar disc herniation – consecutive case series review. *Ann Surg Innov Res* 2008;2:2–5.
41. Ross JS, Robertson JT, Frederickson RC, et al. Association between peridural scar and recurrent radicular pain after lumbar discectomy: magnetic resonance evaluation. *Neurosurgery* 1996;38: 855–63.
42. Fager CA, Freidberg SR. Analysis of failures and poor results of lumbar spine surgery. *Spine* 1980;5:87–94.
43. Key JA, Ford LT. Experimental intervertebral disc lesions. *J Bone Joint Surg* 1948;30:621–30.
44. Kitano T, Zerwekh JE, Edwards ML, et al. Viscous carboxymethylcellulose in the prevention of epidural scar formation. *Spine* 1991;16:820–3.
45. Abitbol JJ, Lincoln TL, Lind BI, et al. Preventing postlaminectomy adhesion: a new experimental model. *Spine* 1994;19:1809–14.
46. Keskimaki I, Seitsalo S, Osterman H, et al. Reoperations after lumbar disc surgery. *Spine* 2000;25:1500–8.
47. Deutsch AL, Howard M, Dawson EG, et al. Lumbar spine following successful surgical discectomy. Magnetic resonance imaging features and implications. *Spine* 1993;18:1054–60.
48. Annertz M, Jonsson B, Stromqvist B, et al. Serial MRI in the early postoperative period after lumbar discectomy. *Neuroradiology* 1995;37: 177–82.
49. Van Goethem JW, Van de Kelft E, Biltjes IG, et al. MRI after successful lumbar discectomy. *Neuroradiology* 1996;38:S90–6.
50. Mannion AF, Elfering A. Predictors of surgical outcome and their assessment. *Eur Spine J* 2006;15:S93–108.
51. Davis RA. A long-term outcome analysis of 984 surgically treated herniated lumbar discs. *J Neurosurg* 1994;80:415–21.
52. Dvorak J, Gauchat MH, Valach L. The outcome of surgery for lumbar disc herniation. I. A 4-17 –years' follow-up with emphasis on somatic aspects. *Spine* 1988;13:1418–22.
53. Loupasis GA, Stamos K, Katonis PG, et al. Seven 20-year outcome of lumbar discectomy. *Spine* 1999;24:2313–7.
54. Little DG, MacDonald D. The use of the percentage change in Oswestry Disability Index score as an outcome measure in lumbar spine surgery. *Spine* 1994;19:2139–43.
55. Carey TS, Mielenz TJ. Measuring outcomes in back care. *Spine* 2007;32:S9–14.
56. Ebeling U, Reichenberg W, Reulen H-J. The use of the percentage change in oswestry disability index score as an outcome measure in lumbar spinal surgery. *Acta Neurochir* 1986;81:45–52.
57. Schofferman J, Reynolds J, Herzog R, et al. Failed back surgery: etiology and diagnostic evaluation. *Spine* 2003;3:400–3.
58. Gill C, Klufmoeller F, Noack W. Experience with Oxiplex/SP gel for the prevention of post-surgical adhesions in decompressive spine surgery. Paper presented at: North American Spine Society 18th Annual Meeting. October 21–25, 2003; San Diego, CA.
59. Simons P. Reduction of radiculopathy using medishield anti-adhesion gel in spinal surgery. Paper presented at: Congress of Neurological Surgeons. October 16–20, 2004; San Francisco, CA.
60. Guizzardi G, Morichi R, Vagaggini A, et al. Use of a novel gel-formulated anti-adhesion barrier for prevention of fibrotic adhesions in lumbar microdiscectomy procedures. Abstract presented at: Congress of Neurological Surgeons Annual Meeting. October 7–12, 2006; Chicago, IL.
61. Assietti R, Mora A, Brayda-Bruno M. Use of carboxymethylcellulose/polyethylene oxide gel in microdiscectomy with interlaminectomy. *Spine* 2008;1762–5.