Reduction of Leg Pain by Oxiplex Gel After Lumbar Discectomy in Patients With Predominant Leg Pain and Elevated Levels of Lower Back Pain

A Prospective, Randomized, Blinded, Multicenter Clinical Study

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Study Design: A prospective, randomized, blinded, multicenter clinical study.

Objective: To evaluate carboxymethylcellulose/polyethylene oxide gel (Oxiplex) in improving clinical outcomes in subjects having predominant leg pain and elevated low back pain undergoing first-time lumbar discectomy for disk herniation.

Summary of Background Data: Clinical studies in the United States and Italy found that Oxiplex reduced leg pain after decompression surgery.

Methods: A total of 68 subjects with herniated lumbar disk were enrolled and randomized into treatment (surgery plus gel) or surgery-only control groups. A prospective statistical analysis assessed the effect of gel in the severe back pain subgroup (prespecified as greater than or equal to median baseline back pain of the population studied). All subjects except 2 controls lost to follow-up completed the study. Preoperative and postoperative visual analogue scale leg pain scores were analyzed and compared between groups at 60 days after surgery.

Results: There were no serious adverse events or neurological safety concerns reported in any patients. Gel-treated patients had statistically significantly lower visual analogue scale leg pain scores at study end compared with controls ($P = 0.0240$), representing a 21% additional reduction in leg pain compared with surgery alone in the severe baseline back pain subgroup ($P = 0.0240$). The proportion of subgroup patients experiencing zero leg pain at study end was significantly higher in the gel treatment group (60%) than in the control group (23%) ($P = 0.0411$).

Conclusions: The data from this study confirm and extend results of 2 previous studies in Italy and the United States that reported statistically significantly greater reductions in leg pain in gel-treated patients with severe preoperative low back pain compared with patients who only underwent decompression surgery.

Key Words: carboxymethylcellulose, polyethylene oxide, Oxiplex, MediShield, leg pain, sciatica, herniated disk, lumbar discectomy, adhesions

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Lumbar disk herniation (LDH) is a common indication for surgical intervention in spinal disease. The typical clinical presentation is a patient with severe unilateral radicular leg pain, whereas the amount of concomitant low back pain (LBP) varies from none to severe. Although the natural history of LDH has been actively studied, the relationship between the extent of disk degeneration and the severity of radicular pain and LBP remains unclear.[1–4] Recently, Kleinstück and colleagues reported that the level of preoperative LBP was a predictor of outcome after surgical decompression. They reported that the greater the amount of preoperative LBP relative to leg pain, the worse the postoperative outcome. As surgery for a herniated disk is primarily performed to alleviate radicular leg pain, the amount of concomitant LBP before surgery affects therapeutic decisions.[5,6]

MATERIALS AND METHODS

Oxiplex Gel (FzioMed Inc., San Luis Obispo, CA) (also known under the trade name, MediShield Anti-Adhesion Gel, distributed by Medtronic Inc., Memphis, TN) is a sterile, absorbable, viscoelastic gel comprised of carboxymethylcellulose and polyethylene oxide. Oxiplex is a device that was shown in preclinical[7] and clinical studies[8,9] to reduce fibrosis and tethering of adjacent tissues when applied to the surgical site and adjacent epidural space after laminectomy and laminotomy. It is placed around neural tissues after spine surgery to reduce adhesion formation and related symptoms such as pain and is approved in nearly 70 countries outside the United

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States for use as a mechanical barrier to adhesion formation. In clinical studies in the United States and Italy, the gel was found to reduce postoperative leg pain and associated symptoms after decompression surgery.[10–13] Interestingly, the reduction of leg pain in patients with both leg pain and severe LBP was significantly greater than in the overall study cohort in a US study of 352 subjects when Oxiplex was used.[13]

To further evaluate the potential utility of Oxiplex, a follow-up clinical study was performed in subjects with LDH undergoing decompression surgery. This study was conducted in 2 parts at 2 tertiary teaching hospitals in Beijing and Xi'an, China. First, 68 subjects were enrolled and followed for 60 days postsurgery. Then, 25 additional subjects were enrolled and followed for the same period. The results for all 93 patients were recently published.[14] The results presented here represent the population in the first part of the study, with results stratified based on the amount of preoperative LBP. These results are compared with 2 similar studies that were independently performed in the United States[13] and Italy.[12] In all 3 studies, the use of Oxiplex resulted in a statistically significantly greater reduction in leg pain in patients who had severe preoperative back pain compared with surgery-only controls.

This is a randomized, controlled study in which preoperative (baseline) and postoperative leg and back pain were measured to evaluate the efficacy of Oxiplex gel in reducing postoperative pain and symptoms beyond that achieved by surgery alone. The study design was similar to that of the US study[13] in which leg pain, back pain, and symptoms were measured using the Lumbar Spine Outcomes Questionnaire (LSOQ).[15] However, as this quality-of-life instrument was not validated in Chinese, a 10 cm visual analogue scale (VAS) was used to measure leg pain and back pain, with the lower end representing no pain and the upper end representing agonizing (or excruciating) pain. At each follow-up visit, the patient indicated on the VAS the amount of pain they were experiencing at the current time. Additional variables, such as VAS back pain and the Oswestry Low Back Pain Disability Questionnaire (ODI), were also measured.

The study was approved by the China State Food and Drug Administration and was a randomized, single-blinded investigation. The subjects filled out the VAS scores and remained blinded to treatment strategy throughout the study. The surgeons could not be blinded due to the need for adjunctive application of the gel in 1 treatment group during surgery. Ethics Committee approvals were obtained at both centers before initiating subject enrollment. Adult subjects undergoing their first surgical intervention for a diagnosed disk herniation at L4–L5 or L5–S1 signed an informed consent and were evaluated for eligibility at baseline (preoperatively) and intraoperatively. Randomization occurred after the subject's surgical procedure had been completed, at the point where hemostasis had been achieved and the surgeon was ready to close the operative site. Randomization occurred on a 2:1 basis (treats:controls) such that the distribution of study subject assignment to treatment arms remained consistent throughout the study.

Medtronic China provided the MediShield gel used in this study and a grant to offset study costs. Subjects were identified by a unique subject identification number only. Data were collected at each site on study-specific Case Report Forms. These data were subsequently provided to FzioMed by Medtronic for analysis by an independent statistician. Before analysis, a prospective statistical analysis plan (SAP) was written by the independent contractor to analyze the clinical data according to the same statistical methodology that was used to analyze the US study results.

Up to 70 subjects were planned for enrollment to obtain 60 evaluable subjects (40 in the study treatment arm and 20 in the study control arm) at 2 investigational sites. Subjects eligible for this study were adults (18–70 y of age) who were scheduled to undergo their first surgical intervention to treat unilateral herniation of a lumbar intervertebral disk. All study subjects had sciatic pain on the same side of their body as the disk herniation. Subjects had radiologic evidence (magnetic resonance image study or computed tomography/myelogram) of nerve root compression, and/or confirmed existence of an extruded or sequestered disk 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 leg pain as determined by visual analogue score (VAS). Subjects were excluded who received steroids within 4 weeks before surgery, a lumbar puncture within 24 hours before surgery, or were diagnosed with foraminal stenosis. Subjects who belonged to a current or anticipated worker's compensation claim or 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 >1 level, exploration of contralateral side, or epidural fat placement.

Eligible subjects were randomized to the treatment group (surgery plus gel) or control group (surgery without gel). Randomization was computer generated and study site specific on a 2:1 basis (treatment:control). 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 through 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. The surgeons who applied the gel did not participate in collection of VAS scores or

clinical outcomes. Subjects were evaluated for efficacy at 60 days postoperatively and for safety at 30 and 60 days postoperatively. In addition, other measures were captured, including wound assessment and documentation of adverse events.

Subjects in the treatment and control groups underwent the 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 epidural 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 a routine manner.

Study Endpoints

Although this study was not initially designed to prospectively focus on the severe baseline back pain subgroup, a prospective SAP was drafted before the analysis of these data to assess the effect of Oxiplex in the severe back pain group, which was prespecified as subjects with baseline back pain greater than or equal to the median baseline back pain of the population studied (ie, the same as the definition in the US study).

The primary effectiveness endpoint was based on a VAS (on a scale of 0–10) to measure leg pain and back pain, with the lower end representing no pain and the upper end representing agonizing (or excruciating) pain. The primary effectiveness outcome was the change from baseline (follow-up visit score minus baseline score) in leg pain as measured by VAS among patients whose baseline back pain was at or above the median.

Statistical Methods

The SAP and data analysis were performed by an independent statistician. The prospective SAP prespecified stratification based on baseline back pain greater than or equal to the median baseline back pain of the population studied. The primary effectiveness variable was evaluated with a 1-sided, 2-sample t test and if variances between the 2 groups were not different, a Wilcoxon rank-sum test could be performed. The study was powered at 80% to show a difference in leg pain at $P < 0.05$ level based on results from a previous feasibility study.[11,12] For safety analyses, the Fisher exact test was used except where otherwise specified to assess statistical significance, and a 2-sided $P < 0.05$ was considered to be significant.

RESULTS

Study Population and Baseline Characteristics

A total of 68 subjects (45 treated and 23 control subjects) were enrolled, including 33 subjects with severe baseline back pain. All subjects completed the study with the exception of 2 control subjects (1 at each site) who were lost to follow-up and were are not included in the analysis. The accountability rate for this study was 66/68 (97.1%) for each study visit at days 30 and 60.

Baseline characteristics such as age, sex, level treated, and neurological abnormality were evaluated to ensure these characteristics did not differ by treatment group and did not impact the study results. The summary of these baseline characteristics for the overall population is presented in Table 1, which compares the baseline characteristics of the treatment groups. Importantly, there were no differences between the treatment groups with respect to baseline leg and back pain. The only parameter that was significantly different between treatment groups was level treated; however, this difference was analyzed and found not to impact treatment response.

Primary Endpoint Analysis

The primary endpoint analysis was performed using patients whose baseline back pain was at or above the median baseline back pain level in the study population (ie, the same method for identifying the severe baseline back

TABLE 1. Baseline Characteristics by Treatment Group

Characteristics	Total*	Control	Oxiplex	P
Age (y)				0.7150†
Mean (SD), N	39.68 (12.51), 62	38.86 (9.77), 21	40.10 (13.80), 41	
Median (min., max.)	38.0 (18, 74)	36.0 (25, 58)	38.0 (18, 74)	
Baseline VAS leg pain				0.9035†
Mean (SD), N	6.12 (2.13), 66	6.17 (2.09), 21	6.10 (2.16), 45	
Median (min., max.)	6 (0, 10)	6.0 (3, 10)	6.0 (0, 10)	
Baseline VAS back pain				0.1733†
Mean (SD), N	4.52 (2.47), 65	5.13 (2.31), 21	4.23 (2.51), 44‡	
Median (min., max.)	5 (0, 10)	5.0 (0, 10)	4.0 (0, 9)	
Sex (male), n/N (%)	39/66 (59.09)	12/21 (57.14)	27/45 (60.00)	1.0000§
Level				0.0314§
L3–L4, n/N (%)	0/65 (0.00)	0/21 (0.00)	0/44 (0.00)	
L4–L5, n/N (%)	38/65 (58.46)	8/21 (38.10)	30/44 (68.18)	
L5–S1, n/N (%)	27/65 (41.54)	13/21 (61.90)	14/44 (31.82)	
Neurological abnormality, n/N (%)	40/66 (60.61)	9/21 (42.86)	17/45 (37.78)	0.7889§

*Demographic data missing for 4 subjects.
†Two-sided 2 sample t test.
‡One Oxiplex subject did not have a baseline back pain recorded.
§Two-sided Fisher exact test.

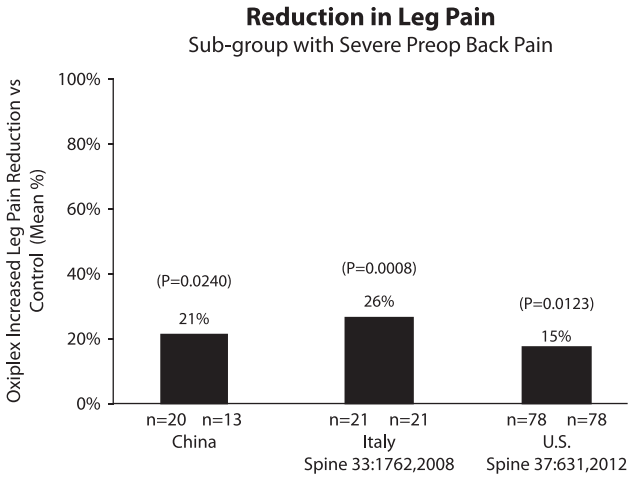

FIGURE 1. Study subjects in China with predominant preoperative leg pain and concomitant severe back pain who received Oxiplex applied to the epidural space and sciatic nerve after lumbar discectomy had 21% greater reduction in leg pain compared with surgery-only controls. This significant reduction in leg pain ($P = 0.0240$) confirmed previous reports of significant reduction in leg pain from similar surgical procedures performed in Italy (26%, $P = 0.0008$, Assietti et al[12]) and the United States ($P = 0.0123$, Rhyne et al[13]).

pain subgroup as in the US study[10]). Analyzing this subgroup required finding the median VAS value in the study population. The median baseline VAS back pain score for subjects in this study was 5.0, on a 0- to 10-point scale.

Therefore, the patients with baseline VAS back pain ≥ 5.00 constituted the severe back pain subgroup. Approximately half of the subjects (N = 33; n = 20 Oxiplex, n = 13 control) are included in this group.

Analysis of Severe Back Pain Subgroup

The change from baseline in VAS leg pain among subjects with severe baseline back pain was significantly greater in the Oxiplex subjects than the improvement in the control group ($P = 0.0240$, 1-sided unequal variance t test). As shown in Figure 2, Oxiplex subjects (N = 20) experienced a 6.74 point improvement from baseline in leg pain during the study, compared with a 5.31 point improvement in the control group (N = 13). Oxiplex conferred a 1.4 point advantage (21% greater reduction) compared with surgery alone with respect to improvement in leg pain among subjects with severe baseline back pain (Fig. 1).

The minimum reduction in leg pain achieved for any study subject in the Oxiplex group was 4.5 points compared with baseline, whereas in the control group, the minimum reduction was 2 points. The SD was also slightly smaller in the Oxiplex group than the control group. As shown in Figure 3, the proportion of patients with severe baseline back pain experiencing zero leg pain at study end was significantly higher in the Oxiplex group (60%) than for the control group (23%) ($P = 0.0411$, 1-sided Fisher exact test). The percentage of patients with zero leg pain in the overall population was also significantly greater for Oxiplex patients (56%) than for control patients (24%) ($P = 0.0148$, 1-sided Fisher exact test).

Safety

The primary safety outcome evaluated was the frequency and severity of adverse events, including surgical complications. There were no adverse events or operative complications reported and, as such, there were no severe adverse events reported. In addition, there were no unanticipated adverse device effects reported. It should also be noted that there were no neurological safety concerns in

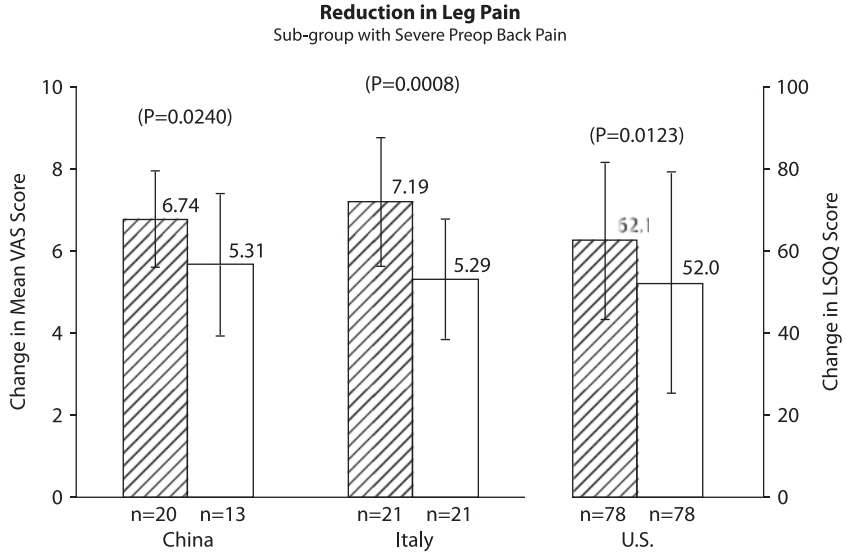

FIGURE 2. Study subjects in China with predominant preoperative leg pain and concomitant severe back pain who received Oxiplex applied to the epidural space and sciatic nerve after lumbar discectomy had a significantly lower visual analogue pain (VAS) score at study end compared with surgery-only controls ($P = 0.0240$). This significant reduction in VAS score confirmed previous reports of significant reductions in VAS scores from similar studies performed in Italy ($P = 0.0008$, Assietti et al[12]) and the United States ($P = 0.0123$, Rhyne et al[13]).

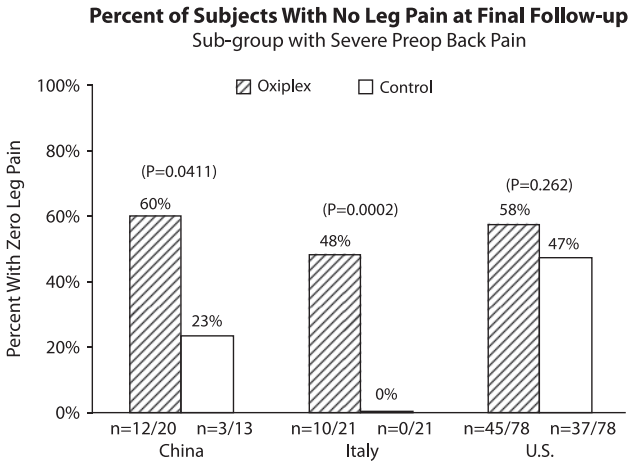

FIGURE 3. Study subjects in China with predominant preoperative leg pain and concomitant severe back pain who received Oxiplex applied to the epidural space and sciatic nerve after lumbar discectomy showed a significant increase in the number of subjects who had no leg pain at study end compared with surgery-only controls (37%, $P = 0.0411$). This significant increase in the number of subjects with no leg pain who received Oxiplex compared with surgery-only confirmed previous reports of increases in the number of subjects with no leg pain from Italy (48%, $P = 0.0002$, Assietti et al[12]) and the United States (6%, Rhyne et al[13]).

any study subject. A L5 left sensory abnormality at baseline remained unchanged in 1 Oxiplex subject. In 2 control subjects with sensory abnormalities, there was improvement at the 30-day follow-up but a return to the baseline level abnormality at the time of the 60-day follow-up. No subjects in either group required reoperation.

DISCUSSION

Patients with sciatica and severe LBP comprise a clinically challenging subgroup of patients with disk herniation.[5,6,16–20] Decompression surgery typically improves sciatica more than LBP.[5,6,20] Patients with a herniated lumbar disk often have a greater density of sensory nerves in the annulus fibrosus and epidural space than patients with less severe back pain.[21–25] The wide variety of pain mediators, including nucleus material, that come in contact with these sensory nerves during and after disk surgery can sensitize neural tissue to postoperative LBP.[26–35] The clinical data reported here are consistent with the hypothesis that Oxiplex gel functions as a physical barrier by coating the sensory nerves (ie, nerve root, annulus fibrosis, and associated neural structures in the epidural space). By reducing the surface area of sensory nerve exposure, the gel barrier reduces exposure of the nerves to irritants and proinflammatory mediators that can cause pain.[7,20,36]

Epidural fibrosis and subsequent tethering of the nerve root to the disk or pedicle may also contribute to postsurgical sciatica and LBP.[37–40] However, results of clinical outcome studies attempting to correlate adhesion formation with pain have not been consistent. In addition, epidural fibrosis may contribute to enhanced sensitization of the sensory nerves in the epidural space. Support for this hypothesis was recently provided by Kobayashi et al,[41,42] who reported a correlation with sciatic pain, perineural fibrosis, and altered nerve root function in potential patients undergoing lumbar discectomy. Kuslich et al[43] and Jou et al[44] 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[45] have published supportive data derived from preclinical study of laminectomy and disk injury.

Although there are no fibrosis data available from the 3 clinical studies evaluating postoperative pain reduction with Oxiplex, Fransen did evaluate the extent of epidural fibrosis in 396 patients who presented with sciatica and were treated with Oxiplex gel after single-level disk herniation.[9] After microdiscectomy, the decompressed nerve root and epidural space including the annulus fibrosis were 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, which facilitated dissection and separation of the nerve root from surrounding tissues.

Rhyne et al[13] demonstrated that the use of Oxiplex significantly increased the improvement in leg pain among patients with severe baseline back pain compared with surgery alone. Oxiplex subjects also achieved a higher minimum improvement in leg pain compared with the control group with a smaller SD, demonstrating more consistent results. In addition, the percentage of patients achieving zero leg pain at the conclusion of the study was significantly increased in both the severe baseline back pain subgroup and the overall population, with over double the proportion of patients achieving zero leg pain in the Oxiplex group compared with the control group in these analyses.

The data from this study confirm and extend results of 2 previous studies (Assietti et al[12] in Italy; Rhyne et al[13] in the United States) that reported a significantly greater reduction in leg pain after the use of Oxiplex in patients with severe preoperative LBP who underwent decompression surgery (Fig. 1). The study of Oxiplex in Italy was a randomized, blinded, 70-patient consecutive case series conducted by surgeons in Milan who evaluated the safety and efficacy of Oxiplex in reducing leg and back pain in subjects undergoing lumbar surgery for treatment of a herniated lumbar disk. Subjects were randomized to receive either gel plus surgery or surgery only. As in the Chinese study reported here, leg and back pain were measured using the VAS. Adults undergoing their first surgical intervention for disk herniation at L4–L5 or L5–S1 were evaluated for eligibility at baseline (preoperatively) and at 30 days, 3, 6, 12, 24, and 36 months after surgery using the VAS scale, and adverse events at 12, 24, and 36 months after surgery. Although this study was not initially designed to prospectively focus on the severe baseline back pain subgroup, the same prospective

SAP that was used to analyze the data from the Chinese study discussed here was used to analyze the Italian data to assess the effect of gel in the severe back pain group (ie, subjects with baseline back pain greater than or equal to the median baseline back pain). A total of 42 subjects with severe baseline back pain were enrolled in the Italian study. The median baseline back pain VAS score for subjects in this study was 2.0 on a 0–10 VAS scale. As shown in Figure 2, gel-treated subjects (N = 21) had a significantly greater improvement in leg pain VAS (7.19 point improvement) compared with controls (N = 21) (5.29 point improvement) ($P = 0.0008$).

The study of Oxiplex in the United States was a prospective, multicenter, randomized, controlled investigation with 352 subjects (177 treated, 175 control[13]). All subjects underwent lumbar disk surgery for herniated nucleus pulposus; the control group received surgery alone, whereas the treatment group received surgery plus gel. Subjects were followed for 6 months after surgery. The LSOQ[15] was the primary outcome measure used to assess leg pain, back pain, and symptoms. Among subjects with severe baseline back pain, improvement in leg pain from baseline to the 6-month visit was significantly greater ($P = 0.0123$) for gel-treated subjects (n = 78) compared with control subjects (n = 78). In addition, a higher percentage of gel-treated subjects (50/92, 54.4%) with severe baseline back pain completed the study with no leg pain at 6 months compared with the control group (48/101, 47.5%) (Fig. 3). The median score in the gel-treated subjects with severe baseline back pain was also zero at final follow-up, compared with a LSOQ score of 13 in the control group. Patients with severe baseline back pain that were treated with gel also experienced significantly greater satisfaction at 6 months when compared with controls (22.7%; $P = 0.015$).

Reoperation rates were also measured in this study and may be considered from the perspective of the SPORT Study, which presented a large series of subjects undergoing similar surgical procedures for LDH using contemporary surgical techniques. Reoperation rates of 4%, 5%, and 7% at 1, 2, and 3 years, respectively, were reported after surgery in the SPORT Study (Weinstein et al[46]). In comparison with those results, Oxiplex-treated subjects experienced reoperation rates ranging from 0% in the Chinese and Italian studies to 0.6% in the US study. The reoperation rates for the control subjects in the Chinese, Italian, and US studies was 0%, 5.7%, and 3.4%, respectively (Fig. 4).

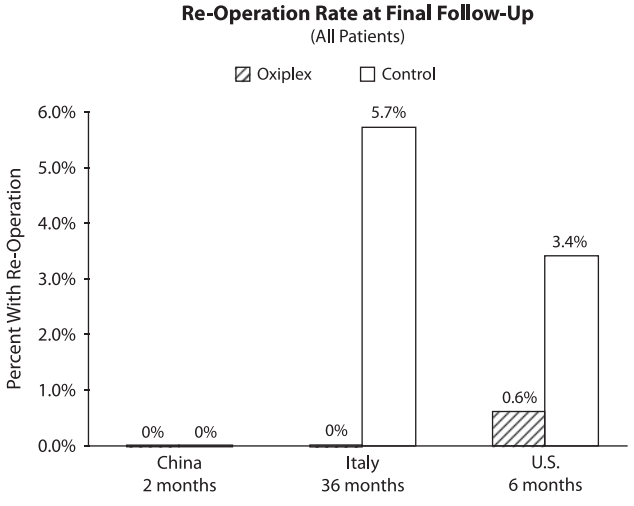

FIGURE 4. None of the study subjects in China with preoperative leg pain and back pain who received Oxiplex applied to the epidural space and sciatic nerve after lumbar discectomy underwent reoperation during the 2-month follow-up period. A reduction in reoperation rates in subjects who received Oxiplex compared with surgery-only controls was reported in the study from Italy (Oxiplex: 0, controls: 5.7% at 36 mo follow up, Assietti et al[12]) and the United States (Oxiplex: 0.6%, controls: 3.4% at 6 mo follow up, Rhyne et al[13]).

CONCLUSIONS

The clinical data presented here from a randomized, blinded, controlled, 2-center study in China confirm the results of the 2 other clinical studies utilizing Oxiplex gel. Taken together, these studies included nearly 500 subjects. As there were no serious device-related or unanticipated adverse events observed in any of the studies, no significant risks seem to be associated with the use of the gel. Among patients with predominant leg pain and concomitant severe baseline back pain, greater leg pain reduction was observed in Oxiplex-treated subjects across all 3 studies compared with control subjects receiving only surgery. The difference in favor of Oxiplex ranged from 15% to 26% and duration of this benefit persisted for at least 6 months.[12,13]

The results of this investigation demonstrated that Oxiplex had a statistically significant and clinically meaningful effect on the degree of reduction in leg pain from baseline, which confirms the findings from the studies performed in the United States[13] and Italy.[12] These observations support the role of Oxiplex in reducing leg pain among challenging patients with concomitant severe baseline back pain.

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