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Dual-Polymer Carboxymethyl Cellulose and Poly(Ethylene Oxide) Gel Reduces Leg and Back Pain in Patients With Severe Leg and Back Pain Following Single-Level Partial Discectomy

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Study Design. Prospective, randomized, double-blinded, multicenter trial.

Objective. Evaluate the safety and effectiveness of Oxiplex (dual-polymer gel) as an adjuvant during single-level partial discectomy in patients with severe leg and back pain.

Summary of Background Data. Dual-polymer gel previously reduced leg and back pain after partial lumbar discectomy in a subgroup of patients with severe leg and back pain.

Methods. Following single-level partial lumbar discectomy, participants were randomized to surgery plus dual-polymer gel (treatment) or surgery alone (control). The primary endpoint was the reduction in leg pain on the visual analog scale (VAS) at 6 months. Secondary outcomes were reductions in Sciatica Bothersomeness Index (SBI), back pain VAS, Oswestry Disability Index (ODI), SF-12 Mental (MCS) and Physical (PCS) Component Summaries, return to work, and patient satisfaction at 6-months.

Results. One hundred thirty-four participants were randomized 2:1 [ITT cohort (N = 134); n = 87 Treatment; n = 47 controls]. There were no clinical differences in safety or adverse events. Following removal of participants with protocol deviations, the Per Protocol cohort was N = 102 (n = 69 treatments; n = 33 controls). Reductions in VAS leg pain, primary outcome measure, were not different (treatment −73.9; control −72.7). However, VAS Leg Pain improved by 100% for 33 of 68 treatments (5% increase *vs.* controls); ≥ 90% for 50 treatments (11% increase *vs.* controls). SBI decreased by 100% for 20 of 67 Treatments (11% increase *vs.* controls); SBI decreased by ≥ 90% for 33 treatments (24% increase *vs.* controls). SBI leg pain component decreased ≥ 80% in treatments *vs.* 66% of controls; $P = 0.039$. More treatments achieved meaningful VAS back pain reduction (≥ 30%) than controls (93% *vs.* 88%). ODI decreased by 100% for 20 of 68 treats (13% increase *vs.* controls).

Conclusion. The addition of dual-polymer gel as an adjuvant to partial discectomy for the treatment of severe pain, reduced leg and back pain, as well as increased the proportion of participants with the best responses to surgery.

Evidence of level: Level I.

Key Words: adhesion, adjuvant, back pain, gel, leg pain, pain, polymer

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Although treatment of ipsilateral leg pain is commonly relieved by decompression of the herniated lumbar disc associated with the nerve compression, when the patient's symptoms are complicated by severe lower back pain (LBP), surgical intervention is often less successful.[1–7] The immune response following disc injury and its role in stimulating local pain following surgery is well known.[8–11] Early inflammatory signaling impacts long-term pain perception. The more stimulation pain receptors experience early on, the longer pain is perceived even after the initial inciting injury has been resolved. Pain diminishes with resolution of the tissue immune response.[12–14] Soon after discectomy, lymphocytes and macrophages infiltrate the epidural space where they release inflammatory protein mediators (inflammatory cytokines including interleukins and growth factors).[11–15] A dual-polymer gel

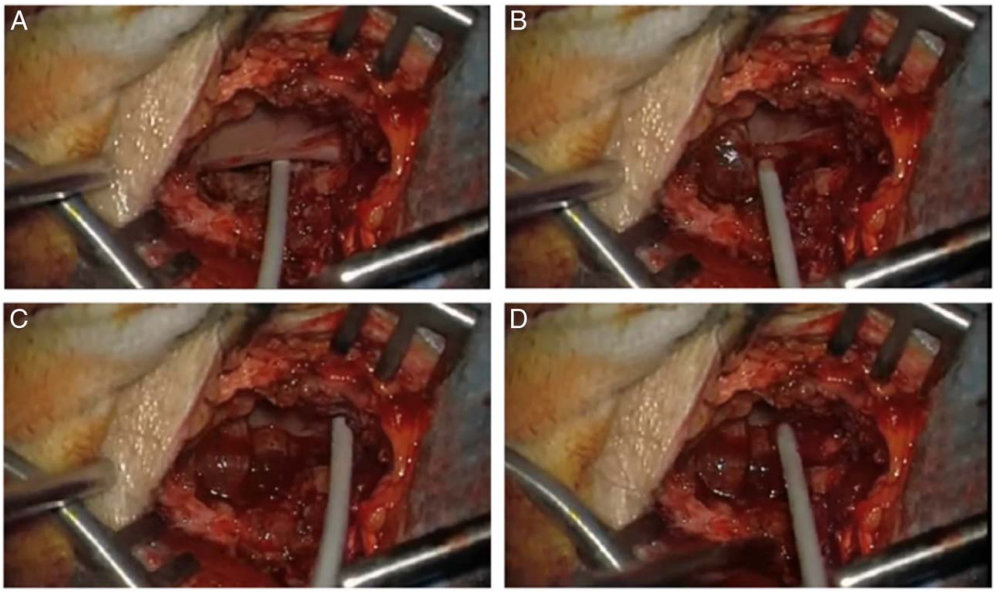

Figure 1. Use of dual-polymer gel applied in epidural space through applicator following partial discectomy: (A) placement of applicator under nerve, (B) administration of gel over posterior surface of nerve, (C) placement of applicator over top of nerve, and (D) administration of gel over anterior surface of nerve, producing circumferential coverage of nerve.

[Oxiplex: carboxymethylcellulose (CMC) and poly (ethylene oxide) (PEO); Fziomed, Inc., San Luis Obispo, CA, Fig. 1] was shown in preclinical studies[16–19] and a clinical report[20] to reduce postoperative fibrosis when applied over the surgical site following spinal surgery. The dual-polymer gel contains PEO, which partitions or disassociates proteins (inflammatory mediators), reducing their biological activity.[21–25] This should limit the availability of inflammatory mediators to pain receptors, thereby reducing their immune-driven stimulation. The feasibility of this hypothesis was recently demonstrated by chitosan hydrogels with immunoregulatory properties that remodeled the inflammatory microenvironment following spinal cord injury in a preclinical model.[26]

When used as a surgical adjuvant, dual-polymer gel was shown to reduce leg pain following partial discectomy over 6 months.[1,27–31] Further analysis identified a subgroup of patients with severe leg and LBP who had significant improvement in both following surgery when dual-polymer gel was used as an adjuvant.[1,31] These observations suggest the etiology of LBP with lumbar disc herniation may involve additional pathology in the epidural space than that of nerve compression alone.[32,33] Accordingly, a prospective, randomized, evaluator and patient blinded study was performed that only included patients with both severe leg and LBP undergoing initial surgery to decompress a herniated lumbar disc to confirm the benefit of dual-polymer gel in this difficult to treat population.

MATERIALS and METHODS

This was a prospective, randomized, multicenter, patient and evaluator-blinded study involving 17 centers in the United States to assess the safety and effectiveness of dual-polymer gel for the reduction of severe ipsilateral leg and LBP following lumbar single-level partial discectomy. The clinical protocol was approved by the FDA (NCT03433391). All participants signed informed consent and followed guidelines for experimental investigation with human subjects required by the institution with which the investigators were affiliated.

Inclusion/Exclusion Criteria

Adults (22–70 years of age) with unilateral herniation of a lumbar disc scheduled for their first surgical intervention to treat severe leg and LBP were screened. participants had severe leg pain ($\geq$60 mm) and back pain ($\geq$50 mm) scores on a visual analog 100 mm scale [VAS], radiologic evidence (MRI or CT scan) of nerve root compression, and/or an extruded or sequestered disc fragment and symptoms at the L4–L5 or L5–S1 level. Preoperative exclusion criteria were a radiographic confirmation of severe facet disease or facet degeneration at the index lumbar level, foraminal stenosis, prior spine surgery, removal of far lateral disc herniation at L4-L5 or L5-S1, trauma to the lumbar spine, or sequestered disc fragment. Intraoperative exclusions were severe facet disease or facet degeneration at the lumbar level, durotomy, spinal fusion, multilevel herniation, or involvement of more than one level, exploration of the contralateral side, or epidural fat placement at the site of the decompression. Participants underwent $\geq$6 weeks of nonoperative treatment unless pain was intractable or loss of neurological function was progressive. Participants were excluded if they received oral or epidural steroids within 4 weeks or NSAIDs within 72 hours before surgery, a lumbar puncture within 24 hours before surgery, subject to a worker's compensation claim or party to personal injury litigation.

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Site-specific randomization in blocks of 2 and 4 was determined after intraoperative eligibility was satisfied. Participants and study personnel who recorded outcome measures were blinded to treatment assignment. Controls underwent standard discectomy surgery. After surgery, participants in the treatment group had their annulus fibrosus, dura, and the exiting nerve root coated with up to 3 mL of dual-polymer gel along the anterior and posterior surfaces following completion of hemostasis. Sufficient gel was applied to fill the surgical site to the vertebral lamina. The wound was closed in routine fashion.

Sample Size Determination

Sample size was informed by a study that measured the effectiveness of dual-polymer gel in leg pain reduction in patients with severe leg and LBP undergoing lumbar surgery for a herniated disc.[31] A two-group *t* test with a 0.025 one-sided significance level was calculated at 90% power to detect a difference in means of −9.9, assuming the pooled standard deviation was 16.3, when sample sizes in the two groups were 88 and 44, respectively [a total sample size of 132 (nQuery Advisor 7.0)].

Statistical Methods

Endpoints

The primary hypothesis test was performed with a 95% two-sided confidence interval for the adjusted month 6 treatment group contrast comparing treatment to control groups using a mixed model for repeated measures.[34] Primary outcome was the change from baseline in leg pain VAS score at 6 months. Variables in the model included treatment group (surgery plus dual-polymer gel *vs.* surgery alone control), visit (week 6, month 3, and month 6), treatment group-by-visit interaction, and baseline value of VAS leg pain. An unstructured covariance matrix was used to allow variances and covariances to vary over time. The model was designed to account for correlations among responses over time. Multiple imputation was used to impute participants without month 6 values. Overlap coefficient measures (OVL) were calculated to evaluate the overlapping areas of response distributions.[35–38]

Derivation of High Responders

Receiver operating characteristics (ROC) curves were constructed to determine "responder" and "high responder" thresholds for continuous effectiveness endpoints. Participants who reported being 'Very Satisfied' on the satisfaction patient-reported outcome (PRO) provided assessments (anchors) that maximized sensitivity and specificity in identifying clinically meaningful thresholds.[39] Table 1 displays the worsened, no response, responder (clinically meaningful), and high responder thresholds for each of the continuous effectiveness endpoints using satisfaction PRO anchor-based thresholds. ROC thresholds were consistent with or higher than published thresholds.[39–42] Participants who met the responder threshold will be responders and participants who exceeded the responder threshold will be high responders.

Adverse Events

Adverse events (AEs) were assessed and categorized by the investigator. The collection of AEs began in the operating room following the incision(s) and was collected through the final visit, reported in eCRFs, and followed to resolution or study exit. A Clinical Events Committee (CEC) comprised of three clinicians (neurosurgeon, orthopedic surgeon, and interventional pain management), blind to treatment assignment, not affiliated with the Sponsor, and not participating in the study, adjudicated all SAEs and adverse events possibly related to the device or procedure.

RESULTS

Comparison of demographic, continuous, and categorical variables are shown in Tables 2 and 3. Safety analysis was conducted on the intent-to-treat (ITT) cohort, which included all participants who received study treatment (N = 134: n = 87 treatment group; n = 47 control group). The method of dual-polymer gel application, performed through microdiscectomy (71%) and non-microdiscectomy (29%) at the end of the procedures, was similar between groups. There were no adverse events considered by principal investigators or CEC to be definitely related to the device (Table 4). There were two events (hematoma resolved by drainage; foot numbness resolved by walking) considered possibly device-related. Secondary surgical interventions were similar between the treatment and control groups (6.9% *vs.* 6.4%, respectively).

Efficacy

A committee of three practicing, academic-based spinal surgeons, not affiliated with the sponsor, and blinded to treatment assignment and outcomes, adjudicated results of screening including radiologic reports and intraoperative records to identify protocol deviations. Participants without protocol deviations comprised the Per Protocol cohort used to evaluate efficacy (N = 102: n = 69 treatment; n = 33 controls).

Ipsilateral Leg Pain

There was not a significant difference in reduction of VAS leg pain between groups at 6-months (treatment: −73.9; control: −72.7). Although the primary outcome measure was not met, VAS leg pain improved by ≥ 68 points (high responders) for 51 of 68 treatment group participants (75.0%), an increase of 12.5% compared with control group participants (Fig. 2); VAS leg pain improved by 100% at 6-months (complete resolution) for 33 of 68 treatment group participants (5% increase compared with control group participants); VAS leg pain reduced by ≥ 90% for 50 of 68 treatment group participants (11% increase compared with the control group, Table 5). OVL (0.559) was consistent with good differentiation in the leg pain outcomes of both study groups (Fig. 3).

Back Pain

VAS back pain improved more in the treatment group than in the control group (−62.5 *vs.* −57.8, respectively).

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TABLE 1. Thresholds for Responder Designations Based on Responder Operating Characteristic (ROC) Analysis Using the Patient Satisfaction PRO as Anchor

Continuous effectiveness endpoint	Worsened	No response (not clinically meaningful)	Responder threshold (clinically meaningful)	High responder threshold (roc-supported optimized outcome)
VAS ipsilateral leg pain	Any increase	0 mm < decrease < 20 mm	20 mm decrease	≤−68.0 mm decrease
		0% < decrease < 30%	30% decrease	80% decrease
Sciatica Bothersomeness Index (SBI)	Any increase	0 point < decrease < 6.5 point decrease	6.5 point decrease	≤−9.0 point decrease
		0% < decrease < 30%	30% decrease	60% decrease
Oswestry Disability Index (ODI)	Any increase	0 point < decrease < 15 point	15 point decrease	≤−37.8 points
		0% < decrease < 15%	15% decrease	30% decrease
VAS back pain	Any increase	0 mm < decrease < 20 mm	20 mm decrease	≤−55.0 mm
		0% < decrease < 30%	30% decrease	80% decrease
SF-12 mental component summary (MCS)	Any decrease	0 < increase ≤ 3.77 points	> 3.77 point increase	≥4.59 points
SF-12 physical component summary (PCS)	Any decrease	0 < increase ≤ 3.29 points	> 3.29 point increase	≥16.29 points

Participants in the treatment group were more likely to achieve clinically meaningful VAS back pain reduction (defined as ≥30% reduction) at 6-months vs. the control group participants (treatment group = 93% vs.. control group = 88%).

Sciatica Bothersomeness Index (SBI)

SBI decreased by ≥90% for 33 of 67 treatment group participants (24.3% increase compared with control group participants, Table 5); SBI decreased by ≥80% for 45 of 67 treatment group participants (23.4% increase in number of high responders compared with control group participants, Fig. 2); SBI decreased by 100% for 20 of 67 treatment group participants (11% increase compared with control group participants, Table 5). SBI leg pain component decreased by 80% from baseline at 6 months in treatment group participants compared with 66% of control group participants. This 14% greater reduction in leg pain in the dual-polymer gel cohort was statistically significant ($P = 0.039$; Fig. 4). OVL (0.693) was consistent with good differentiation in SBI outcomes of study groups (Fig. 3).

Oswestry Disability Index (ODI)

ODI decreased by 100% for 20 of 68 treatment group participants (13% reduction compared with the control group participants; Table 5). Notably, all participants in both groups were considered "completely disabled" at screening (mean ODI > 50). ODIs at 6 months for the treatment and control group were 6.7 and 8.9, respectively.

TABLE 2. Demographics and Baseline Continuous Variables

	Surgery+Oxiplex		Surgery alone control		
Demographic/continuous variable	N	Mean ± SD	N	Mean ± SD	*P*
All					
Age (yr)	69	44.52 ± 13.41	33	47.09 ± 12.36	0.356
BMI (kg/m^2)	69	30.02 ± 5.48	33	29.52 ± 6.38	0.682
Height (inches)	69	68.33 ± 4.10	33	67.61 ± 3.87	0.399
Weight (lbs)	69	199.57 ± 41.97	33	191.64 ± 42.06	0.374
Female					
Age (yr)	38	43.49 ± 11.98	15	45.66 ± 13.20	0.567
BMI (kg/m^2)	38	30.03 ± 5.74	15	30.62 ± 8.23	0.769
Height (inches)	38	65.66 ± 2.57	15	64.74 ± 2.77	0.255
Weight (lbs)	38	183.75 ± 35.04	15	181.77 ± 46.65	0.867
Male					
Age (yr)	31	45.79 ± 15.09	18	48.29 ± 11.87	0.550
BMI (kg/m^2)	31	30.00 ± 5.24	18	28.59 ± 4.34	0.341
Height (inches)	31	71.60 ± 3.16	18	69.99 ± 2.93	0.085
Weight (lbs)	31	218.96 ± 42.12	18	199.86 ± 37.14	0.117
Clinical scores					
Oswestry Disability Index	69	58.13 ± 16.02	33	63.70 ± 14.26	0.092
VAS back	69	77.91 ± 16.00	33	75.55 ± 14.99	0.477
VAS ipsilateral leg	69	85.13 ± 9.76	33	83.70 ± 12.48	0.528
VAS contralateral leg	69	8.30 ± 19.32	33	7.61 ± 18.04	0.862
Sciatica Bothersomeness Index (SBI)	69	18.64 ± 4.32	33	19.45 ± 3.29	0.339
SF12 PCS	69	30.10 ± 8.26	33	26.35 ± 6.20	0.023
SF12 MCS	69	43.50 ± 11.21	33	43.95 ± 12.60	0.854

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TABLE 3. Demographic and Baseline Categorical Data

Categorical Value	N (%) Surgery+Oxiplex N = 69	Surgery alone control N = 33	*P*
Race			
American Indian or Alaska Native	0	0	> 0.999
Asian	0	0	
Black or African American	8 (12)	4 (12)	
Native Hawaiian or Other Pacific Islander	0	0	
White	59 (86)	29 (88)	
Declined to specify	0	0	
Unknown	2 (3)	0	
Ethnicity			
Hispanic or Latino	4 (6)	1 (3)	> 0.999
Not Hispanic or Latino	65 (94)	32 (97)	
Ipsilateral leg			
Right	32 (46)	14 (42)	0.832
Left	37 (54)	19 (58)	
Duration of ipsilateral leg pain			
Fewer than 6 mo	28 (41)	19 (58)	0.292
6 mo to 1 yr	21 (30)	8 (24)	
More than 1 yr	20 (29)	6 (18)	
Not applicable	0	0	
Nicotine use			
Current	12 (17)	6 (18)	0.896
Former	8 (12)	5 (15)	
None	49 (71)	22 (67)	

SF-12 Mental Component Summary (MCS) and Physical Component Summary (PCS)

The treatment group had a 5% increase in participants who had an improvement in their MCS of ≥ 5 compared with controls at 6-months (70.6% *vs.* 65.6%) and a 12.5% improvement in high responders (75.0% *vs.* 62.5%). There were no differences in PCS (58%).

Patient Satisfaction and Return to Work

Although satisfaction scores were the same for both groups at 6-months (88%), more control group participants did not return to work at 6-months compared with treatment group participants (16% *vs.* 7%).

DISCUSSION

Previously, we reported results of clinical trials in the US[1] and China[30,31] of patients with leg pain treated with laminectomy/laminotomy and dual-polymer gel as an adjuvant for decompression of disc herniation at L4-L5 and L5-S1. Use of dual-polymer gel significantly reduced both leg pain and LBP after lumbar discectomy in patients pre-

TABLE 4. Adverse Events (ITT Cohort)

AE type	Surgery+Oxiplex (n = 87) Events	Subjs	%	Surgery alone control (n = 47) Events	Subjs	%	*P*
All events	71	43	49.4	40	24	51.1	0.999
Cancer	1	1	1.1	0	0	0.0	0.999
Cardiac and vascular	4	4	4.6	5	4	8.5	0.450
Dermatologic	2	2	2.3	0	0	0.0	0.541
Gastrointestinal	1	1	1.1	1	1	2.1	0.999
Genitourinary	4	4	4.6	4	3	6.4	0.696
Immunologic	1	1	1.1	0	0	0.0	0.999
Infection	1	1	1.1	1	1	2.1	0.999
Musculoskeletal – lumbar	1	1	1.1	2	2	4.3	0.281
Musculoskeletal – Nonlumbar	3	3	3.4	3	3	6.4	0.423
Neurological – Lower extremity	2	2	2.3	4	3	6.4	0.343
Neurological – Upper extremity	1	1	1.1	0	0	0.0	0.999
Neurological – central nervous system	4	2	2.3	0	0	0.0	0.541
Pain – spine	25	23	26.4	12	12	25.5	0.999
Pain – extremity	7	6	6.9	3	3	6.4	0.999
Pain – other	3	3	3.4	3	3	6.4	0.423
Psychosocial	1	1	1.1	0	0	0.0	0.999
Respiratory	2	2	2.3	0	0	0.0	0.541
Trauma	2	2	2.3	0	0	0.0	0.541
Wound issue – index procedure	4	4	4.6	2	2	4.3	0.999
Other primary classification	2	2	2.3	0	0	0.0	0.541

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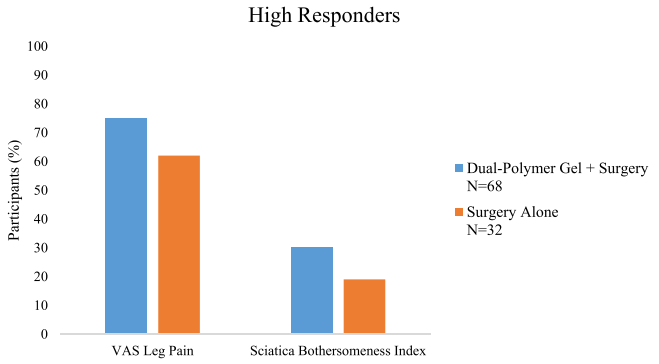

Figure 2. ROC-based threshold analysis of patient satisfaction PRO applied to endpoints at month 6 to define thresholds of high responders. Participants in the dual-polymer gel+surgery group contained a greater percentage of participants who were high responders to treatment compared with the surgery alone group.

senting with severe leg and back pain. The current study included only participants with both severe leg pain and LBP undergoing single-level lumbar laminectomy/laminotomy for partial removal of a herniated disc. Although the primary efficacy endpoint was not met using the VAS score, leg pain reduction in the treatment group was statistically greater compared with the control group using the SBI measure for leg pain (Fig. 4). In contrast to VAS,[43] the SBI leg pain score includes multiple questions as well as a statistically significant correlation ($P < 0.01$) with straight leg raise and SF-36, both long-established assessments of sciatic nerve pain from herniated lumbar discs.[44] Meaningful clinical benefit from dual-polymer gel was also shown by 5%, 11%, and 9% increases in the proportion of participants who had 100%, 90%, or 80% relief of VAS leg pain at 6 months, respectively, compared with surgery alone (Table 5). The proportion of treatment group participants who were high responders (VAS improvement of ≥ 68 mm at 6 mo) was 75% compared with 62% of controls (Fig. 2).

TABLE 5. Leg Pain, SBI, ODI Improvement At Six Months

	n (%)		
	Surgery + Oxiplex N = 68	**Surgery Alone N = 32**	**Δ**
VAS leg pain improvement			
100%	33 (49)	14 (44)	5%
Minimum 90% decrease	50 (74)	20 (63)	11%
Minimum 80% decrease	55 (81)	23 (72)	9%
Minimum 70% decrease	61 (90)	29 (91)	−1%
Minimum 60% decrease	63 (93)	32 (100)	−7%
Minimum 20% decrease	68 (100)	32 (100)	0%
Minimum 0% decrease	68 (100)	32 (100)	0%
Participants who became worse	0	0	0%
	Surgery + Oxiplex N = 67	Surgery Alone N = 32	Δ
Sciatica Bothersomeness Index (SBI) improvement at 6 Mo			
100% decrease	20 (30)	6 (19)	11%
Minimum 90% decrease	33 (49)	8 (25)	24%
Minimum 80% decrease	45 (67)	14 (44)	23%
Minimum 50% decrease	57 (85)	26 (81)	4%
Minimum 30% decrease	60 (90)	30 (94)	−4%
Minimum 10% decrease	66 (99)	32 (100)	−1%
Minimum 0% decrease	66 (99)	32 (100)	−1%
Participants who became worse	1 (1)	0	1%
	Surgery + Oxiplex N = 68	Surgery alone N = 32	Δ
Oswestry Disability Index (ODI) improvement at 6 Mo			
100% decrease	20 (29)	5 (16)	13%
Up to 100% decrease	28 (41)	12 (38)	3%
Up to 90% decrease	38 (56)	18 (56)	0%
Up to 80% decrease	57 (84)	28 (88)	−4%
Up to 50% decrease	64 (94)	31 (97)	−3%
Up to 30% decrease	68 (100)	32 (100)	0%
Up to 10% decrease	68 (100)	32 (100)	0%
Participants who became worse	0	0	0%

Evaluation of adjuvant therapies by PROs at the end of surgery is often obscured by the patient's response to surgery.[45,46] Patient's recollection of comparative pain levels asked by a single question (*e.g.*, VAS) separated from baseline by many months adds additional challenges to sample size determination of minimal clinically im-

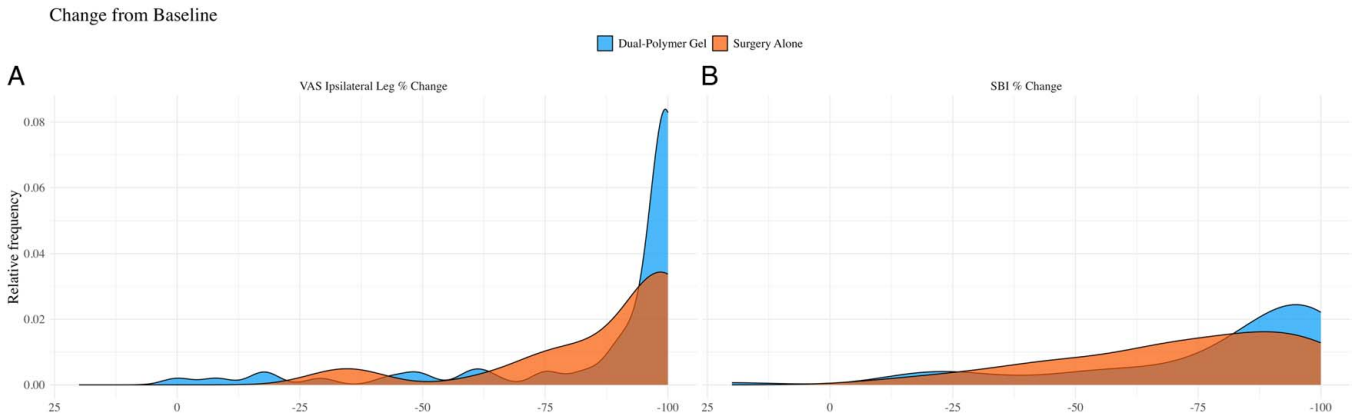

Figure 3. Distributions of participants in dual-polymer gel treatment group (gel+surgery group: blue) and surgery alone control group (orange) displayed as relative frequency of change from baseline in each participant's score. Overlap coefficients (A: 0.559; B: 0.693) demonstrated a good differentiation of responses between participants in the treatment and control groups.

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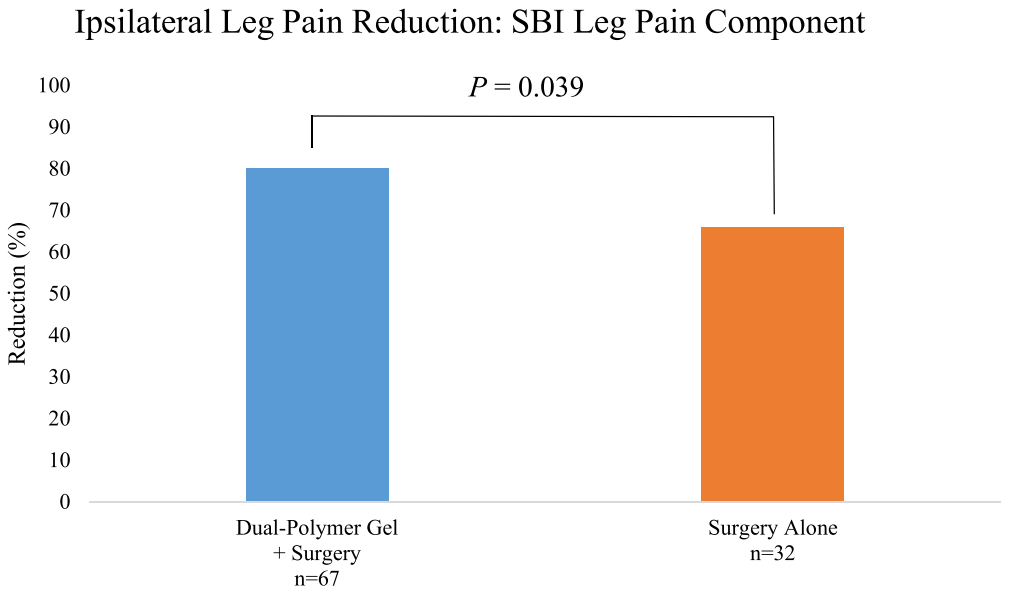

Figure 4. Sciatica Bothersomeness Index Leg Pain Component decreased by 80% from baseline at 6 months in dual-polymer gel +surgery (treatment group) compared with 66% of the surgery alone group (control group). This 14% greater reduction in leg pain in the dual-polymer gel cohort was statistically significant ($P = 0.039$).

portant differences.[47–50] In addition, site heterogeneity is common in medical device trials, especially involving surgery and PROs, further challenging the demonstration of statistical benefit from the adjuvant.[46,50,51] Responder operating characteristics (ROC) analysis, used to determine thresholds of clinical benefit, identify clinically meaningful responders and high responders to treatment.[39] Meaningful increases in clinical benefit were illustrated by comparing the distribution of their group's PRO scores. Difference in distributions is expressed as the overlap coefficient (OVL) which measures proportion of overlap in the response distributions.[35–38] There was "good differentiation" between the treatment and control group, demonstrated by a greater percentage of participants in the treatment group with larger reductions in leg pain VAS and SBI (Fig. 3).

Typical presentation of lumbar disc herniation is a patient with radicular leg pain, whereas back pain varies from none to severe. The greater the preoperative back pain relative to leg pain, usually the worse the postoperative outcome.[2,4,6,7] Patients with a herniated lumbar disc often have a greater density of sensory nerves in the annulus fibrosus and along annular tears.[52–55] Pain mediators, including the nucleus pulposus, that stimulate these sensory nerves during and after disc surgery can sensitize neural tissue to postoperative leg pain and LBP. Increase in sensory nerve excitability after decompression surgery often prolongs sensory nerve sensitization resulting in pain and hyperalgesia long after the surgical procedure.[56,57]

Epidural fibrosis can sensitize sensory nerves in the epidural space. Spinal nerve roots encased in fibrin become sensitized to external stimulation.[33,58–61] Contribution of fibrosis to chronic radicular pain following decompression surgery was demonstrated by Gerdesmeyer and colleagues who followed 381 patients for up to 10 years with chronic lumbar radicular pain. These patients experienced pain reduction after percutaneous epidural neurolysis of adhesions >4 years following surgery.[62] Fransen[20] reported a reduction in epidural fibrosis in 396 patients who presented with sciatic pain and were treated with dual-polymer gel after removal of a herniated disc. Decompressed nerve root and epidural space, including the annulus fibrosis, were covered with dual-polymer gel. Five patients underwent reoperation for recurrent herniation, two after less than a week, one after a month, and two within the first year after surgery. During the reoperation, there was little or no epidural fibrosis noted.

Results of the current study are consistent with previous dual-polymer gel trials following decompression of herniated lumbar discs in patients with severe leg pain and LBP. A multivariate analysis of participants with severe leg pain and LBP in a US study demonstrated 18.4% greater reduction in leg pain *versus* surgery alone.[1] A follow-on study in China evaluated the effectiveness of dual-polymer gel as adjunctive therapy during single-level partial lumbar discectomy.[30,31] In participants with severe leg pain and LBP, dual-polymer gel treated participants experienced a 21% greater reduction in leg pain compared with controls. An Italian series evaluated 70 consecutive participants with lumbar disc herniation undergoing microdiscectomy by the same surgeon treated with dual-polymer gel. In a subset of participants with severe leg pain and LBP, treated participants experienced a 26% greater reduction in leg pain compared with controls.[29] In these reports, there were no safety concerns or increased rate of reherniation or subsequent surgery. Potential risks

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associated with dual-polymer gel use are low due to its composition of two synthetic, biocompatible materials.[63]

CONCLUSION

The clinical data support several adjunctive benefits from the use of dual-polymer gel in spinal surgery, including a more complete reduction in leg pain and reduced neurological symptoms. The study also confirmed that participants who received dual-polymer gel had the best chance for significant or complete leg pain reduction at 6 months following surgery. Results from this study confirm and extend the safety and effectiveness of dual-polymer gel as an adjuvant in lumbar discectomy for the treatment of severe leg pain and LBP. This data aligns with the hypothesis that reducing early exposure to inflammatory mediators lowers nociceptor sensitization, leading to sustained pain reduction. Although dual-polymer gel is absorbed within 30 days, by limiting exposure to inflammatory mediators in the critical early phase following discectomy, the dual-polymer gel appears to reduce/prevent long-term sensitization of nociceptors, leading to clinically significant pain reduction at the 6-month follow-up.

➢ Key Points

- ❑ Dual-polymer gel (Oxiplex: CMC+PEO) was safe and reduced leg pain and back pain in patients presenting with both severe leg and back pain when used as an adjuvant to partial discectomy of a herniated disc at L4-L5 or L5-S1.
- ❑ Utilization of dual-polymer gel increased the likelihood of achieving high or complete resolution of leg pain at 6 months.
- ❑ Overlap coefficients provide useful illustrations of clinical outcome benefits.
- ❑ Receiver operating characteristics (ROC) used with an anchor (patient satisfaction) identify high responders to treatment.
- ❑ Use of patient-reported outcomes following surgery to measure change in clinical response over time can be challenging.

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