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Randomized Trial

MiDAS ENCORE: Randomized Controlled Clinical Trial Report of 6-Month Results

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Disclaimer: Drs. Staats and Benyamin are Study Principal Investigators for the MiDAS ENCORE Study. *Investigators in the MiDAS ENCORE Study are listed in the Appendix.
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Background: Patients suffering from neurogenic claudication due to lumbar spinal stenosis (LSS) often experience moderate to severe pain and significant functional disability. Neurogenic claudication results from progressive degenerative changes in the spine, and most often affects the elderly. Both the MILD® procedure and epidural steroid injections (ESIs) offer interventional pain treatment options for LSS patients experiencing neurogenic claudication refractory to more conservative therapies. MILD provides an alternative to ESIs via minimally invasive lumbar decompression.

Study Design: Prospective, multi-center, randomized controlled clinical trial.

Setting: Twenty-six US interventional pain management centers.

Objective: To compare patient outcomes following treatment with either MILD (treatment group) or ESIs (active control group) in LSS patients with neurogenic claudication and verified ligamentum flavum hypertrophy.

Methods: This prospective, multi-center, randomized controlled clinical trial includes 2 study arms with a 1-to-1 randomization ratio. A total of 302 patients were enrolled, with 149 randomized to MILD and 153 to the active control. Six-month follow-up has been completed and is presented in this report. In addition, one year follow-up will be conducted for patients in both study arms, and supplementary 2 year outcome data will be collected for patients in the MILD group only.

Outcome Measures: Outcomes are assessed using the Oswestry Disability Index (ODI), numeric pain rating scale (NPRS) and Zurich Claudication Questionnaire (ZCQ). Primary efficacy is the proportion of ODI responders, tested for statistical superiority of the MILD group versus the active control group. ODI responders are defined as patients achieving the validated Minimal Important Change (MIC) of ≥10 point improvement in ODI from baseline to follow-up. Similarly, secondary efficacy includes proportion of NPRS and ZCQ responders using validated MIC thresholds. Primary safety is the incidence of device or procedure-related adverse events in each group.

Results: At 6 months, all primary and secondary efficacy results provided statistically significant evidence that MILD is superior to the active control. For primary efficacy, the proportion of ODI responders in the MILD group (62.2%) was statistically significantly higher than for the epidural steroid group (35.7%) ($P < 0.001$). Further, all secondary efficacy parameters demonstrated statistical superiority of MILD versus the active control. The primary safety endpoint was achieved, demonstrating that there is no difference in safety between MILD and ESIs ($P = 1.00$).

Limitations: Limitations include lack of patient blinding due to considerable differences in treatment protocols, and a potentially higher non-responder rate for both groups versus standard-of-care due to study restrictions on adjunctive pain therapies.

Conclusions: Six month follow-up data from this trial demonstrate that the MILD procedure is statistically superior to epidural steroids, a known active treatment for LSS patients with neurogenic claudication and verified central stenosis due to ligamentum flavum hypertrophy. The results of all primary and secondary efficacy outcome measures achieved statistically superior outcomes in the MILD group versus ESIs. Further, there were no statistically significant differences in the safety profile between study groups. This prospective, multi-center, randomized controlled clinical trial provides strong evidence of the effectiveness of MILD versus epidural steroids in this patient population.

Clinical Trial Registration: NCT02093520

Key words: MILD, lumbar central spinal stenosis, minimally invasive lumbar decompression, interlaminar epidural steroid injection, neurogenic claudication, ligamentum flavum, Oswestry Disability Index, ODI, Numeric Pain Rating Scale, NPRS, Zurich Claudication Questionnaire, ZCQ

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Lumbar spinal stenosis (LSS) is a common cause of moderate to severe low back and lower extremity pain, and often leads to significant functional disability. Especially prevalent in the elderly, lumbar central spinal stenosis is caused by progressive degenerative changes in the spine, which result in structural narrowing of the central vertebral canal. This narrowing, which can be caused by many factors including osteophyte formation, facet hypertrophy, disk herniation, and ligamentum flavum hypertrophy, compresses neural elements resulting in nerve root ischemia and leads to painful neurogenic claudication symptoms (1-3).

Many therapeutic modalities have been advocated for the treatment of lumbar central spinal stenosis. Treatment strategies generally begin with conservative measures that may include physical therapy, oral analgesics, or many other non-invasive options. Once more conservative therapies fail, LSS patients are often treated with epidural injections which have been reported to provide significant short-term improvement for this patient population (4-9). More invasive interventions such as interspinous spacers and decompressive surgery, with or without fusion, are also options for these patients, but are associated with higher complication rates (10,11).

The objective of MiDAS ENCORE (Evidence-based Neurogenic Claudication Outcomes Research) is to provide strong evidence of the effectiveness of MILD (treatment group) versus epidural steroid injections (ESIs) (the active control) in managing neurogenic claudication symptoms in LSS patients. This prospective, multicenter, randomized controlled clinical trial compares patient outcomes following treatment with either MILD or the active control in LSS patients with neurogenic claudication and having verified ligamentum flavum hypertrophy as a contributing factor. This study was designed to assess 2 minimally invasive therapies, with epidural steroids, an active control considered to be a standard treatment with a high level of evidence. MiDAS ENCORE has been approved by the Centers for Medicare & Medicaid Services (CMS) as a Coverage with Evidence Development (CED) study to provide high quality evidence supporting the clinical safety and effectiveness of the MILD procedure (12). MiDAS ENCORE is registered with the US Clinical Trial Registry (NCT02093520). This is a report of 6-month results for patients participating in this trial.

Methods

MiDAS ENCORE is being conducted at 26 interventional pain management centers in the United States. The trial protocol was approved by Institutional Review Boards for all participating sites and Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed (13). The study design of MiDAS ENCORE has been previously described (14).

Patients

Study participants include 302 Medicare beneficiaries who met all study inclusion/exclusion criteria, as well as an additional symptomatic diagnosis screening assessment to confirm symptoms of neurogenic claudication (15) (Table 1). All patients provided written informed consent. Patients in both study arms are required to complete study follow-up evaluations at 6 months and one year. Supplementary safety and efficacy outcome data will be collected for patients in the MILD arm through 2 years.

Randomization

Patients were randomized in an allocation ratio of 1-to-1 to the MILD or ESI study cohorts. Randomization was implemented automatically through an online electronic data collection system. The treatment regimens were substantially different between the 2 groups, including the allowance of multiple ESI procedures for the active control group during the study period. As a result, neither investigator nor patient blinding was feasible. In order to minimize advance patient knowledge of study group, sites were advised to inform patients of their randomization group on the day of the procedure. Preoperative instructions and workup were the same for all patients.

Table 1. Selection criteria and neurogenic claudication symptomatic diagnosis

Inclusion Criteria	Exclusion Criteria
1. 65 years or older and a Medicare beneficiary. 2. Patients experiencing neurogenic claudication symptoms for at least 3 months duration which has failed to respond or poorly responded to physical therapy, home exercise programs, and oral analgesics. 3. Lumbar spinal stenosis with neurogenic claudication diagnosed via a. Symptomatic diagnosis (see below) **and** b. Radiologic evidence of LSS with unilateral or bilateral ligamentum flavum > 2.5 mm confirmed by pre-op MRI or CT performed within 12 months of baseline visit. 4. Patients with comorbid conditions commonly associated with spinal stenosis, such as osteophytes, facet hypertrophy, minor spondylolisthesis, foraminal stenosis, and/or disk protrusion may be included unless the treating physician has determined that the condition is too advanced. 5. Available to complete 6-month and 1-year follow-up visits.	1. ODI Score < 31 (0-100 ODI Scale). 2. NPRS Score < 5 (0-10 NPRS Scale). 3. Prior surgery at any treatment level. 4. History of spinal fractures with current related pain symptoms. 5. Patients with Grade III or higher spondylolisthesis. 6. Motor deficit or disabling back and/or leg pain from causes other than LSS neurogenic claudication. 7. Unable to walk ≥ 10 feet unaided before being limited by pain. 8. Patients previously randomized and/or treated in this clinical study. 9. Patients that have previously received the MILD procedure. 10. ESI during 8 weeks prior to study enrollment. 11. Epidural lipomatosis (if deemed to be a significant contributor of canal narrowing by the physician). 12. On (or pending) Workman's Compensation or known to be considering litigation associated with back pain.
Neurogenic Claudication Symptomatic Diagnosis	
1. Pain/Discomfort in leg, buttocks, or lower back while walking or standing. 2. Pain relief experienced when bending forward or sitting down. 3. Flexion forward while walking. 4. Inability to stand unaided for more than 15 minutes without bending at the waist. 5. Inability to walk unaided for more than one quarter mile without bending at the waist. 6. History of symptoms ≥ 12 weeks.	

Interventions

MILD percutaneous lumbar decompression uses a dorsal approach to decompress the spinal canal by selectively removing small portions of lamina and hypertrophic ligamentum flavum, while minimizing trauma to surrounding tissue. Generally conducted using local anesthetic and moderate sedation, this procedure is performed ipsilaterally through a small 6-gauge port and does not involve the use of implants. Contrast-enhanced fluoroscopic guidance provides visualization throughout the MILD procedure. The MILD procedure has been previously described (14,16-24).

In the active control group, ESIs are administered via an interlaminar approach, using intermittent fluoroscopy with contrast to guide needle placement. Patients assigned to ESIs may have up to 4 treatments per year, consistent with American Society of Interventional Pain Physicians (ASIPP) guidelines (25). The interval between ESIs was recommended to be 2 months or longer, provided that > 50% relief was obtained for 2 months (25). Patients received 80 mg of Kenalog® or Depo-Medrol® (40 mg for diabetics) during the initial ESI procedure, and between 40 mg and 80 mg during subsequent procedures. For both study arms, treatment could be unilateral or bilateral, and at multiple levels.

Patients were discharged per institutional standard of care, and provided instructions regarding the use of any adjunctive conservative therapies. MILD patients are prohibited from receiving ESIs in the lumbar region during the study period. The use of opioid and non-opioid analgesics for neurogenic claudication pain are recorded.

Outcome Measures

Multiple validated outcome measures are used including the Oswestry Disability Index (ODI), Numeric Pain Rating Scale (NPRS), and Zurich Claudication Questionnaire (ZCQ). ODI is used to evaluate functional disability by providing an assessment of the effect of back pain on activities of daily living (26). ODI ranges from 0 to 100, with lower scores indicating less severe symptoms. NPRS measures the level of back and leg pain on a 0 to 10 scale, from no pain to the worst pain imaginable (27). ZCQ is an assessment tool specific to LSS that evaluates symptom severity, physical function characteristics, and patient satisfaction following treatment. ZCQ is comprised of symptom severity and physical

function domains. The ZCQ symptom severity domain is divided into 2 subdomains—pain and neuroischemic. For each of these domains, lower scores indicate better health status. The ZCQ patient satisfaction domain is recorded at follow-up only, and lower scores indicate higher patient satisfaction with the procedure (19,22).

For all protocol-defined outcome measures, efficacy is determined by comparing the percentage of responders between the 2 study groups. The primary efficacy outcome measure is the proportion of ODI responders, tested for statistical superiority of MILD versus epidural steroids, a known active treatment. ODI responders are defined as patients who report a $\geq$ 10 point improvement in ODI score from baseline to follow-up. Published validation studies have indicated that a 10-point Minimal Important Change (MIC) improvement in ODI score represents a clinically significant efficacy threshold (28,29). Patients who did not experience a 10-point improvement in ODI at follow-up, or who received or intended to receive a disallowed treatment in the lumbar region, or who voluntarily withdrew because of poor response to the study procedure were considered non-responders.

Secondary efficacy endpoints include evaluation of the proportion of NPRS and ZCQ responders in each of the 2 study groups using validated MIC thresholds. An improvement in NPRS of 2 points has been determined to be a MIC (28-32). An improvement of 0.5 in ZCQ domains denotes a MIC, and an absolute patient satisfaction score of $\leq$ 2.5 indicates that a patient is satisfied with the procedure (33-36). Statistical superiority is determined by comparing the proportion of responders between the study groups.

All device or procedure-related adverse events, as well as all serious adverse events regardless of relationship, are reported. The primary safety outcome measure is the incidence of device or procedure-related adverse events. All reportable adverse events through 6-month follow-up have been evaluated and adjudicated by the study principal investigators, and adjudicated outcomes are used for reporting. For standardization of reporting, all adverse events have been coded by an outside agency into MedDRA System Organ Class and Preferred Term classifications.

Sample Size and Power

Sample size was calculated to obtain at least 80% power for testing the primary superiority hypothesis. The total sample size of 302 is sufficient to meet this objective under the assumption of a 2-sided hypothesis, type 1 error of 0.05, power (1-β) at least 80%, randomization ratio of 1:1, and accounting for dropouts.

Statistical Methods

Descriptive summaries are presented by randomized group for all baseline and outcome measures. Continuous data is summarized using means and standard deviations, while categorical variables are summarized using frequency counts and percentages. All *P* values presented are 2-sided, with values less than 0.05 considered statistically significant.

The primary efficacy objective is to demonstrate statistical superiority of MILD to epidural steroids on the proportion of ODI responders. The hypothesis is tested by constructing the 2-sided 95% confidence interval around the difference between the population proportions (pmild – pESI). If the lower bound of the 2-sided confidence interval is greater than 0, superiority is declared and the endpoint met. Secondary efficacy endpoints are also tested for superiority of MILD to epidural steroids. The primary safety endpoint is met if the device or procedure-related adverse event rate is not significantly greater with MILD than with epidural steroids.

Results

Participant Flow

MiDAS ENCORE patients were enrolled from June 2014 through April 2015. A total of 302 patients were included out of 320 patients assessed for eligibility. Eighteen patients did not meet the study selection criteria and were excluded. Group allocation included 149 patients randomized to MILD and 153 to epidural steroids. Following randomization, 6 MILD and 22 epidural steroid patients voluntarily withdrew prior to study treatment, leaving 143 and 131 patients in the MILD and ESI cohorts, respectively. Of these, 2 ESI patients missed their 6-month follow-up visit, resulting in 143 MILD and 129 ESI patients for 6-month data analysis. Fig. 1 presents the participant flow through 6 months.

Patient Characteristics

Patient characteristics and baseline clinical data are provided in Table 2. There was a significant difference in gender between the 2 groups, with a larger proportion of men in the MILD group. The most commonly reported lumbar spine presenting co-factors included bulging disc, foraminal narrowing, facet hypertrophy, and facet arthropathy, and were similar in incidence except that the epidural steroid group had significantly

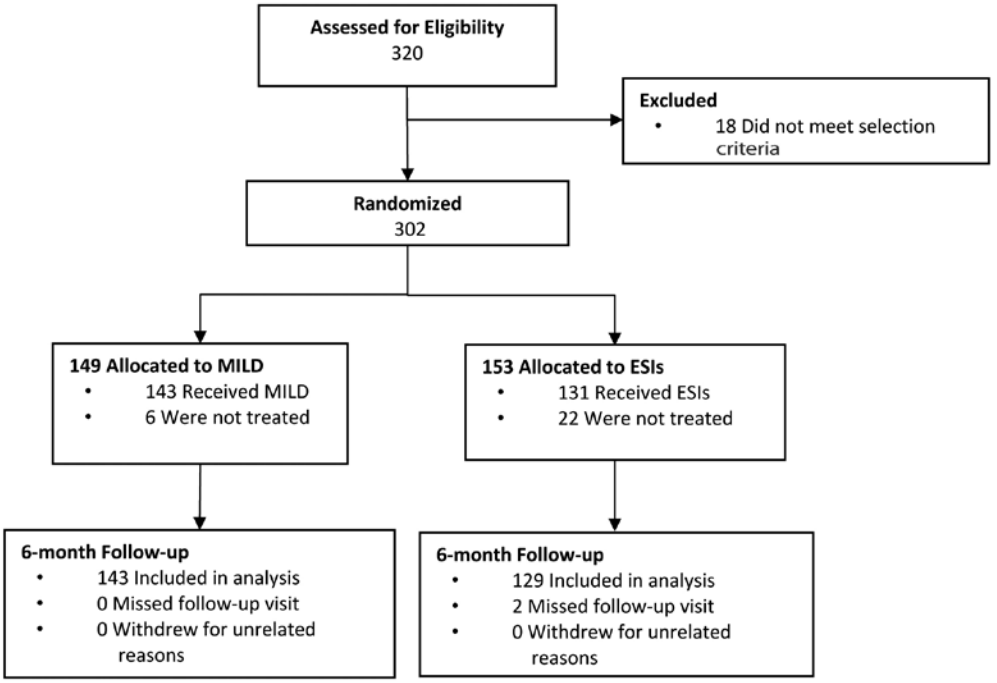

Fig. 1. *Presentation of patient flow through 6-month follow-up.*

Table 2. *Patient characteristics.*

Characteristic	MILD N=149	ESI N=153	*P*-value
Age (Years)†	75.6 ± 7.0	75.0 ± 7.0	0.479
Gender			
Male	49.7% (74)	37.9% (58)	0.039*
Female	50.3% (75)	62.1% (95)	
Lumbar Spine—Presenting Co-Factors			
Ligamentum flavum hypertrophy	100.0% (149)	100.0% (153)	1.000
Bulging disc	89.9% (134)	91.5% (140)	0.638
Foraminal narrowing	87.2% (130)	88.2% (135)	0.794
Facet hypertrophy	86.6% (129)	81.0% (124)	0.192
Facet arthropathy	76.5% (114)	86.3% (132)	0.029*
Degenerative disc disease	67.8% (101)	74.5% (114)	0.197
Disc space loss	59.1% (88)	63.4% (97)	0.439
Lateral recess narrowing	57.0% (85)	53.6% (82)	0.546
Osteophytes	47.7% (71)	47.7% (73)	0.991
Spondylosis	47.0% (70)	54.9% (84)	0.169
Spondylolisthesis	44.3% (66)	52.3% (80)	0.165
Nerve root impingement	33.6% (50)	36.6% (56)	0.579
Herniated disc	27.5% (41)	36.6% (56)	0.091
Scoliosis	22.1% (33)	26.8% (41)	0.348
Other	19.5% (29)	21.6% (33)	0.651
Oswestry Disability Index (ODI)†	53.0 ± 12.9	51.7 ± 12.0	0.361
Numeric Pain Rating Scale (NPRS)†	7.7 ± 1.4	7.8 ± 1.3	0.682
Zurich Claudication Questionnaire (ZCQ)†			
Pain subdomain	3.8 ± 0.5	3.8 ± 0.5	0.391
Neuroischemic subdomain	3.2 ± 0.9	3.2 ± 0.8	0.741
Physical function domain	2.9 ± 0.5	2.8 ± 0.4	0.308

*significant difference between groups
† Mean ± SD

more patients presenting with facet arthropathy than the MILD group. Baseline values for ODI, NPRS, and ZCQ domains are also presented in Table 2. There were no significant differences between the groups at baseline.

Previous conservative therapies were documented (Table 3). All patients had a history of physical therapy and had undergone a program of home exercise, while approximately half had prior experience with chiropractic adjustment. Aquatic therapy was the only prior conservative treatment that was different between the groups with a significantly higher incidence in the epidural steroid group.

Procedures

Procedure data is provided in Table 4. Procedure times for MILD patients were significantly greater than for ESI (mean of 43.0 minutes versus 7.7 minutes, respectively). Significantly more ESI patients underwent the study procedure outside of an ambulatory surgery center (ASC) or hospital, with ESI procedures primarily occurring in an office setting. Anesthesia was most commonly delivered via monitored anesthesia care (MAC) sedation for MILD patients, and by MAC sedation or local anesthesia only for ESI. The administration of ESIs is almost always done at a single level with the expectation of steroid migration to other levels, whereas MILD requires treatment at each level. In the MILD group, 67.7% (97 patients) received treatment at one level, 29.4% (42 patients) received treatment at 2 levels, and the remaining 2.8% (4 patients) received treatment at 3 levels. Specific lumbar levels treated in the MILD group were as follows: 9.8% (14 patients) L2-L3, 39.9% (57 patients) L3-L4, 77.6% (111 patients) L4-L5, 7.7% (11 patients) L5-S1. Frequency of unilateral and bilateral treatments did not differ between the groups. All patients were discharged within 24 hours of the procedure.

While Table 4 reflects initial procedure data, patients in the ESI arm are allowed up to 4 ESI treatments during the one year study period. The 131 ESI patients underwent a total of 217 ESI procedures during the first 6 months of the trial. On average, ESI patients received 1.7 ESI treatments during the first 6 months (including initial treatment) with a range of one to 4, and a median of one.

Medications

At baseline, 90.6% of MILD and 83.0% of ESI patients reported use of medication for neurogenic claudication, and there were no significant differences between the groups (P = 0.075). At 6 months, the percent of patients using these medications in the MILD arm decreased slightly to 89.5%, and in the ESI arm increased to 85.3%. None of these changes were significant, and there were no significant differences between the groups (P = 0 .44) (Table 5).

Function and Pain Outcomes

For the primary efficacy endpoint, the proportion of ODI responders in the MILD group was statistically significantly higher than the proportion of ODI responders in the ESI group at 6-month follow-up. The ODI responder rate for the MILD arm was 62.2% versus 35.7% in the ESI arm (P < 0.001). In addition, for all secondary efficacy endpoints, the proportion of responders in the MILD group was statistically significantly higher than the proportion of responders in the ESI group. Results of primary and secondary efficacy outcome measures are presented in Table 6. Fig. 2 provides a graphic illustration of the proportion of responders at 6 months for all primary and secondary efficacy endpoints.

Table 3. *Lumbar spine history – previous treatments.*

Treatment	MILD % (n/N)	ESI % (n/N)	*P*-value
Physical therapy	100% (149/149)	100% (153/153)	1.000
Home exercise program	100% (149/149)	100% (153/153)	1.000
Back brace	33.8% (50/148)	27.6% (42/152)	0.248
Bed rest	6.0% (9/149)	10.5% (16/153)	0.164
Walking aids	46.3% (69/149)	41.8% (64/153)	0.433
Aquatic therapy	13.4% (20/149)	24.8% (38/153)	0.012*
Acupuncture	20.8% (31/149)	13.7% (21/153)	0.103
Chiropractic adjustment	50.3% (75/149)	46.4% (71/153)	0.494
TENS unit	28.2% (42/149)	26.8% (41/153)	0.787
Biofeedback	1.3% (2/149)	0.0% (0/153)	0.150
Activity restriction	18.1% (27/149)	19.0% (29/153)	0.852
Other	6.8% (10/148)	7.2% (11/152)	0.871

*significant difference between groups

Table 4. *Initial procedure information.*

Metric	MILD N=143	ESI N=131	*P*-value
Procedure time (min)	43.0 ± 24.3 (142)	7.7 ± 6.7 (131)	<0.001*
Procedure setting			
Ambulatory Surgery Center (ASC)	65.7% (94)	62.6% (82)	
Hospital outpatient	33.6% (48)	21.4% (28)	
Hospital inpatient	0.0% (0)	0.8% (1)	
Other (includes office setting)	0.7% (1)	15.3% (20)	<0.001*
Anesthesia type			
General only	0.7% (1)	0.0% (0)	
General and local	0.7% (1)	0.0% (0)	
Local only	1.4% (2)	44.3% (58)	
MAC sedation	86.0% (123)	45.8% (60)	
Local and other	4.2% (6)	9.2% (12)	
Other	7.0% (10)	0.8% (1)	<0.001*
Unilateral Treatment	6.3% (9)	13.7% (18)	
Bilateral Treatment	93.7% (134)	86.3% (113)	0.063

*significant difference between groups

Table 5. *Medication for neurogenic claudication at 6-month follow-up.*

Medication at 6 Months	MILD N=133 % (n) [events]	ESI N=109 % (n) [events]	*P*-value
ALL MEDICATIONS for Neurogenic Claudication	89.5% (119) [236]	85.3% (93) [190]	0.44
Acetaminophen And Hydrocodone	26.3% (35) [36]	23.9% (26) [31]	0.77
Gabapentin	20.3% (27) [28]	15.6% (17) [18]	0.44
Tramadol	18.0% (24) [26]	20.2% (22) [22]	0.80
Ibuprofen	15.0% (20) [20]	11.9% (13) [13]	0.61
Acetaminophen	14.3% (19) [19]	14.7% (16) [16]	1.00
Naproxen	13.5% (18) [19]	11.9% (13) [13]	0.86
Hydrocodone	9.0% (12) [12]	7.3% (8) [8]	0.81
Acetaminophen And Oxycodone	7.5% (10) [11]	9.2% (10) [10]	0.82
Celecoxib	4.5% (6) [6]	0.9% (1) [1]	0.20
Meloxicam	3.8% (5) [5]	3.7% (4) [4]	1.00
Oxycodone	3.8% (5) [5]	2.8% (3) [3]	0.94
Diclofenac Topical	3.0% (4) [4]	1.8% (2) [2]	0.87
Acetaminophen And Codeine	3.0% (4) [4]	0.9% (1) [2]	0.49
Lidocaine Topical	2.3% (3) [3]	5.5% (6) [6]	0.32
Pregabalin	2.3% (3) [3]	3.7% (4) [5]	0.80
Diclofenac	2.3% (3) [3]	2.8% (3) [3]	1.00

Note: An additional 33 medications were reported to be in use by less than 4% of patients at 6 months.

Table 7 presents mean change in ODI, NPRS, and ZCQ domain scores from baseline to 6-month follow-up. A comparison of mean changes between the study groups shows statistically significantly greater improvement in the MILD arm versus the active control for all outcome measures. The mean (± SE) ZCQ Patient Satisfaction score for MILD was 2.3 ± 0.1 versus 3.0 ± 0.1 for the active control ($P < 0.001$). In addition, for both groups and for all efficacy endpoints, the within group change from baseline to follow-up was statistically significant.

Table 6: *Primary and secondary efficacy—proportion of responders at 6 months.*

Outcome Measure: Responder Definition	MILD % (n/N)	ESI % (n/N)	*P*-value (between groups)
Primary Efficacy: ODI: ≥10 point improvement	62.2% (89/143)	35.7% (46/129)	<0.001*
Secondary Efficacy: NPRS: ≥2.0 point improvement	55.9% (80/143)	33.3% (43/129)	<0.001*
ZCQ: ≥0.5 point improvement in each domain			
Pain subdomain	58.0% (83/143)	42.6% (55/129)	0.011*
Neuroischemic subdomain	50.0% (71/142)	30.2% (39/129)	0.001*
Physical function domain	52.4% (75/143)	14.0% (18/129)	<0.001*
ZCQ: Patient satisfaction ≤2.5†	64.8% (92/142)	30.2% (39/129)	<0.001*

*significant difference between groups
†Lower scores indicate a higher level of satisfaction with the procedure.

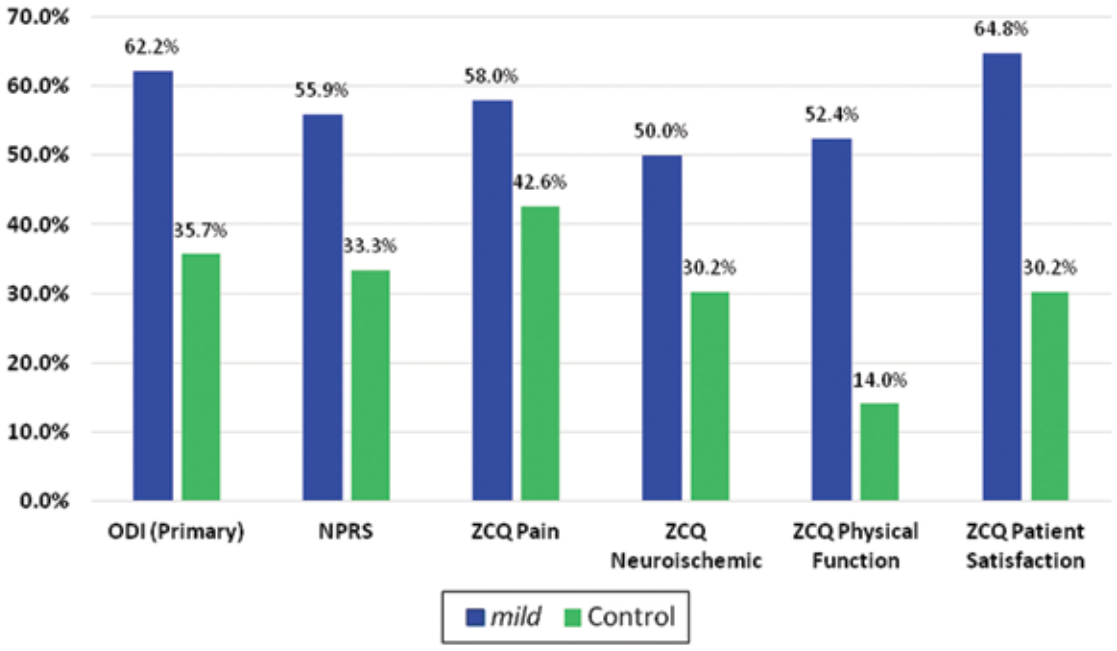

Fig. 2. *Illustration of proportion of responders at 6 months for all efficacy endpoints.*

Safety

As the primary safety analysis, Table 8 presents the incidence of device or procedure-related adverse events in each cohort. With the same percentage of patients in each study arm experiencing a device or procedure-related adverse event (1.3%), there was no significant difference in safety between the 2 study groups ($P = 1.00$). There were no serious device or procedure-related adverse events in either cohort. There also is no statistical difference between the groups in any of the MedDRA System Organ Class or Preferred Term classifications. During one MILD case, a procedural hemorrhage was reported. In this case, intraoperative oozing was observed at the decompression site and Gelfoam® was administered through the cannula into the interlaminar space. This event was categorized by the site as "mild," and this characterization was upheld with subsequent adjudication. The patient was discharged on the same day as the procedure with no complications. A further

Table 7. *Mean change in outcome measures at 6 months.*

Outcome Measure	MILD	ESI	*P*-value (between groups)
Oswestry Disability Index			
Mean ± SE	-18.5 ± 1.6 (143)	-5.6 ± 1.3 (129)	
Median (min, max)	-17.1 (-77.1, 20.0)	0.0 (-45.7, 31.4)	<0.001*
P-value (within group)	<0.001†	<0.001†	
Numeric Pain Rating Scale			
Mean ± SE	-2.9 ± 0.3 (143)	-0.9 ± 0.2 (129)	
Median (min, max)	-2.0 (-10.0, 3.0)	0.0 (-6.0, 3.0)	<0.001*
P-value (within group)	<0.001†	<0.001†	
Zurich Claudication Questionnaire			
Pain subdomain			
Mean ± SE	-0.8 ± 0.1 (143)	-0.4 ± 0.1 (129)	<0.001*
Median (min, max)	-0.5 (-3.2, 0.8)	-0.2 (-2.8, 1.0)	
P-value (within group)	<0.001†	<0.001†	
Neuroischemic subdomain			
Mean ± SE	-0.7 ± 0.1 (142)	-0.3 ± 0.1 (129)	<0.001*
Median (min, max)	-0.5 (-3.3, 2.0)	0.0 (-2.7, 1.3)	
P-value (within group)	<0.001†	0.001†	
Physical function domain			
Mean ± SE	-0.6 ± 0.1 (143)	-0.1 ± 0.1 (129)	<0.001*
Median (min, max)	-0.6 (-2.6, 1.0)	0.0 (-1.4, 0.8)	
P-value (within group)	<0.001†	0.003†	

*significant difference between groups
†significant difference with baseline values within the group

Table 8. *Adverse events.*

Adverse event	MILD N=149 % (n) [events]	ESI N=153 % (n) [events]	*P*-value
Total related AEs	1.3% (2) [2]	1.3% (2) [3]	1.00
Total related SAEs	0.0% (0) [0]	0.0% (0) [0]	1.00
MedDRA system organ class / preferred term			
Cardiac disorders	0.0% (0) [0]	0.7% (1) [1]	1.00
Sinus bradycardia	0.0% (0) [0]	0.7% (1) [1]	1.00
Injury, poisoning and procedural complications	1.3% (2) [2]	0.0% (0) [0]	0.47
Procedural haemorrhage	0.7% (1) [1]	0.0% (0) [0]	0.99
Procedural pain	0.7% (1) [1]	0.0% (0) [0]	0.99
Musculoskeletal and connective tissue disorders	0.0% (0) [0]	0.7% (1) [2]	1.00
Back pain	0.0% (0) [0]	0.7% (1) [1]	1.00
Pain in extremity	0.0% (0) [0]	0.7% (1) [1]	1.00

comparison of the incidence of all serious, non-related adverse events identified no statistically significant differences between groups (10.1% and 7.2% for MILD and the active control, respectively) ($P = 0.49$).

Discussion

All primary and secondary efficacy endpoints of this randomized controlled clinical trial provided statis-

tically significant evidence that MILD is superior to ESIs in the treatment of LSS patients suffering from neurogenic claudication and having verified ligamentum flavum hypertrophy. It is also important to highlight that the within group change was statistically significant for all efficacy endpoints for both study groups. This result supports the comparative design of this study, and reiterates the efficacy of the active control for these patients. Enrolled patients met precise study selection criteria, as well as symptomatic diagnosis screening criteria confirming neurogenic claudication.

Twenty-eight patients voluntarily withdrew prior to study treatment, and of those, a disproportionate number were randomized to ESIs (22 patients) versus MILD (6 patients). Of the 22 ESI patients, 8 decided to have surgery or other non-study therapy, 8 withdrew for personal or insurance reasons, and 6 withdrew because of dissatisfaction with randomization results. In the MILD arm, 5 withdrew for personal or insurance reasons and one was unwilling to comply with study assessments. Ultimately, 143 MILD and 131 ESI patients underwent treatment in the trial.

Following treatment, 10 MILD and 20 ESI patients withdrew prior to 6-month follow-up due to poor response to the study treatment or intention to receive an invasive non-study procedure. These patients are included in the analysis and are considered to be non-responders in their study arm. Of 10 MILD patients in this category, 8 received ESIs and 2 received facet blocks with steroids. Of 20 ESI patients, 8 opted for surgical treatment, 4 chose to undergo MILD, 2 received medial branch blocks with steroids, 2 received transforaminal ESIs, and 4 stated that their symptoms did not improve and they chose to withdraw. The number of ESI patients withdrawn due to poor response to their study procedure is numerically although not significantly greater than for MILD.

The safety and efficacy outcomes of patients treated with MILD in this trial are supported by numerous previous reports of MILD patient series. Mekhail and colleagues (37) reported one-year follow-up for 40 patients treated prospectively with MILD at a single center. Patients in this study experienced statistically significant improvement in function and neurogenic claudication symptoms at 3, 6, 9, and 12 months post procedure. Deer et al (38) reported one-year follow-up of 46 patients treated with MILD at a single center. In this prospective study, MILD patients experienced significant improvement in mobility and reduction of pain at 12-week, 6-month, and one-year follow-up. The longest follow-up was reported by Chopko (39) in a report of 45 MILD patients treated prospectively at 11 US sites. At 2 years, MILD patients in this study experienced statistically significant pain relief and improved functionality. This significant improvement was initially observed at one week post MILD, and proved to be durable through 2 years (39). These 3 studies with one and 2-year follow-up indicate that improvements in patient outcomes following MILD ligamentum flavum debulking remain stable over the long term. While there is no conclusive data regarding ligamentum flavum regrowth, physiologically the fibrous connective tissue of the ligamentum flavum does not have significant blood supply, and therefore regeneration is most likely slow. In the only other published randomized controlled trial comparing MILD with ESIs, Brown (17) reported significantly greater improvements in pain and function for MILD versus ESI patients at 6 weeks. No significant device or procedure-related adverse events were reported in any of these studies.

It is common for LSS patients presenting with neurogenic claudication to also suffer from other pathophysiological causes of low back pain and reduced mobility. While all study patients presented with hypertrophic ligamentum flavum, there were numerous other lumbar spine co-factors frequently reported (Table 2). It is notable, that while the MILD procedure debulks the hypertrophic ligamentum flavum specifically, these patients with multiple lumbar spine co-factors experienced significant improvement in neurogenic claudication symptoms. While ESIs did not demonstrate the same level of efficacy as MILD in this trial, some published studies have reported successful outcomes using ESIs to treat discogenic and radicular pain (40-44). Given the range of pathophysiological causes of low back pain, including inflammation in many cases, ESIs may be an appropriate adjunct therapy for patients undergoing MILD.

Three patients were treated with the alternate study therapy, instead of the therapy to which they were randomized. Per ITT methodology, these patients are included with their original randomization group, however a supplementary "as treated" analysis was conducted. In this analysis, the proportion of ODI responders still demonstrated statistically significant superiority of MILD versus ESIs. The ODI responder rate for MILD patients was 61.3% (87/142) compared to 36.9% (48/130) for ESI patients ($P = 0.001$). In addition, the proportion of responders for all secondary efficacy endpoints was still statistically significantly higher with MILD versus the active control, and there was no difference in safety between groups.

A covariate effects analysis determined that the 3 significant baseline differences did not meaningfully impact the primary endpoint outcome. Additionally, covariates of clinical interest (gender, age, baseline ODI score, facet arthropathy, degenerative disc disease, lateral recess narrowing, and spondylolisthesis) were examined in subgroup analyses to evaluate their effect on the primary endpoint success. The superiority of the treatment effect of MILD is unaffected by the introduction of these potential predictors into the primary effectiveness model.

There were certain limitations of this trial. In order to minimize confounding between the 2 study arms, adjunctive pain therapy within the lumbar region is restricted. As a result, responder rates may be lower for both groups within the trial compared to a non-study setting, as previously described (14). In addition, due to significant differences in treatment protocols between the 2 groups, including multiple ESI procedures during the study period, patient blinding was not possible.

Conclusion

The data from this trial demonstrate that at 6-month follow-up, the MILD procedure is statistically superior to epidural steroids, a known active treatment for LSS patients with neurogenic claudication and verified central stenosis due to ligamentum flavum hypertrophy. The results of all primary and secondary efficacy outcome measures achieved statistically superior outcomes in the MILD group versus ESIs. Further, there were no statistically significant differences in the safety profile between study groups. These results collectively confirm that the study's primary safety and efficacy hypotheses are met at 6 months. This prospective, multi-center, randomized controlled clinical trial provides strong evidence of the effectiveness of MILD versus epidural steroids in this patient population.

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Appendix

The following investigators enrolled patients in the study, with institutions listed in order from highest to lowest enrollment of patients: *Deaconess Comprehensive Pain Center – West*, Evansville, IN: F. McDonnell, J. Waling; *Michigan Interventional Pain Center*, Brownstown Township, MI: R. Haladjian, N. Patel; Spine Intervention Medical Corp, Fresno, CA: W. Von Kaenel; *Roanoke-Chowan Pain Management*, Ahoskie, NC: B. Chafin; *Newport Beach Headache and Pain*, Newport Beach, CA: R. Paicius; *Southeastern Spine Institute*, Mt. Pleasant, SC: W.B. Richardson, M. Netherton; *Premier Pain Centers*, Shrewsbury, NJ: S. Li; *Willow Creek Pain Center*, Vincennes, IN: G. Chartier; *Florida Pain Institute*, Merritt Island, FL: S. Golovac; *Millennium Pain Center*, Bloomington, IL: R. Vallejo; *Pain Consultants of San Diego*, La Mesa, CA: M. Verdolin; *Michigan Pain Specialists*, Ypsilanti, MI: E. Washabaugh, J. Chatas, L. Bojrab; *Regenerative Institute of Newport Beach*, Newport Beach, CA: K. Zaffarkhan, H. Sata; *Kramer Orthopedics*, Newport Beach, CA: S. Kramer; *SC Pain & Spine Specialists*, Murrells Inlet, SC: J. Rosenberg; *The Knox Surgical Center*, Covington, GA: M. Hanowell; *Frankfort Pain Clinic*, Frankfort, KY: R. Lingreen; *The Spine Institute*, Murrieta, CA: V. Johnson; *Montefiore Medical Center*, Bronx, NY: S. Wahezi; *Valley Pain Consultants*, Scottsdale, AZ: D. Choi; *The Center for Pain Relief*, Charleston, WV: C. Kim, R. Bowman; *Texas Spine and Joint Hospital*, Tyler, TX; A. Calodney; *Advanced Pain Management*, Rancho Mirage, CA: R. Reinhart; *Mayo Clinic*, Rochester, MN: T. Lamer, B. Hoelzer; *Comprehensive Center for Pain Management*, Toledo, OH: N. Moghal, W. James.

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