

Randomized Trial

MILD® is an Effective Treatment for Lumbar Spinal Stenosis with Neurogenic Claudication: MiDAS ENCORE Randomized Controlled Trial

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Disclaimer: Drs. Benyamin and Staats are Study Principal Investigators for the MiDAS ENCORE

Study * Investigators in the MiDAS ENCORE Study are listed in the Appendix. Conflict of interest: Each author certifies that he, or member of his immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript. Disclaimer and Conflict of interest on P. 239.

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Background: Lumbar spinal stenosis (LSS) is a common degenerative condition of the spine, which is a major cause of pain and functional disability for the elderly. Neurogenic claudication symptoms are a hallmark of LSS, where patients develop low back or leg pain when walking or standing that is relieved by sitting or lumbar flexion. The treatment of LSS generally begins with conservative management such as physical therapy, home exercise programs, and oral analgesics. Once these therapies fail, patients commonly move forward with interventional pain treatment options such as epidural steroid injections (ESIs) or MILD® as the next step.

Objective: To assess improvement of function and reduction in pain for Medicare beneficiaries following treatment with MILD (treatment group) in LSS patients with neurogenic claudication and verified ligamentum flavum hypertrophy and to compare to a control group receiving ESIs.

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

Setting: Twenty-six US interventional pain management centers.

Methods: Patients in this trial were randomized one to one into 2 study arms. A total of 302 patients were enrolled, with 149 randomized to MILD and 153 to the active control. 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 ESI 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 is the 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. This report presents safety and efficacy results at 1-year follow-up. Outcomes at 2 years will be collected and reported for patients in the MILD group only.

Results: At 1-year follow-up, ODI, NPRS, and all 3 ZCQ domains (Symptom Severity, Physical Function and Patient Satisfaction) demonstrated statistically significant superiority of MILD versus the active control. For primary efficacy, the 58.0% ODI responder rate in the MILD group was higher than the 27.1% responder rate in the epidural steroid group ($P < 0.001$). The primary safety endpoint was achieved, demonstrating that there is no difference in safety between MILD and ESIs ($P = 1.00$).

Limitations: There was a 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 adjunctive pain therapy study restrictions. Study enrollment was not limited to patients that had never received ESI therapy.

Conclusions: One-year results of this randomized controlled clinical trial demonstrate that MILD is statistically superior to ESIs in the treatment of LSS patients with neurogenic claudication and verified central stenosis due to ligamentum flavum hypertrophy. Primary and secondary efficacy outcome measures achieved statistical superiority in the MILD group compared to the control group. With 95% of patients in this study presenting with 5 or more LSS co-factors, it is important to note that patients with spinal co-morbidities also experienced statistically significant improved function that was durable through 1 year.

Key words: MILD, minimally invasive lumbar decompression, interlaminar epidural steroid injections, ESI neurogenic claudication, ligamentum flavum, ENCORE, PILD, CED Study, LSS

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Lumbar spinal stenosis (LSS) is a common degenerative spinal condition which is a major cause of pain and functional disability for the elderly. LSS is characterized by anatomical narrowing of the spinal canal which may occur in the central canal, lateral recess, or intervertebral foramen (1,2). The reduction in diameter of the central spinal canal and lateral recesses may be attributable to disc protrusion, facet hypertrophy, facet joint cartilage degeneration, spondylolisthesis, ligamentum flavum hypertrophy, osteophyte formation, foraminal stenosis or a combination of factors (2,3). These biomechanical changes in spinal structures and the resulting stenosis eventually lead to compression of neural elements resulting in limited mobility and pain (4,5).

Neurogenic claudication symptoms are a hallmark of LSS, where patients develop low back or leg pain that is aggravated by prolonged standing or lumbar extension, and is relieved by sitting or flexing the lumbar spine (5-7). It is believed that compression of neural elements causes nerve root ischemia resulting in painful neurogenic claudication (1,6,8,9).

The treatment of LSS generally follows a similar progression for most patients, beginning with conservative management such as physical therapy, home exercise programs, and oral analgesics. Once these therapies no longer provide relief, patients commonly move forward with interventional pain treatment options such as epidural injections or MILD® (Vertos Medical, Aliso Viejo, CA) as the next step (10-16). Ultimately, patients may choose surgery which can include the use of interspinous spacers or decompressive surgery, with or without fusion (17,18).

The MiDAS ENCORE (Evidence-based Neurogenic Claudication Outcomes Research) randomized controlled trial was designed to assess outcomes of MILD and compare these outcomes with epidural injections

in patients with LSS and neurogenic claudication symptoms and having verified ligamentum flavum hypertrophy as a contributing factor. Patients were treated with either MILD (treatment group) or ESIs (active control). 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 (19). This report presents 1-year function and pain outcomes for MiDAS ENCORE patients.

METHODS

MiDAS ENCORE is being conducted at 26 interventional pain management centers throughout 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 (20). MiDAS ENCORE is registered with the US Clinical Trial Registry (NCT02093520). A full description of the study design, as well as 6-month follow-up results, have been previously published (21,22).

Patients

Enrollment included 302 Medicare beneficiaries. All patients were required to meet study inclusion/exclusion criteria, and underwent a predefined supplemental symptomatic diagnosis screening assessment to confirm symptoms of neurogenic claudication (Table 1) (23). Written informed consent was obtained from all patients.

Selection Criteria

Study inclusion criteria required that patients be ≥ 65 years old, a Medicare beneficiary, and have had neurogenic claudication symptoms for at least 3 months that was refractory to physical therapy, home exercise programs, and oral analgesics. LSS with ligamentum flavum > 2.5mm was confirmed by preoperative magnetic resonance imaging or computed tomography. All patients underwent predefined and precise diagnostic screening to confirm symptoms of neurogenic claudication prior to enrollment in the study (Table 1) (23). Patients with lumbar spine comorbid conditions commonly associated with spinal stenosis, including osteophytes, facet hypertrophy, minor spondylolisthesis, foraminal stenosis, and disc protrusion, were included unless the treating physician determined that the condition was too advanced.

Patients with an Oswestry Disability Index (ODI)

Table 1. MiDAS ENCORE — Neurogenic Claudication Symptomatic Diagnosis

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 ≥ 3 months.

score < 31 or Numeric Pain Rating Scale (NPRS) score < 5 were excluded. Patients with a history of spinal fracture with current related pain, prior surgery at any treatment level, or motor deficit or disabling back or leg pain from causes other than LSS neurogenic claudication were not included. Patients with Grade III or higher spondylolisthesis, and those suffering from epidural lipomatosis, if deemed to be a significant contributor of canal narrowing by the physician, were also excluded. Past epidural injection therapy was not an exclusion criteria. Finally, patients unable to walk ≥ 10 feet unaided before being limited by pain were not included (21,22). A review of radiological images and reports was conducted by study investigators, and in the event of discrepancies, the final radiologist report was the determinant.

Interventions

The MILD procedure has been previously described (21,24-33). MILD provides percutaneous lumbar decompression of the spinal canal without destabilizing adjacent structures, and does not involve the use of implants. Using a dorsal approach, the percutaneous MILD system is used to remove small portions of lamina and selectively debulk the hypertrophic ligamentum flavum. MILD is performed ipsilaterally through a small 6-gauge port, and is generally conducted using local anesthetic and moderate sedation. Contrast medium-enhanced fluoroscopic guidance provides visualization throughout the MILD procedure, and decompression is confirmed through visual changes in the epidurogram and improved contrast medium flow. MILD may then be performed on the contralateral side for bilateral decompression, as well as at multiple levels.

In the active control group, lumbar interlaminar epidural steroid injections (ESIs) were administered using intermittent fluoroscopy and contrast medium to guide needle placement. Patients received 80mg of triamcinolone acetonide or methylprednisolone acetate (40mg for diabetics) during the initial procedure, and between 40mg and 80mg during subsequent procedures. Patients assigned to the active control were allowed up to 4 treatments during the 1-year study period, consistent with American Society of Interventional Pain Physicians guidelines (34). Patients were discharged per institutional standard of care, and provided instructions regarding the use of any adjunctive conservative therapies. Disallowed treatments for patients in both study arms included adhesiolysis, neurostimulator, lumbar facet block with steroids, lumbar nerve root block with steroids, surgery, and any central canal or other

intraspinous procedure. Patients in the MILD arm could not receive any type of ESIs, and patients in the ESI arm could not receive MILD or transforaminal/caudal ESIs.

Outcome Measures

Six-month and 1-year follow-ups were conducted for all patients, and 2-year data will be collected for patients receiving MILD only. Clinical outcome measures included multiple validated assessment tools for evaluating function and pain. ODI is used to evaluate functional disability (35), NPRS measures back and leg pain (36), and the Zurich Claudication Questionnaire (ZCQ) domains evaluate symptom severity, physical function, and patient satisfaction following treatment (37,38).

Efficacy was evaluated by comparing the proportion of patients who demonstrated a clinically meaningful improvement and who were satisfied with their treatment at each follow-up. Primary efficacy is the proportion of ODI responders in the MILD group versus ESIs, where ODI responders are defined as patients reporting a ≥ 10 -point improvement in ODI score from baseline to follow-up as a clinically meaningful improvement in function (39,40). Secondary efficacy is the comparison of the proportion of NPRS and ZCQ responders between the 2 study groups using clinically significant efficacy thresholds of a 2.0-point improvement in NPRS (39-43), a 0.5-point improvement in ZCQ domains, and an absolute ZCQ Patient Satisfaction score of ≤ 2.5 (37,38,44,45). Patients 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 included in the analysis as non-responders in their treatment arm. Primary safety is the incidence of device- or procedure-related adverse events through one year.

Randomization

Patients were randomized in an allocation ratio of one to one between study groups. Randomization was electronically generated using the random permutation block method stratified by site. To minimize advance patient knowledge of treatment, sites were advised to implement randomization and inform patients of their randomization group on the day of the procedure. Preoperative instructions and workup were the same for all patients.

Statistical Methods

Continuous data are 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 significant.

The primary efficacy objective was to demonstrate statistical superiority of MILD compared to ESIs on the proportion of ODI responders, tested by comparing the lower bound of the 2-sided 95% confidence interval around the difference between the population proportions to zero. Secondary efficacy endpoints were also tested for superiority of MILD to the control. The primary safety endpoint was met if the device- or procedure-related adverse event rate was not significantly greater with MILD than with ESI. One-year efficacy was assessed using the one year follow-up visit, or 6-month values in the absence of one year data.

Primary study analyses were conducted with patients assigned to the group to which they were randomized. For the primary endpoints, as-treated analyses were also performed post hoc. As an a priori sensitivity analysis, propensity scoring was used for a covariate-adjusted analysis of the primary efficacy endpoint. Exploratory analyses included evaluation of change scores for the efficacy endpoints, as well as subgroup analyses of primary efficacy for the most common lumbar co-factors.

Sample size was calculated to obtain 80% power for testing the primary superiority hypothesis. The total sample size of 302 was sufficient to meet this objective under Type 1 error of 0.05 and 1:1 randomization, accounting for dropouts.

RESULTS

Participant Flow

A total of 302 patients were enrolled in MiDAS ENCORE from June 2014 through April 2015. Of 320 patients assessed for eligibility, 18 were excluded because they did not meet the study selection criteria. Randomization allocation resulted in 149 patients receiving MILD and 153 patients receiving ESIs. Six patients assigned MILD and 22 assigned ESIs voluntarily withdrew prior to study treatment. Of the 6 patients assigned MILD, 5 withdrew for personal or insurance reasons and one was unwilling to comply with study assessments. In the ESI arm, 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. Ultimately, 143 patients underwent MILD and 131 patients underwent ESI treatment

in the trial. Between 6-month and 1-year follow-up, 2 patients in the MILD arm died of unrelated causes (one cardiopulmonary arrest and one cardiac arrest) and 2 patients in the ESI arm withdrew for unrelated health reasons. Per the statistical plan, these 4 patients were included in the one year analysis using their 6-month follow-up data which was carried forward. Two additional patients in the ESI arm missed both the 6-month and 1-year follow-ups (one lost to follow-up and one refused to return for follow-up) and were not included in this analysis. Therefore, outcomes for 143 patients who received MILD and 129 patients who received ESIs were included in this one year report. Figure 1 presents the participant flow through one year follow-up.

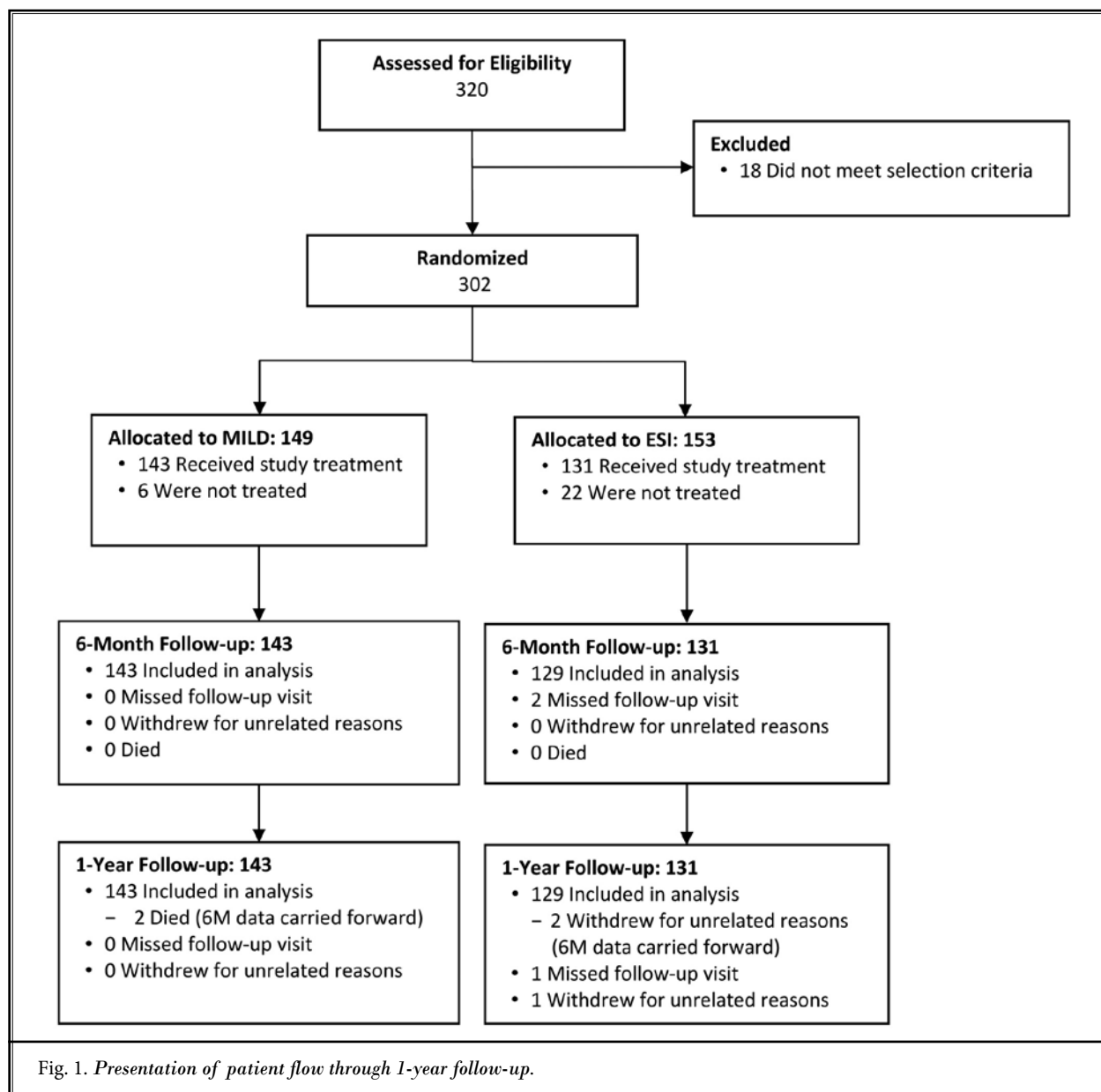
Patient Characteristics

Demographics, presenting LSS co-factors, and baseline clinical data are shown in Table 2. A significant difference in gender was identified between the groups, with a larger proportion of males in the MILD group. Bulging disc, foraminal narrowing, facet hypertrophy, facet arthropathy, and degenerative disc disease were the most frequently reported presenting LSS co-factors, and were similar in incidence between the study groups except facet arthropathy, which was significantly more common in the ESI group. There were no significant differences in baseline values for ODI, NPRS, and ZCQ domains between the study groups.

Prior conservative treatments for all patients in this study included physical therapy and a program of home exercise. The next most frequently reported conservative therapies included chiropractic adjustment (48%) and the use of walking aids (44%). Aquatic therapy, reported by 19% of patients, was the only prior conservative treatment that was different between groups with a significantly higher incidence in the ESI group.

Procedures

Table 3 presents initial procedure data for both study groups. ESIs were administered at a single level with expectation of steroid migration to other levels, whereas MILD required treatment at each level. In the MILD group, 67.8% (97 patients), 29.4% (42 patients), and 2.8% (4 patients) received treatment at 1, 2 and 3 levels, respectively. Specific lumbar levels treated in the MILD group were as follows: L2-L3, 9.8% (14 patients); L3-L4, 39.9% (57 patients); L4-L5, 77.6% (111 patients); L5-S1, 7.7% (11 patients). In addition, 93.7% (134) and 6.3% (9) of patients in the MILD arm received bilateral treatment and unilateral treatment, respectively. Pa-



tients in the ESI arm were allowed up to 4 ESI treatments during the one year study period, and on average received 2.0 (including initial treatment). All patients were discharged within 24 hours of their assigned procedure.

Medications

The baseline usage of medication for neurogenic claudication was 90.6% of patients in the MILD arm and 83.0% of patients in the ESI arm ($P = 0.075$). At one year, only minor changes were observed in these rates with a slight decrease in the MILD arm to 88.2%, and a

slight increase in the ESI arm to 84.2%. None of these changes were significant, and there were no significant differences between the groups ($P = 0.51$) (Table 4).

Function and Pain Outcomes

At one year, the proportion of ODI responders in the MILD group was statistically significantly higher than the proportion of ODI responders in the ESI group. The ODI responder rate was 58.0% in the MILD group versus 27.1% for the ESI group ($P < 0.001$), demonstrating clinically meaningful improvement in function for patients

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			0.039*
Male	49.7% (74)	37.9% (58)	
Female	50.3% (75)	62.1% (95)	
Presenting LSS 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)†			
Symptom Severity Domain	3.5 ± 0.5	3.5 ± 0.6	0.494
Physical Function Domain	2.9 ± 0.5	2.8 ± 0.4	0.308

*Significant difference between groups

†Mean ± standard deviation

Table 3. 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			< 0.001*
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)	
Anesthesia type			< 0.001*
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)	

*Significant difference between groups

in the MILD group. Likewise, for NPRS and all 3 ZCQ domains, the proportion of responders in the MILD group was statistically significantly higher than the proportion of responders in the ESI group (Table 5 and Fig. 2).

A between-group comparison of mean changes in efficacy outcomes from baseline to one year follow-up shows statistically significantly greater improvement in the MILD arm versus the active control for all outcome

Table 4. Medication for Neurogenic claudication at 1-year follow-up.

Medication at 1 Year*	MILD N = 119 % (n) [events]	ESI N = 95 % (n) [events]	P Value
All Medications for Neurogenic Claudication	88.2% (105) [215]	84.2% (80) [177]	0.51
Acetaminophen and Hydrocodone	27.7% (33) [36]	24.2% (23) [28]	0.67
Tramadol	19.3% (23) [26]	23.2% (22) [22]	0.61
Gabapentin	18.5% (22) [24]	18.9% (18) [18]	1.00
Acetaminophen	13.4% (16) [16]	20.0% (19) [19]	0.27
Ibuprofen	13.4% (16) [16]	13.7% (13) [13]	1.00
Naproxen	12.6% (15) [16]	6.3% (6) [6]	0.19
Oxycodone and Acetaminophen	6.7% (8) [9]	10.5% (10) [10]	0.45
Hydrocodone	5.9% (7) [7]	6.3% (6) [6]	1.00
Meloxicam	5.0% (6) [6]	3.2% (3) [3]	0.73
Celecoxib	4.2% (5) [5]	2.1% (2) [2]	0.64
Acetaminophen and Codeine	3.4% (4) [4]	1.1% (1) [2]	0.51
Diclofenac	3.4% (4) [4]	2.1% (2) [2]	0.89
Oxycodone	3.4% (4) [4]	4.2% (4) [4]	1.00
Pregabalin	3.4% (4) [4]	2.1% (2) [2]	0.89
Morphine	2.5% (3) [6]	1.1% (1) [2]	0.78
Diclofenac Topical	2.5% (3) [3]	2.1% (2) [2]	1.00
Lidocaine Topical	2.5% (3) [3]	5.3% (5) [5]	0.49

*Report of all neurogenic claudication medications taken by at least 2% of all study patients.

Table 5. Primary and secondary efficacy outcomes—Proportion of responders.

Outcome Measure	6 Months				1 Year			
	MILD % (n/N)	ESI % (n/N)	Difference (95% CI)	P Value	MILD % (n/N)	ESI % (n/N)	Difference (95% CI)	P Value
Primary Efficacy: ODI ^b	62.2% (89/143)	35.7% (46/129)	26.6% (14.4%, 38.8%)	< 0.001 ^a	58.0% (83/143)	27.1% (35/129)	30.9% (19.0%, 42.8%)	< 0.001 ^a
Secondary Efficacy: NPRS ^c	55.9% (80/143)	33.3% (43/129)	22.6% (10.4%, 34.9%)	< 0.001 ^a	57.3% (82/143)	27.1% (35/129)	30.2% (18.3%, 42.1%)	< 0.001 ^a
ZCQ ^d Symptom Severity domain	52.8% (75/142)	28.7% (37/129)	24.1% (12.1%, 36.2%)	< 0.001 ^a	51.7% (74/143)	31.8% (41/129)	20.0% (7.8%, 32.2%)	0.001 ^a
Physical Function domain	52.4% (75/143)	14.0% (18/129)	38.5% (27.6%, 49.4%)	< 0.001 ^a	44.1% (63/143)	17.8% (23/129)	26.2% (15.0%, 37.4%)	< 0.001 ^a
Patient Satisfaction ^e	64.8% (92/142)	30.2% (39/129)	34.6% (22.7%, 46.5%)	< 0.001 ^a	61.5% (88/143)	33.3% (43/129)	28.2% (16.1%, 40.3%)	< 0.001 ^a

a Significant difference between groups

b ODI responder definition: ≥ 10-point improvement

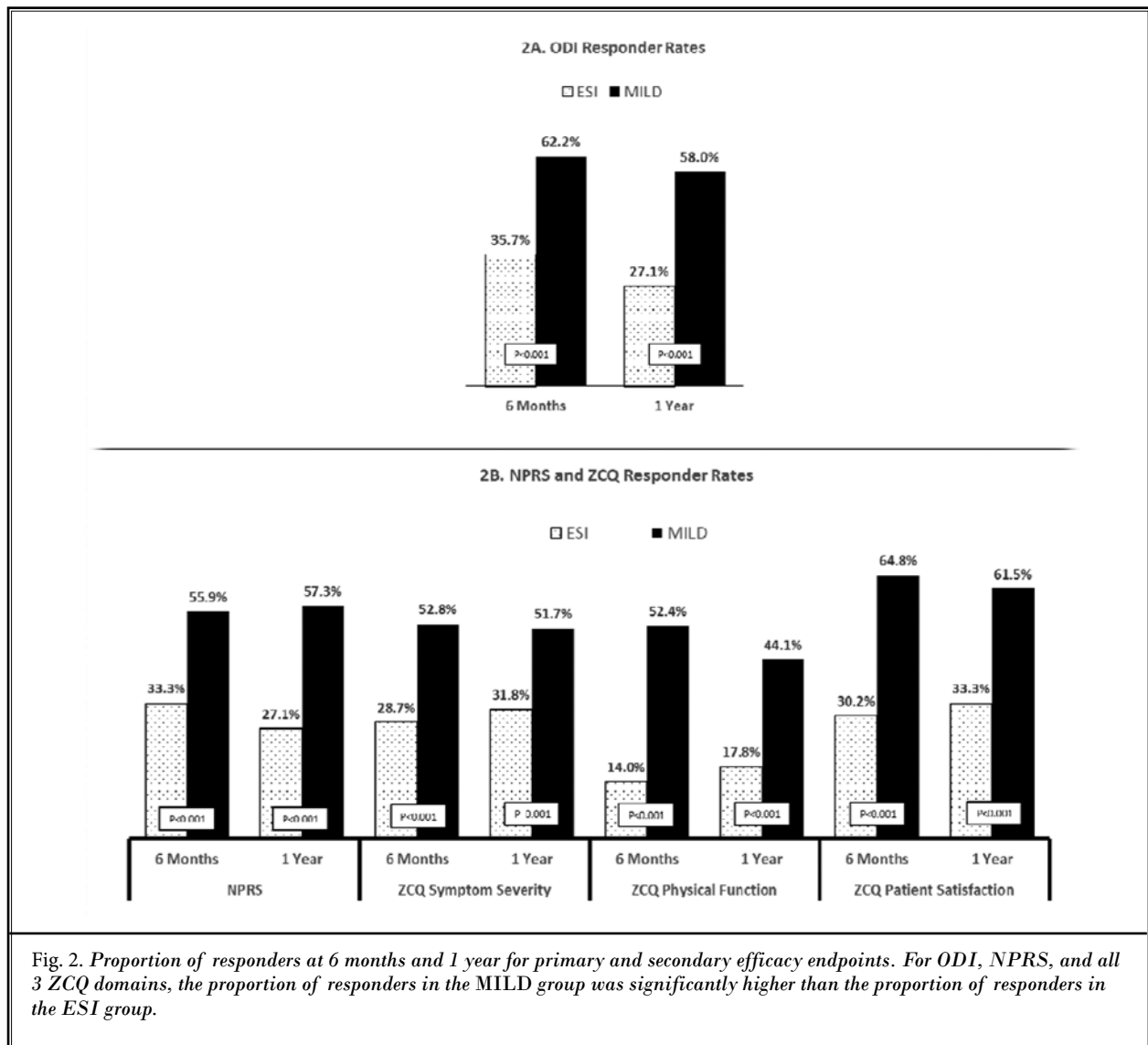
c NPRS responder definition: ≥ 2.0-point improvement

d ZCQ domain responder definition: ≥ 0.5-point improvement in each domain

e ZCQ Patient Satisfaction responder definition: ≤ 2.5, Lower scores indicate a higher level of satisfaction with the procedure.

measures. Notably, the within-group change from baseline to one year follow-up was statistically significant for both groups and for all efficacy endpoints (Table 6 and Fig. 3). The ZCQ Patient Satisfaction score for MILD

was 2.4 ± 0.1 (mean ± standard error) versus 3.1 ± 0.1 for ESIs (*P* < 0.001), demonstrating a statistically significantly higher level of patient satisfaction with the MILD procedure.



Twenty-two patients who received MILD and 32 patients who received ESI withdrew prior to the one year follow-up due to poor response to the study treatment and/or their intention to receive a disallowed procedure. Of the 22 patients in the MILD group, 2 received surgery, 10 crossed over to receive interlaminar ESIs, 8 underwent other disallowed therapy, and 2 indicated being non-responsive to the MILD procedure but did not report receipt of alternate therapy. Of the 32 patients who received ESI, 12 received surgery, 6 crossed over to receive MILD, 10 underwent other disallowed therapy, and 4 indicated being non-responsive

to ESIs but did not report receipt of alternate therapy. The number of patients in the ESI group withdrawn due to poor response to their study procedure was numerically, although not significantly, greater than for mild ($P = 0.16$).

Safety

Two patients who received MILD (2 events) and 2 patients who received ESIs (3 events) experienced device- or procedure-related adverse events (1.3%, $P = 1.00$) in this study. Of these, one event was adjudicated as a serious procedure-related adverse event. In this case, a

Table 6. Mean change in outcome measures.

Outcome Measure	6 Months			1 Year		
	MILD	ESI	P Value	MILD	ESI	P Value
ODI						
Mean ± SE (n)	-18.5 ± 1.6 (143)	-5.6 ± 1.3 (129)	< 0.001*	-16.2 ± 1.6 (143)	-4.5 ± 1.1 (129)	< 0.001*
Median (min, max)	-17.1 (-77.1, 20.0)	0.0 (-45.7, 31.4)		-14.3 (-77.1, 20.0)	0.0 (-45.7, 28.6)	
P value (within-group)	< 0.001†	< 0.001†		< 0.001†	< 0.001†	
NPRS						
Mean ± SE (n)	-2.9 ± 0.3 (143)	-0.9 ± 0.2 (129)	< 0.001*	-2.8 ± 0.3 (143)	-0.7 ± 0.2 (129)	< 0.001*
Median (min, max)	-2.0 (-10.0, 3.0)	0.0 (-6.0, 3.0)		-2.0 (-10.0, 3.0)	0.0 (-9.0, 3.0)	
P value (within-group)	< 0.001†	< 0.001†		< 0.001†	< 0.001†	
ZCQ						
Symptom Severity domain						
Mean ± SE (n)	-0.8 ± 0.1 (142)	-0.3 ± 0.1 (129)	< 0.001*	-0.7 ± 0.1 (143)	-0.3 ± 0.1 (129)	< 0.001*
Median (min, max)	-0.6 (-2.9, 0.9)	-0.1 (-2.4, 1.1)		-0.6 (-2.7, 1.1)	-0.1 (-2.0, 1.0)	
P value (within-group)	< 0.001†	< 0.001†		< 0.001†	< 0.001†	
Physical Function domain						
Mean ± SE (n)	-0.6 ± 0.1 (143)	-0.1 ± 0.1 (129)	< 0.001*	-0.5 ± 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)		-0.4 (-2.6, 1.0)	0.0 (-1.8, 1.6)	
P value (within-group)	< 0.001†	0.003†		< 0.001†	0.011†	

*Significant difference between groups.

†Significant difference with baseline values within the group.

patient who received ESI experienced sinus bradycardia following treatment. This patient briefly lost consciousness at discharge and was admitted to the hospital for observation. The patient was discharged from the hospital within 24 hours with no complications. There were no serious device- or procedure-related adverse events reported in the MILD group. A non-serious procedural hemorrhage was reported during one MILD case in which intraoperative oozing was observed at the decompression site and Gelfoam® (Pfizer Injectables, New York, NY) was administered through the cannula into the interlaminar space. The patient was discharged on the same day as the procedure with no complications. Considering all serious, unrelated adverse events, no significant differences between groups were identified (MILD: 12.1%, ESI: 8.5%, $P = 0.40$).

Discussion

This randomized controlled clinical trial produced Level I evidence that MILD is statistically significantly superior to ESIs in providing long-term clinically meaningful improvement in function and reduction in pain for Medicare beneficiaries with LSS. Multiple validated outcome measures were used to assess improvement in both function and pain. ODI, the primary efficacy outcome measure, is recommended for assessing “back-specific function” (46-48). An additional measure of functional outcome was collected through the secondary efficacy ZCQ Physical Function domain. Both of these

measures of functional outcome showed that statistically significantly more patients who received MILD achieved clinically meaningful improvement in physical function than patients who received ESIs. In addition, both NPRS and ZCQ Symptom Severity measures demonstrated that statistically significantly more patients who received MILD achieved clinically meaningful pain reduction than patients who received ESIs (Table 5 and Fig. 2).

A supplementary between-group comparison of mean change over time showed significantly better improvement in the MILD group versus the ESI group for all physical function and pain efficacy endpoints at both 6 months and one year (Table 6 and Fig. 3). These MILD results were further bolstered by a within-group analysis that demonstrated that mean change from baseline to both 6-month and one year follow-up, for all study outcome measures, achieved both statistical significance and clinically meaningful improvement. Specifically, mean improvement in the MILD group from baseline to one year follow-up was 16.2 for ODI, 2.8 for NPRS, 0.5 for ZCQ Physical Function, and 0.7 for ZCQ Symptom Severity. Clinical meaningful improvement was ≥ 10 points for ODI, ≥ 2.0 points for NPRS, and ≥ 0.5 for both ZCQ Physical Function and ZCQ Symptom Severity. Finally, the ZCQ Patient Satisfaction score of 2.4 at one year exceeded the validated clinically meaningful threshold of ≤ 2.5 . For the ESI cohort, the within-group analysis of mean change from baseline to both 6-month and one year follow-up also demonstrated

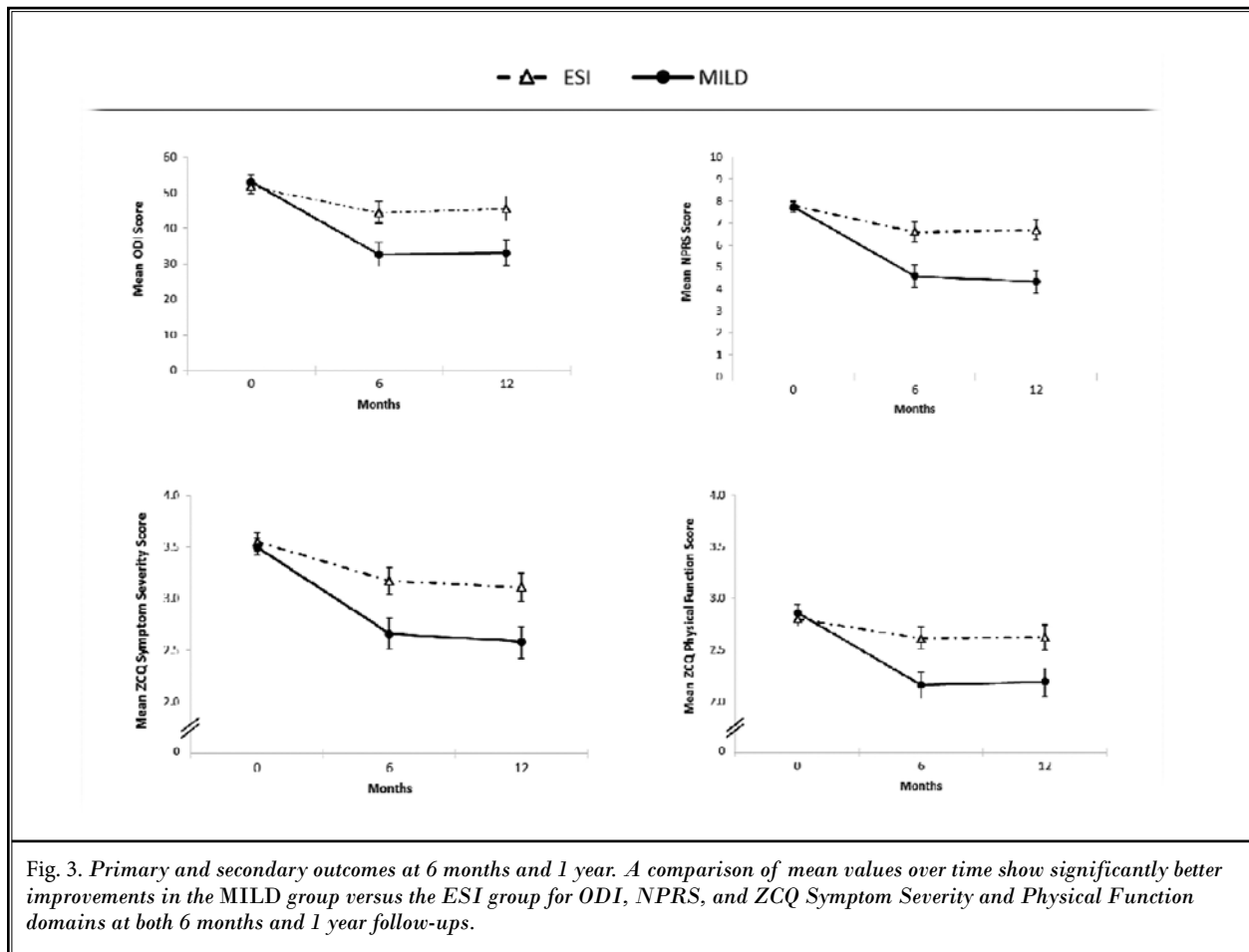


Fig. 3. Primary and secondary outcomes at 6 months and 1 year. A comparison of mean values over time show significantly better improvements in the MILD group versus the ESI group for ODI, NPRS, and ZCQ Symptom Severity and Physical Function domains at both 6 months and 1 year follow-ups.

significant improvement for all efficacy endpoints.

LSS co-factors were extremely common in this study, with 95% of patients presenting with 5 or more co-factors. The most common presenting co-factors, besides ligamentum flavum hypertrophy, included bulging disc (90.7%), foraminal narrowing (87.7%), facet hypertrophy (83.8%), facet arthropathy (81.5%), and degenerative disc disease (71.2%) (Table 2). ODI responder rates at one year for patients in the MILD group presenting with these co-factors were as follows: bulging disc, 61.7%; foraminal narrowing, 58.1%; facet hypertrophy, 59.3%; facet arthropathy, 60.0%; and degenerative disc disease, 61.2%. These MILD responder rates, which are in line with the overall ODI responder rate for all patients who received MILD (58.0%), demonstrated that patients with common spinal co-morbidities experience a high rate of improved function that is durable through one year. Given the multi-factorial nature of low back pain, it

may be advantageous to treat multiple conditions during a single procedure with other minimally invasive spinal therapies such as ESIs, radiofrequency ablation, or adhesiolysis. In the event radicular, discogenic, or axial pain is identified, ESI may be an appropriate adjunct therapy based on successful outcomes reported in the literature (49-57).

Under a propensity-scoring analysis adjusted for baseline covariates, MILD showed significantly better improvement than control group on the primary efficacy endpoint by a similar margin as in the unadjusted analysis ($P < 0.001$).

These study results are consistent with the only other published randomized controlled trial comparing MILD and ESIs. In 2012, Brown (25) reported that at 6 weeks, patients treated with MILD experienced significantly greater improvement in functional mobility and pain reduction, as well as a higher level of procedure satisfaction than ESI patients. Brown's study was a

double-blind, randomized, prospective study that used similar validated outcome measures. In a meta-analysis published by Levy and Deer (58), one year efficacy was reported for 134 MILD patients identified through a systematic literature review. For this patient population, mobility as measured by ODI improved by a mean of 16.0 points at one year, a significant and clinically meaningful improvement. At one year, these patients also experienced significant and clinically meaningful pain reduction. One year efficacy outcomes described by Levy and Deer are consistent with one year results provided in this report, both showing long-term durability of patient outcomes following MILD treatment.

The frequency of injections received by patients in the ESI group in this study was determined by the patient and treating physician based on requirements for symptom management. The average number of injections during the one year study period may be different from other ESI studies; a difference that can be explained by protocol design and patient selection criteria. This study required the presence of neurogenic claudication, whereas other published ESI studies targeted LSS in general and demonstrated efficacy in the treatment of radicular, discogenic, and axial pain (12-15, 49-57). In addition, some patients may have received and failed to respond to epidural injections.

Study limitations include the lack of patient blinding due to significant differences in treatment protocols between study arms, including multiple ESI procedures during the study period versus one MILD procedure. Also, adjunctive pain therapy within the lumbar region was restricted, and therefore responder rates may be lower for both study groups compared to those outside of study confines. Study enrollment was not limited to patients that had never received ESI therapy. Study limitations have been previously described (21,22).

CONCLUSION

One year results of this trial demonstrate that MILD is statistically superior to ESIs in the treatment of LSS patients with neurogenic claudication and verified central stenosis due to ligamentum flavum hypertrophy. Primary and secondary efficacy outcome measures achieved statistical superiority in the MILD group

compared to the control group. With 95% of patients presenting with 5 or more LSS co-factors, it is important to note that patients with spinal co-morbidities also experienced statistically significant improved function durable through one year. There were no significant differences in the safety profiles between groups. This prospective, multi-center, randomized controlled clinical trial provides Level I evidence of the superior effectiveness of MILD versus the control in this patient population.

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DISCLOSURES

Author Contributions

Both Dr. Benyamin and Dr. Staats were involved in the development of this manuscript during all phases. Drs. Benyamin and Staats managed literature searches, contributed extensively to the first draft of the original text, edited subsequent revisions for intellectual content, and provided final approval of the manuscript.

Conflict of Interest

Drs. Benyamin and Staats are Study Principal Investigators for MiDAS ENCORE. In this role, Drs. Benyamin and Staats have been responsible for trial oversight and reporting of results. Responsibilities have included protocol review, assistance with site selection, site investigator support, oversight of patient enrollment and protocol compliance, and adjudication of adverse events.

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Clinical Trial Registration: NCT02093520

APPENDIX

The following investigators enrolled patients in the study; they are listed by institution, with institutions ordered 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, A. Udeshi; 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 Rehab 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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