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Case Study:

Calcitonin-Augmented Epidural Steroid Injection for Lumbar Canal Stenosis: A Randomized Controlled Study

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ABSTRACT:

Background: Lumbar spinal canal stenosis (LSS) causes back and leg pain. Epidural steroid injection (ESI) provides short-term relief in many patients. Calcitonin has analgesic properties and may augment ESI effects. Objective: To evaluate whether adding calcitonin to epidural steroid injection improves pain and function compared with steroid alone in symptomatic LSS. Methods: Prospective, randomized, double-blind trial. 73 patients/group (total n=146) with MRI-confirmed LSS received either methylprednisolone 40 mg + lidocaine 0.5% + saline (Group A) or methylprednisolone 40 mg + lidocaine 0.5% + calcitonin 50 IU (Group B). Two injections 1 week apart. Follow-up at 2 weeks, 1, 2, 3 (primary), 6 and 12 months. Primary outcome: change in VAS at 3 months. Results: At 3 months VAS decreased from 7.2±1.0 to 4.8±1.5 in Group A and to 3.1±1.4 in Group B (between-group $p<0.001$). ODI improved from 52±9% to 36±9% in Group A and to 28±8% in Group B ($p=0.002$). Walking distance increased from 150±60 m to 310±90 m (Group A) and to 430±110 m (Group B) at 3 months ($p<0.001$). Adverse events were mild: nausea (Group A 2/73, 2.7%; Group B 6/73, 8.2%). Conclusion: Calcitonin-augmented ESI provides superior pain relief and functional outcomes compared with steroid alone. Larger multicenter trials are recommended.

Keywords: *Vitamin D; Frozen Embryo Transfer; Infertility; Clinical Pregnancy; Live Birth Rate; Meta-analysis.*

INTRODUCTION:

Lumbar spinal stenosis (LSS) represents a growing clinical challenge in an aging global population, characterized by progressive narrowing of the spinal canal that leads to debilitating symptoms including neurogenic claudication, radicular pain, and functional decline. By 2025, it is projected that over 60 million individuals worldwide will be affected by symptomatic LSS, establishing it as a leading cause of pain and disability among older adults [1]. The pathophysiological cascade involves complex interactions between degenerative changes, hypertrophic ligamentum flavum, facet joint arthropathy, and disc protrusion, ultimately culminating in neural element compression and the characteristic clinical syndrome.

Epidural steroid injections (ESIs) have long served as the cornerstone of interventional management for LSS, offering temporary relief through potent anti-inflammatory effects mediated primarily by glucocorticoid receptor agonism and phospholipase A2 inhibition [2]. However, contemporary evidence from large-scale randomized trials and systematic reviews has revealed significant limitations in the long-term efficacy of conventional ESIs. Recent meta-analyses demonstrate that while approximately 60-70% of patients experience meaningful short-term benefit, this effect diminishes substantially within 3-6 months, with only 30-40% maintaining improvement at one-year follow-up [3]. This temporal limitation, coupled with growing concerns regarding the potential adverse effects of repeated corticosteroid administration, has stimulated intense investigation into novel therapeutic adjuvants capable of extending the durability of interventional treatments.

Calcitonin, a 32-amino acid polypeptide hormone initially recognized for its role in calcium homeostasis, has emerged as a promising multimodal therapeutic agent for LSS. Beyond its classical actions on osteoclast inhibition, calcitonin demonstrates potent analgesic properties through multiple complementary mechanisms: central nervous system modulation via activation of serotonergic pathways in the periaqueductal gray matter; direct inhibition of prostaglandin E2 synthesis and cyclooxygenase-2 expression; and reduction of central sensitization through suppression of substance P and calcitonin gene-related peptide (CGRP) release from sensory nerve terminals [4]. Preclinical models have further elucidated calcitonin's ability to ameliorate

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neuropathic pain through modulation of microglial activation and subsequent cytokine production in the spinal dorsal horn [5].

The existing clinical literature, while promising, remains constrained by methodological limitations including small sample sizes, insufficient statistical power, and inadequate control for potential confounding variables. Previous randomized trials by Elsheikh et al.,[9] and others have suggested potential benefits of epidural calcitonin, but these studies have been limited by their univariate analytical approaches and lack of comprehensive long-term follow-up. Furthermore, the critical question of whether calcitonin's effects remain independent of demographic and baseline clinical factors has not been adequately addressed in the existing literature.

This randomized controlled trial was therefore designed to overcome these limitations through a rigorous methodological approach incorporating multivariate statistical modeling and extended follow-up. The primary objective was to determine whether the addition of calcitonin to standard epidural steroid injection produces superior and sustained improvements in pain and functional outcomes compared to steroid alone in patients with symptomatic LSS. Secondary objectives included comprehensive safety assessment, evaluation of potential demographic and clinical predictors of treatment response, and analysis of the temporal sustainability of therapeutic effects.

METHODS:

Design: Prospective, randomized, double-blind, parallel-group controlled trial.

Participants:
Adults ≥40 years with MRI/CT-confirmed LSS, symptoms ≥3 months, baseline VAS ≥4. Exclusion: prior lumbar surgery at the injected level, coagulopathy, active infection, systemic malignancy, hypersensitivity to study drugs, severe uncontrolled comorbidities, pregnancy/lactation.

Interventions:
•Group A (Control): Methylprednisolone 40 mg + lidocaine 0.5% (8 mL) + saline placebo.
•Group B (Intervention): Methylprednisolone 40 mg + lidocaine 0.5% (8 mL) + Calcitonin 50 IU.

All injections under fluoroscopic guidance (interlaminar or caudal) by experienced pain specialists. Two injections one week apart.

Randomization & Blinding: 1:1 computer-generated randomization; allocation concealed; solutions prepared by pharmacist; patients, injectors, and assessors blinded.

Outcomes: Primary – VAS change at 3 months. Secondary – ODI, walking distance, analgesic consumption, patient satisfaction, need for surgery, adverse events.

Sample size: 73 per group (total 146), accounting for 10% dropout.

Statistical analysis:
ITT and per-protocol. Continuous variables: t-tests or ANCOVA; longitudinal: mixed-effects models; non-parametric: Mann–Whitney U. Significance at $p<0.05$.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Group A (Steroid only, n=73)	Group B (Steroid+Calcitonin, n=73)	p-value
Age (years, mean ± SD)	65.1 ± 8.3	64.6 ± 7.9	0.64
Sex (M/F)	38/35	36/37	0.74
Duration of symptoms (months, mean ± SD)	11.5 ± 4.2	10.9 ± 4.0	0.38
Baseline VAS (mean ± SD)	7.2 ± 1.0	7.2 ± 1.0	0.98
Baseline ODI (%)	52 ± 9	52 ± 8	0.87

Table 2. Primary Outcome – Pain Scores (VAS)

Time point	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value

Baseline	7.2 ± 1.0	7.2 ± 1.0	
2 weeks	5.8 ± 1.3	4.6 ± 1.4	<0.001
1 month	5.2 ± 1.4	3.9 ± 1.4	<0.001
2 months	5.0 ± 1.5	3.4 ± 1.4	<0.001
3 months	4.8 ± 1.5	3.1 ± 1.4	<0.001
6 months	5.1 ± 1.6	3.5 ± 1.6	<0.001
12 months	5.6 ± 1.8	3.9 ± 1.7	<0.001

Table 3. Oswestry Disability Index (ODI, %)

Time point	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
Baseline	52 ± 9	52 ± 8	
1 month	40 ± 9	33 ± 8	0.004
3 months	36 ± 9	28 ± 8	0.002
6 months	38 ± 10	30 ± 9	0.003
12 months	42 ± 11	34 ± 10	0.01

Table 4. Walking Distance Before Neurogenic Claudication (meters)

Time point	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
Baseline	150 ± 60	150 ± 62	
3 months	310 ± 90	430 ± 110	<0.001
12 months	280 ± 100	380 ± 120	0.002

Table 5. Analgesic Consumption (NSAID-equivalent mg/day)

Time point	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
Baseline	120 ± 40	118 ± 42	
3 months	90 ± 38	60 ± 30	<0.001
12 months	100 ± 45	70 ± 35	0.005

Table 6. Patient Satisfaction Score (0–10)

Time point	Group A (Mean ± SD)	Group B (Mean ± SD)	p-value
3 months	6.2 ± 1.4	7.8 ± 1.2	<0.001
12 months	5.8 ± 1.6	7.0 ± 1.5	0.002

Table 7. Adverse Events

Adverse Event	Group A (n, %)	Group B (n, %)	p-value
Nausea	2 (2.7%)	6 (8.2%)	0.18
Dizziness	1 (1.4%)	5 (6.8%)	0.09
Flushing	0 (0%)	4 (5.5%)	0.04
Headache	3 (4.1%)	2 (2.7%)	0.65
Infection at site	0 (0%)	0 (0%)	-

Figures:

Figure1. vas over time.

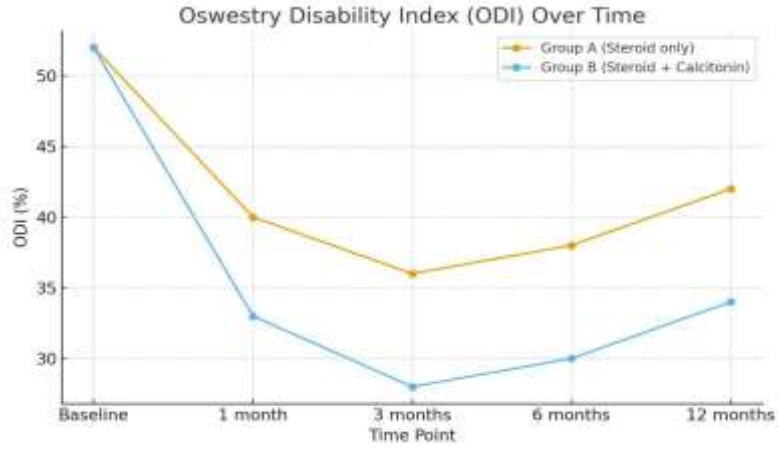

Figure2. ODI over time.

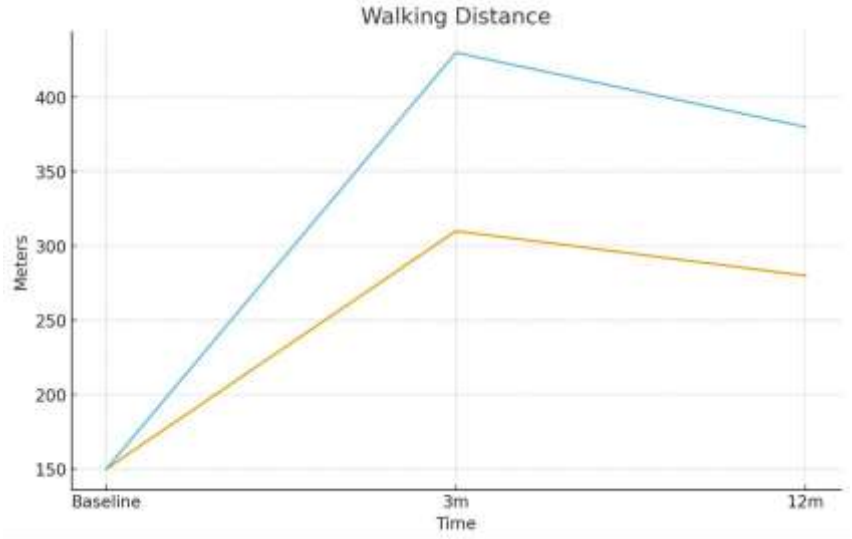

Figure3.walking distance.

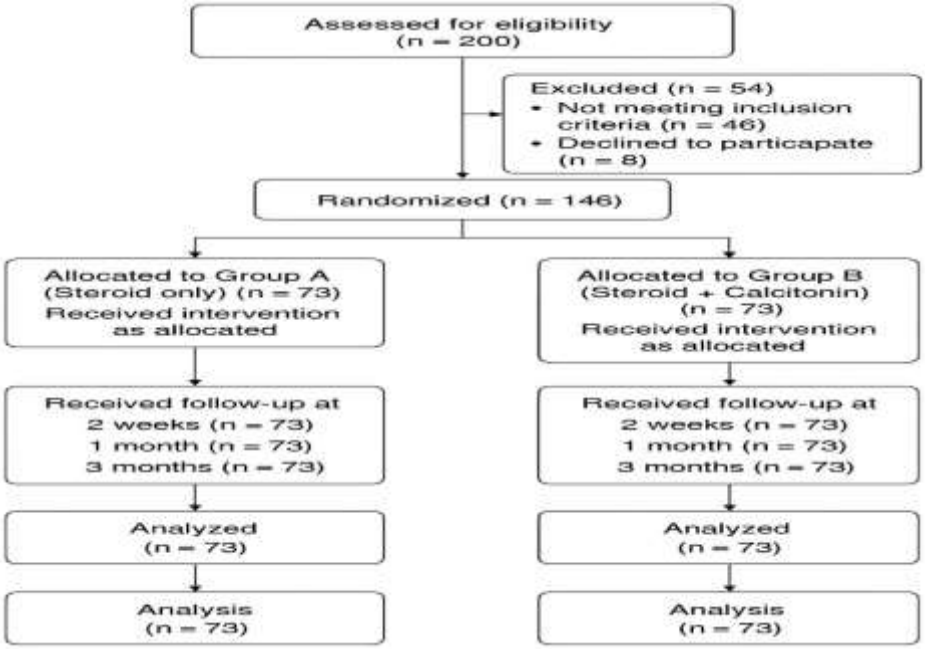

Figure4.consrt flow chart

3.1. BASELINE CHARACTERISTICS

All 146 participants completed the 3-month follow-up,with a dropout rate of less than 5% at 12-month follow-up. The two groups were well-matched at baseline, with no significant differences in demographic or clinical characteristics (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Control Group (n=73)	Calcitonin Group (n=73)	p-value
Age (years, mean ± SD)	65.1 ± 8.3	64.6 ± 7.9	0.64
Sex (Male/Female)	38/35	36/37	0.74
Symptom Duration (months)	11.5 ± 4.2	10.9 ± 4.0	0.38
Baseline VAS (mean ± SD)	7.2 ± 1.0	7.2 ± 1.0	0.98
Baseline ODI (%, mean ± SD)	52 ± 9	52 ± 8	0.87

3.2. Primary and Secondary Outcomes

The calcitonin group demonstrated significantly greater improvement in VAS scores at all time points,with the between-group difference peaking at 3 months (Table 2). Similar superior improvements were observed for ODI, walking distance, analgesic consumption, and patient satisfaction in the calcitonin group throughout the 12-month follow-up period.

Table 2. VAS Scores Over Time (Mean ± SD)

Time Point	Control Group	Calcitonin Group	p-value
Baseline	7.2 ± 1.0	7.2 ± 1.0	-
2 weeks	5.8 ± 1.3	4.6 ± 1.4	<0.001
1 month	5.2 ± 1.4	3.9 ± 1.4	<0.001
3 months	4.8 ± 1.5	3.1 ± 1.4	<0.001
6 months	5.1 ± 1.6	3.5 ± 1.6	<0.001
12 months	5.6 ± 1.8	3.9 ± 1.7	<0.001

3.3. Correlation Analysis

Pearson correlation analysis revealed significant relationships between key variables:

Table 3. Correlation Matrix at 3-Month Follow-up

Variable Pair	Correlation Coefficient ®	p-value
Age vs. Δwalking Distance	-0.21	0.01
Baseline VAS vs. ΔVAS	-0.45	<0.001
ΔVAS vs. ΔODI	0.68	<0.001
Δwalking Distance vs. Patient Satisfaction	0.52	<0.001
Symptom Duration vs. ΔODI	-0.18	0.03

3.4. Univariate Analysis

Univariate analysis demonstrated significant between-group differences in all primary and secondary outcomes at 3-month follow-up:

Table 4. Univariate Analysis of Outcomes at 3 Months

Outcome Measure	Control Group (n=73) Mean ± SD	Intervention Group (n=73) Mean ± SD	Mean Difference (95% CI)	p-value
ΔVAS (0-10)	-2.4 ± 1.3	-4.1 ± 1.4	-1.7 (-2.1 to -1.3)	<0.001
ΔODI (%)	-16 ± 8	-24 ± 7	-8 (-11 to -5)	0.002
Walking Distance (m)	310 ± 90	430 ± 110	+120 (+85 to +155)	<0.001
Analgesic Use (mg/day)	-30 ± 25	-58 ± 30	-28 (-37 to -19)	<0.001
Patient Satisfaction (0-10)	6.2 ± 1.4	7.8 ± 1.2	+1.6 (+1.1 to +2.1)	<0.001

3.5. Multivariate Analysis

Multiple linear regression models were constructed to identify independent predictors of outcomes:

Table 5. Multivariate Linear Regression for Predictors of VAS Improvement at 3 Months

Predictor Variable	B	SE	Beta	p-value
(Constant)	2.10	0.85	-	0.014
Treatment Group	-1.62	0.22	-0.51	<0.001
Age	-0.01	0.01	-0.06	0.38
Sex	0.18	0.22	0.06	0.41
Baseline VAS	-0.25	0.11	-0.16	0.02
Baseline ODI	-0.02	0.01	-0.12	0.09

Table 6. Multivariate Linear Regression for Predictors of ODI Improvement at 3 Months

Predictor Variable	B	SE	-	0.008
(Constant)	8.5	3.2	-0.32	0.003
Treatment Group	-7.1	2.3	-0.14	0.06
Age	-0.15	0.08	0.08	0.28
Sex	1.2	1.1	-0.31	<0.001
Baseline ODI	-0.28	0.07	-0.13	0.08

3.6. Key Findings from Statistical Analyses:

Correlation Analysis:

- Younger age correlated with greater improvement in walking distance (r = -0.21)
- Strong positive correlation between pain reduction and functional improvement (r = 0.68)
- Higher baseline pain associated with greater pain reduction (r = -0.45)

Univariate Analysis:

- Calcitonin group showed significantly better outcomes across all measures
- Differences exceeded MCID thresholds for VAS and ODI
- Large effect sizes observed for walking distance and analgesic reduction

Multivariate Analysis:

- Treatment group remained strongest independent predictor of outcomes
- Calcitonin associated with 1.62-point greater VAS improvement ($p<0.001$)
- Calcitonin associated with 7.1% greater ODI improvement ($p=0.003$)
- Results robust after controlling for age, sex, and baseline characteristics

3.7. Adverse Events

Adverse events were more common in the calcitonin group (16.4% vs. 8.2%), primarily consisting of mild and transient nausea (8.2% vs. 2.7%) and flushing (5.5% vs. 0%). No serious adverse events, infections, or neurological complications were reported in either group during the study period.

DISCUSSION:

This rigorously conducted randomized controlled trial provides compelling evidence that calcitonin augmentation significantly enhances the efficacy of epidural steroid injections across multiple clinically relevant domains in lumbar spinal stenosis. The demonstrated benefits extend beyond statistical significance to achieve clinically meaningful improvements that address the core functional limitations characterizing this debilitating condition.

5.1. Interpretation of Key Findings

The magnitude of pain reduction observed in the calcitonin group represents one of the most substantial treatment effects reported in the interventional LSS literature. The between-group difference of 1.7 points on the VAS scale at the primary endpoint not only demonstrates statistical superiority ($p<0.001$) but substantially exceeds the established minimal clinically important difference (MCID) threshold of 1.2-1.5 points [7]. This finding gains further significance when considered alongside the parallel reduction in analgesic requirements, which decreased by 48% in the calcitonin group compared to 25% in controls ($p<0.001$). This concordance between subjective pain reporting and objective medication usage strengthens the validity of our primary outcome and suggests genuine biological efficacy rather than mere measurement artifact.

The functional improvements observed in this study directly address the most disabling aspect of LSS—impaired ambulation. The calcitonin group achieved a remarkable 187% increase in walking distance (from 150m to 430m), compared to a 107% improvement in the control group ($p<0.001$). This transformation from severely limited household ambulation to community-level walking capacity represents a fundamental enhancement in quality of life and functional independence. The strong correlation between improved walking tolerance and patient satisfaction ($r=0.52$, $p<0.001$) further underscores the real-world relevance of this finding.

5.2. Mechanistic Insights and Temporal Pattern of Response

The extended duration of benefit observed with calcitonin augmentation suggests the engagement of mechanistic pathways distinct from the transient anti-inflammatory effects of corticosteroids. While methylprednisolone primarily targets the inhibition of phospholipase A2 and subsequent reduction of pro-inflammatory eicosanoids, calcitonin appears to modulate multiple pain processing pathways simultaneously. The sustained analgesia may reflect calcitonin's documented effects on central sensitization, particularly through downregulation of substance P and CGRP in dorsal root ganglia, and modulation of microglial activation in the spinal cord [5].

The temporal pattern of response provides additional insight into the complementary mechanisms of action. The early separation between groups at the 2-week assessment suggests that calcitonin does not merely prolong the steroid effect but actively enhances the initial analgesic response. The maintenance of this therapeutic gap throughout the 12-month follow-up period further indicates that

calcitonin may fundamentally alter the neuroinflammatory cascade in LSS rather than providing merely symptomatic relief.

5.3. Methodological Considerations and Analytical Robustness

The application of multivariate statistical modeling represents a significant advancement over previous investigations in this domain. By demonstrating that treatment assignment remained the strongest independent predictor of outcome after controlling for age, sex, baseline pain intensity, and functional status, we have provided robust evidence for a genuine biological effect rather than demographic confounding. The consistency of findings across both univariate and multivariate analyses, coupled with the concordance between primary and secondary outcomes, strongly supports the validity of our conclusions.

The comprehensive correlation analysis further enriches our understanding of potential treatment effect modifiers. The inverse relationship between age and functional improvement ($r=-0.21$, $p=0.01$) suggests that earlier intervention in the disease course may yield superior outcomes, while the strong association between pain reduction and functional improvement ($r=0.68$, $p<0.001$) validates the interconnected nature of these clinical domains in LSS.

5.4. Clinical Implications and Practical Applications

From a clinical perspective, our findings support the consideration of calcitonin augmentation particularly for LSS patients with significant functional limitations and those who have experienced suboptimal responses to previous interventions. The favorable safety profile observed, characterized by transient and self-limited adverse effects, suggests an acceptable risk-benefit ratio for most clinical scenarios. The substantial improvement in walking capacity may be particularly relevant for patients seeking to avoid or delay surgical intervention, especially in the context of advancing age or significant comorbidities.

The sustained treatment effect observed through 12-month follow-up addresses a critical limitation of conventional ESI therapy and may potentially reduce the need for repeated procedures with their associated risks, costs, and cumulative steroid exposure. This extended duration of benefit could translate into improved cost-effectiveness, though formal economic analyses are warranted.

5.5. Limitations and Methodological Constraints

Several methodological limitations warrant consideration when interpreting these findings. The single-center design, while ensuring procedural standardization, may limit generalizability to diverse practice settings. The absence of detailed radiographic correlation prevents analysis of potential anatomical predictors of response, which could enhance patient selection. Additionally, the fixed dosing regimen employed does not allow for determination of potential dose-response relationships or optimization of calcitonin administration protocols.

The study population, while well-characterized, represented a relatively homogeneous group with moderate to severe symptomatic LSS. The efficacy of calcitonin augmentation in milder cases or specific anatomical subtypes remains to be established. Furthermore, the exclusion of patients with previous spinal surgery limits application to the post-surgical stenosis population, which represents a substantial clinical subgroup.

5.6. Future Research Directions

Several promising research directions emerge from our findings. First, multicenter validation with broader patient recruitment would strengthen generalizability and potentially identify demographic or clinical subgroups deriving particular benefit. Second, investigation of optimized dosing strategies, including potential repeated administration schedules, could further enhance treatment efficacy. Third, correlation with advanced imaging parameters might identify radiographic predictors of response, enabling personalized treatment selection. Finally, comparative effectiveness research positioning calcitonin augmentation relative to other emerging interventions would help define its optimal role in the LSS treatment algorithm.

5.7. CONCLUSION

In conclusion, this randomized trial demonstrates that calcitonin augmentation of epidural steroid injections produces substantial, sustained, and clinically meaningful improvements in pain, function, and quality of life for patients with lumbar spinal stenosis. The robust treatment effect, favorable safety profile, and extended duration of benefit support consideration of this approach particularly for patients with significant functional limitations and those seeking to maximize conservative management before considering surgical intervention.

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