

Comparative Effectiveness of Fluoroscopy-Guided Caudal Epidural Steroid Injection with or without Hyaluronidase in Chronic Lumbo-Sacral Radiculopathy: A Single-Blind Randomized Clinical Trial

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ABSTRACT

Background: Chronic lumbosacral radiculopathy involves persistent radicular pain associated with mechanical and inflammatory processes. Caudal epidural steroid injections (ESIs) are commonly used for chronic radicular pain. Hyaluronidase has been proposed as an adjunct to facilitate epidural spread, but evidence regarding its incremental benefit remains limited.

Methods: In this single-blind randomized controlled trial, 40 patients with chronic lumbosacral radiculopathy due to lumbar disc protrusion and/or lumbar canal stenosis were randomly assigned to two groups. Group A received 10 mL of 5% saline, followed by 10 mL of 1% ropivacaine and 40 mg dexamethasone. Group B received 5 mL of 5% saline followed by the same dose of 1% ropivacaine and dexamethasone plus 5 mL containing 1500 U hyaluronidase. All procedures were performed under fluoroscopic guidance. The primary outcome was the change in pain intensity measured by the Numeric Rating Scale (NRS) at 3 months. Secondary outcomes included sleep disturbance, sitting and standing intolerance, neurogenic claudication assessed by walking distance, lower extremity muscle strength, and procedure-related adverse events.

Results: Group B had a greater reduction in NRS at 3 months than Group A (between-group mean difference 1.60, 95% confidence interval [CI] 0.45–2.75; $P = 0.009$). Sleep disturbance improved more in Group B, with a 54.3% reduction at 3 months ($P = 0.012$). Neurogenic claudication also improved more in Group B, with 75% of patients able to walk ≥ 300 meters at 3 months versus 30% in Group A ($P = 0.010$).

Conclusion: Adding hyaluronidase to fluoroscopy-guided caudal epidural steroid injection was associated with greater pain reduction and improvement in selected functional outcomes over 3 months. These findings warrant confirmation in larger randomized trials with longer follow-up and validated disability measures.

The authors declare no conflicts of interest.

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Introduction

Low back pain (LBP) is a highly prevalent musculoskeletal condition and a major contributor to disability worldwide. Chronic lumbosacral radiculopathy is characterized by persistent axial and/or radicular pain, typically lasting longer than 12 weeks, and may be associated with sensory, reflex, or motor abnormalities corresponding to the affected nerve root. Epidemiological studies indicate that most individuals experience at least one episode of LBP during their lifetime [1].

Lumbar disc herniation is an important structural cause of lumbosacral radiculopathy, particularly when nerve-root compression occurs at the L4–L5 or L5–S1 levels [2]. Management ranges from conservative measures, including pharmacological treatment and rehabilitation, to surgical decompression in selected patients. Epidural injections are also used as an interventional treatment to reduce radicular symptoms and may help defer or avoid surgery in appropriately selected patients [2].

Epidural steroid injections (ESIs) are widely used for the management of lumbosacral radicular pain. Their therapeutic effects are thought to involve both anti-inflammatory and neural mechanisms, addressing inflammatory responses associated with disc pathology as well as abnormal ectopic neural activity. Local anesthetics may provide additional analgesia through transient suppression of neural conduction, while corticosteroids primarily target inflammatory processes [2–5].

The analgesic effects of ESIs are multifactorial and are not completely understood. Proposed mechanisms include attenuation of ectopic neural activity, modulation of nociceptive signaling, and reduction of local inflammatory responses. Corticosteroids may decrease inflammatory cell activity and tissue edema, thereby reducing processes that contribute to radicular pain [3,4]. Nevertheless, clinical responses to ESIs vary considerably, and symptom relief may be incomplete or transient in some patients [3].

Epidural adhesiolysis has been developed as a targeted interventional approach for patients in whom epidural fibrosis or other anatomical factors may limit the spread of injected medications. The technique uses a catheter to deliver therapeutic agents toward the presumed pain-generating region and has been investigated in conditions such as lumbar spinal stenosis, disc herniation, and persistent pain after spinal surgery [5]. However, catheter-directed adhesiolysis is technically more demanding than conventional caudal ESI and may not be necessary in every patient.

Hyaluronidase has been investigated as an epidural adjuvant because enzymatic modification of the extracellular matrix may facilitate the spread of injected

solutions through tissue planes. By degrading hyaluronic acid within the extracellular matrix, hyaluronidase can transiently increase tissue permeability and potentially improve the distribution of co-administered medications. This mechanism has led to its use in conjunction with epidural injections and adhesiolysis procedures, although the clinical benefit of adding hyaluronidase to conventional caudal ESI remains uncertain [6–9].

Therefore, this randomized clinical trial compared fluoroscopy-guided caudal epidural steroid injection with and without hyaluronidase in patients with chronic lumbosacral radiculopathy. We hypothesized that adding hyaluronidase would improve pain and functional outcomes compared with caudal ESI alone.

Methods

Study Design and Participants

This single-blind randomized controlled trial was conducted at two educational hospitals affiliated with Tehran University of Medical Sciences: Imam Khomeini Hospital Complex and Dr. Shariati Hospital, Tehran, Iran, from February 2023 to October 2024. The study compared the efficacy of fluoroscopy-guided caudal epidural steroid injection with and without hyaluronidase in patients with chronic lumbosacral radiculopathy secondary to lumbar disc protrusion and/or lumbar canal stenosis.

The study protocol was approved by the Institutional Review Board and Ethics Committee of the Neuroscience Institute, Tehran University of Medical Sciences (approval code: IR.TUMS.NI.REC.1403.010). The trial was registered in the Iranian Registry of Clinical Trials (IRCT20240310060712N1; <https://www.irct.ir/trial/60712>). Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and was reported according to the CONSORT 2010 statement.

The CONSORT flow diagram showing patient screening, randomization, follow-up, and analysis is presented in (Figure 1).

Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they were 18–65 years or older and had chronic low back pain with unilateral or bilateral lower limb radicular pain for at least 6 months. Eligible patients had imaging and/or electrodiagnostic evidence of lumbar canal stenosis or lumbar disc protrusion consistent with their clinical symptoms, as well as clinical findings suggestive of lumbosacral radiculopathy, including a positive Straight Leg Raise (SLR) test when applicable. Additional inclusion criteria were failure to respond adequately to conservative treatment, including pharmacological therapy, physical therapy, and exercise-based

rehabilitation, no history of invasive or minimally invasive procedures for low back pain during the preceding year, and willingness to participate in the trial.

Patients were excluded if they had a history of previous spinal surgery, rheumatologic disease, coagulopathy, infection at the injection site, significant hepatic, renal, or cardiovascular dysfunction, type 1 or type 2 diabetes mellitus, cauda equina syndrome, or progressive neurological deficits requiring urgent surgical evaluation. Patients were also excluded if they had spinal canal space-occupying lesions or other relevant spinal pathologies, spondylolisthesis greater than grade 1, substance abuse, or inability to communicate adequately or complete the study questionnaires.

Randomization and Blinding

Participants were randomly assigned in a 1:1 ratio to either the steroid-only group (Group A) or the steroid-plus-hyaluronidase group (Group B). The randomization sequence was computer-generated by an independent statistician. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were opened immediately before the procedure.

This was a single-blind trial. Participants were unaware of their treatment allocation.

Because of the procedural nature of the intervention and preparation of the injectate, blinding of the proceduralist was not feasible. Outcome assessment and data analysis were performed by investigators who were blinded to group allocation.

Procedures

After being transferred to the operating room, patients were placed in the prone position with a pillow under the abdomen to reduce lumbar lordosis.

The lower limbs were positioned in slight abduction and internal rotation to provide optimal fluoroscopic visualization of the sacral hiatus. Standard monitoring was applied, including five-lead electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring. All procedures were performed under sterile conditions, and a prophylactic dose of cefazolin 1 g was administered before the intervention.

A caudal approach was used in all patients. After local infiltration of the skin and subcutaneous tissues with 1% lidocaine, an 18-gauge Tuohy epidural needle was introduced through the sacral hiatus into the sacral canal under fluoroscopic guidance. Then, 10 mL of iohexol 240 radiopaque contrast medium was injected to confirm correct epidural placement and to evaluate contrast spread, including the presence of any filling defects suggestive of epidural adhesions. A PVC catheter was then introduced through the epidural needle and advanced into the caudal epidural space for administration of the study injectate; no catheter-directed mechanical adhesiolysis was performed.

Patients in Group A received 10 mL of 5% saline followed by 10 mL of 1% ropivacaine plus 40 mg dexamethasone. Patients in Group B received 5 mL of 5% saline followed by 10 mL of 1% ropivacaine plus 40 mg dexamethasone and an additional 5 mL solution containing 1500 U hyaluronidase diluted in 5% saline.

After the procedure, patients were transferred to the recovery care unit for 3 hours of observation. During this period, vital signs were monitored, and procedure-related complaints were assessed. Sensory and motor examinations were performed hourly to ensure that no neurological injury had occurred. Patients were discharged if they were clinically stable.

All patients received pregabalin 75 mg twice daily for 90 days after the procedure for neuropathic pain management, with dose adjustment in patients with abnormal body weight when clinically indicated.

Image guidance:

All caudal epidural injections were performed under real-time C-arm fluoroscopic guidance using a Siemens Cios Select system (Siemens Healthineers, Germany).

Data Collection

Before enrollment, demographic and baseline clinical data were collected for all participants, including age, sex, baseline pain intensity, pain radiation pattern, use of a walking aid, sleep disturbance, sitting and standing intolerance, cough sign, Straight Leg Raise (SLR) test findings, neurogenic claudication, and lower extremity muscle strength.

Before the intervention, all participants received standardized instructions on how to report pain intensity using the Numeric Rating Scale (NRS), where 0 indicates no pain, and 10 indicates the worst imaginable pain. Follow-up assessments were performed at 2 weeks and 3 months after the procedure during outpatient visits. A telephone follow-up was also conducted after one month.

At each follow-up, pain intensity was assessed using the NRS. Additional clinical outcomes included pain radiation pattern; sleep disturbance; sitting and standing intolerance; cough sign; neurogenic claudication assessed by walking distance; and lower extremity muscle strength.

The walking distance was categorized according to the patient's ability to walk predefined distances, including at least 300 meters.

Lower extremity muscle strength was assessed through hip, knee, and ankle flexion and extension and graded using the standard Medical Research Council (MRC) scale.

All adverse events and procedure-related complications were prospectively monitored throughout the study period. Predefined safety outcomes included neurological deficits, sensory or motor changes, infection, bleeding, allergic reactions, post-procedural headache, and injection-site pain.

Outcome measures

The primary outcome was the change in pain intensity measured by the Numeric Rating Scale (NRS) at 3 months after the intervention. Secondary outcomes included sleep disturbance, sitting and standing intolerance, cough sign, Straight Leg Raise (SLR) test findings, neurogenic claudication assessed by walking distance, lower extremity muscle strength, and procedure-related adverse events.

Pain intensity was measured using the NRS, where 0 indicates no pain, and 10 indicates the worst imaginable pain. Neurogenic claudication was assessed based on the maximum walking distance tolerated by the patient and was categorized into predefined distance categories, including the ability to walk at least 300 meters. Lower extremity muscle strength was assessed for hip, knee, and ankle flexion and extension and graded using the Medical Research Council (MRC) scale from 0 to 5, where 0 indicates no visible or palpable muscle contraction, and 5 indicates normal strength against full resistance.

Sample size calculation

Sample size estimation was based on detecting a clinically meaningful between-group difference in NRS scores. Assuming a standard deviation of 1.2, a minimal clinically important difference of 1.5 points on the NRS, a power of 90%, and a two-sided α of 0.05, at least 15 patients were required in each group. Considering an anticipated dropout rate of 20%, 20 patients were enrolled in each group.

Statistical analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics. Continuous variables were reported as mean and standard deviation (SD), and categorical variables were reported as frequency and percentage. Between-group comparisons of baseline variables were performed using appropriate statistical tests according to the type and distribution of the data.

Longitudinal categorical outcomes were analyzed using generalized estimating equations (GEE) with an exchangeable correlation structure and were adjusted for baseline NRS, age, and sex when applicable. Continuous repeated outcomes, including NRS scores over time, were analyzed using mixed-effects models with random intercepts. Effect sizes were reported as mean differences or odds ratios with corresponding 95% confidence intervals (CI). A two-sided P value of <0.05 was considered statistically significant.

Results

Participant flow

A total of 40 participants were enrolled and randomly assigned to the two study groups. The patient randomization, follow-up, and analysis processes are shown in (Figure 1).

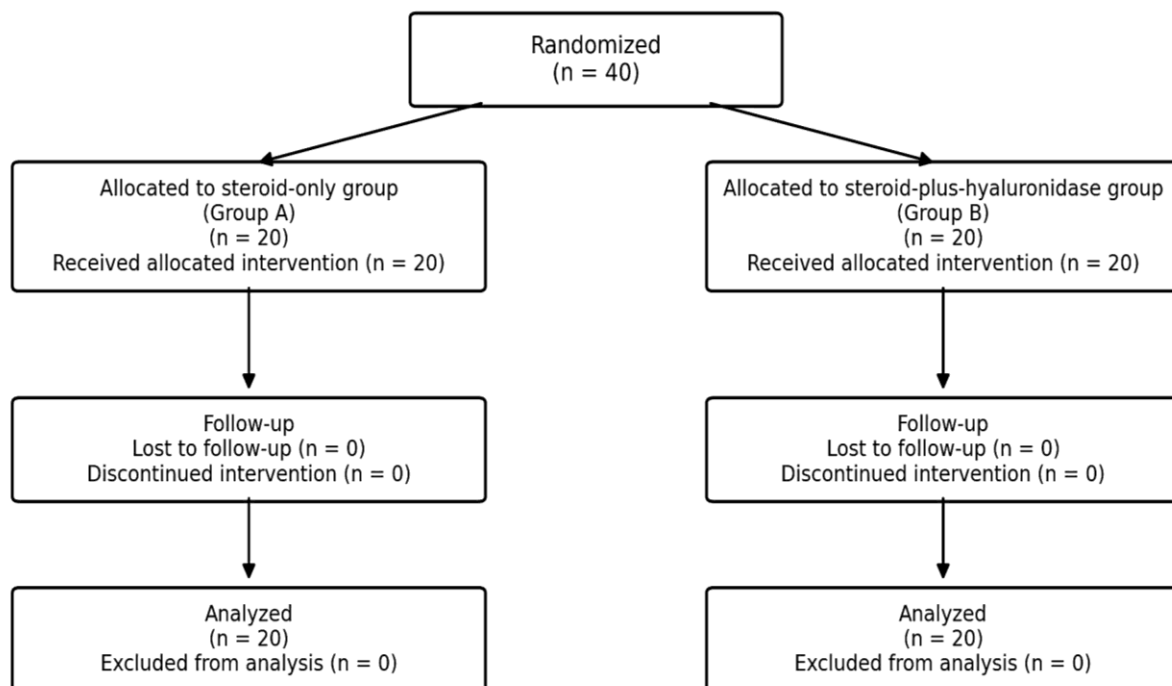


Figure 1- Flow diagram of randomization, follow-up, and analysis.

Baseline characteristics

The mean age was 53.00 ± 12.98 years in the steroid-only group and 53.05 ± 15.75 years in the steroid-plus-hyaluronidase group, with no statistically significant between-group difference ($P = 0.991$). The gender distribution was similar between the two groups. In the steroid-only group, 45% of participants were male and 55% were female, while in the steroid-plus-hyaluronidase group, 40% were male and 60% were female ($P = 0.749$). Baseline age and sex distributions are summarized in Tables 1 and 2.

Primary outcomes

There was no statistically significant between-group difference in baseline use of a walking aid. Cane use was reported by 2 patients (10.0%) in each group ($P = 1.000$; Table 3).

Pain intensity

Both groups showed a reduction in NRS scores over time. The between-group difference in NRS reduction became statistically significant at 3 months, favoring the steroid-plus-hyaluronidase group. At 3 months, the between-group mean difference was 1.60 points (95% CI 0.45–2.75; $P = 0.009$; Table 4).

Sleep disturbance

Sleep disturbance improved over time in both groups; however, the improvement was greater in the steroid-plus-hyaluronidase group.

Generalized estimating equation (GEE) analysis showed that Group B had a greater overall reduction in sleep disturbance (59.8% reduction; $P = 0.040$). At 1 month after the procedure, the probability of sleep disturbance decreased by 47.9% ($P = 0.087$), and at 3 months it decreased by 54.3% ($P = 0.012$).

Standing intolerance

Standing intolerance improved over time in both groups ($\chi^2 = 32.058$, $P < 0.001$). Compared with baseline, standing intolerance decreased during follow-up, with improvement observed at both 1 month and 3 months ($\chi^2 = 6.308$, $P = 0.043$). A between-group difference was observed at 1 month ($P = 0.019$), but this difference was not maintained at 3 months ($P = 0.067$).

Sitting intolerance

Sitting intolerance improved over time in both groups ($P = 0.002$). However, there was no statistically significant difference between the steroid-only group and the steroid-plus-hyaluronidase group in the improvement of sitting tolerance ($P = 0.911$).

Cough sign

The cough sign decreased over time in both groups. Compared with baseline, the cough sign showed a 91.7% reduction at 1 month ($OR = 0.083$, $P < 0.001$) and a 66.7% reduction at 3 months ($OR = 0.333$, $P = 0.014$). Pairwise comparisons showed no statistically significant between-group difference at 1 month ($P = 0.112$) or at 3 months ($P = 0.217$).

Straight Leg Raise test

Straight Leg Raise (SLR) test findings improved over time in both lower limbs. On the right side, SLR positivity decreased by 95.7% at 1 month ($OR = 0.043$, $P = 0.002$) and by 72.8% at 3 months ($OR = 0.272$, $P = 0.006$). On the left side, SLR positivity decreased by 90.9% at 1 month ($OR = 0.091$, $P = 0.001$) and by 64.9% at 3 months ($OR = 0.351$, $P = 0.014$). No statistically significant differences were observed between the two groups for SLR improvement.

Neurogenic claudication

Neurogenic claudication improved over time in both groups. However, the improvement was greater in the steroid-plus-hyaluronidase group.

At 1 month after treatment, 45% of patients in the steroid-plus-hyaluronidase group were able to walk at least 300 meters, compared with 10% of patients in the steroid-only group ($P = 0.031$). This between-group difference persisted at 3 months, when 75% of patients in the steroid-plus-hyaluronidase group and 30% of patients in the steroid-only group were able to walk at least 300 meters ($P = 0.010$; Table 5).

At 3 months, improvement in neurogenic claudication, defined as the ability to walk ≥ 300 meters, was observed in 75% of patients in the steroid-plus-hyaluronidase group compared with 30% in the steroid-only group. This corresponded to an odds ratio of 7.00 (95% CI 1.74–28.18), indicating a statistically significant between-group difference in functional walking capacity (Table 5).

No significant between-group difference was observed in lower extremity muscle strength during follow-up.

Safety outcomes

No serious adverse events were observed in either group during the study period. Minor procedure-related complaints, including transient headache and mild injection-site pain, were self-limiting and comparable between groups. No cases of persistent neurological deficit, infection, bleeding, allergic reaction, or clinically significant motor weakness were recorded.

Table 1- Baseline age of participants.

Variable	Steroid-only group (A) Mean $\pm$ SD (range)	Steroid-plus-hyaluronidase group (B) Mean $\pm$ SD (range)	P value
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Age, years	53.00 ± 12.98 (25-71)	53.05 ± 15.75 (24-76)	0.991
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Table 2- Sex distribution of participants

Sex	Steroid-only group (A)	Steroid-plus-hyaluronidase group (B)	P value
Male	45.0%	40.0%	0.749
Female	55.0%	60.0%	

Table 3- Baseline cane use in the two study groups

Variable	Steroid-only group (A)	Steroid-plus-hyaluronidase group (B)	P value
Cane use, n (%)	2 (10.0%)	2 (10.0%)	1.000

Table 4- Between-group comparison of NRS scores over time

Time point	Comparison	Mean difference	Standard error	P value
Baseline	Steroid-only vs. steroid-plus-hyaluronidase	0.300	0.438	0.498
1 month	Steroid-only vs. steroid-plus-hyaluronidase	0.300	0.549	0.588
3 months	Steroid-only vs. steroid-plus-hyaluronidase	1.600	0.584	0.009

Abbreviations: NRS, Numeric Rating Scale; CI, confidence interval.

Table 5- Effect of treatment on neurogenic claudication

Time point	Walking distance	Steroid-only group, n (%)	Steroid-plus-hyaluronidase group, n (%)	P value
Before treatment	<300 m	19 (95%)	18 (90%)	1.000
	≥300 m	1 (5%)	2 (10%)	
1 month	<300 m	18 (90%)	11 (55%)	0.031
	≥300 m	2 (10%)	9 (45%)	
3 months	<300 m	14 (70%)	5 (25%)	0.010
	≥300 m	6 (30%)	15 (75%)	

Values are presented as a number (%). P values were calculated using Fisher's exact test.

Discussion

This study evaluated whether adding hyaluronidase to fluoroscopy-guided caudal epidural steroid injection improves pain and selected clinical outcomes in patients with chronic lumbosacral radiculopathy. At 3 months, the steroid-plus-hyaluronidase group showed a greater reduction in NRS scores than the steroid-only group, with a between-group mean difference of 1.60 points (95% CI 0.45–2.75; $P = 0.009$). The magnitude of this difference may be clinically relevant, although larger studies are needed to determine its reproducibility and durability. Both groups also showed improvement in several secondary outcomes, including sleep disturbance, standing intolerance, sitting intolerance, cough sign, and SLR findings, while between-group differences were not observed consistently across these measures. Epidural injections remain commonly used interventional treatments for selected patients with persistent spinal pain and radicular symptoms [12–15,21–28].

Comparison with Previous Studies

The potential benefit of hyaluronidase as an adjunct to epidural interventions has been investigated in several clinical settings, although the available evidence is heterogeneous. Its proposed role is related to modification of the extracellular matrix and facilitation of injectate distribution, which may be relevant when

epidural tissue changes limit the spread of therapeutic agents.

In a randomized, multicenter pilot study, Rapčan et al. compared mechanical adhesiolysis alone with adhesiolysis combined with corticosteroid and hyaluronidase administration during epiduroscopy and reported improved outcomes with the combination at longer follow-up [30]. Similarly, Budisulistyo et al. reported improvements in pain and functional outcomes after caudal epidural adhesiolysis with 1500 IU hyaluronidase administered before steroid injection [7]. However, these studies differed from the present trial in procedural technique, use of catheter-directed adhesiolysis, patient characteristics, and follow-up duration.

In contrast, Heavner et al. found no significant difference in VAS outcomes among patients receiving hypertonic saline, isotonic saline, or hyaluronidase after mechanical adhesiolysis, although subsequent treatment requirements differed among groups [31]. These mixed findings suggest that the effect of hyaluronidase may depend on the procedural technique, accompanying injectate, patient population, and timing of outcome assessment. Overall, previous studies provide some support for the use of hyaluronidase as an epidural adjunct, but direct evidence for its incremental benefit when added to fluoroscopy-guided caudal ESI without catheter-directed adhesiolysis remains limited.

Differences in procedural technique, injectate composition, patient selection, and outcome measures further limit direct comparison across studies.

Our findings

In the present trial, both treatment groups demonstrated improvement in pain intensity over time, with a greater reduction in NRS scores in the steroid-plus-hyaluronidase group at the 3-month assessment. The between-group difference was 1.60 points (95% CI 0.45–2.75; $P = 0.009$), suggesting a statistically significant and potentially clinically meaningful difference in pain reduction.

A further finding was the greater improvement in walking capacity among participants receiving hyaluronidase. At 3 months, 75% of patients in the steroid-plus-hyaluronidase group achieved a walking distance of at least 300 meters, compared with 30% in the steroid-only group. Because walking capacity was used as an indicator of neurogenic claudication in this study, this finding may indicate a functional benefit associated with the addition of hyaluronidase. However, this outcome has not been consistently assessed in previous studies, limiting direct comparison with the existing literature.

Sleep disturbance is common among patients with persistent pain, and pain intensity and sleep quality may influence one another. In the present study, sleep disturbance improved in both treatment groups, with a greater improvement in the steroid-plus-hyaluronidase group. This pattern occurred alongside the greater reduction in pain intensity observed in that group and may reflect the close relationship between pain burden and sleep quality.

Safety Considerations and Complications

No serious adverse events were observed in either group during the follow-up period. Minor procedure-related complaints, including transient headache and mild injection-site pain, were self-limited and occurred at similar frequencies between groups. No persistent neurological deficit, clinically significant motor weakness, infection, bleeding, or allergic reaction was recorded. These findings do not indicate an increase in clinically important short-term adverse events with the addition of 1500 IU hyaluronidase in this study.

Nevertheless, the relatively small sample size and limited follow-up preclude firm conclusions regarding uncommon or delayed adverse events.

Nevertheless, the sample size and follow-up duration were limited. Therefore, the safety findings should be interpreted cautiously and confirmed in larger studies with longer follow-up periods.

Study Limitations

Several methodological limitations should be considered when interpreting these findings. First, the study did not include a placebo or sham-procedure

control group; therefore, the observed improvements cannot be attributed solely to the pharmacological effect of hyaluronidase. Second, the sample size was modest, which may have limited the statistical power for detecting between-group differences in some secondary outcomes, including lower extremity muscle strength.

Third, the follow-up period was limited to 3 months, and the durability of the observed clinical benefits beyond this period remains uncertain.

Fourth, validated functional disability and quality-of-life instruments, such as the Oswestry Disability Index or SF-36, were not assessed. Fifth, although participants, outcome assessors, and data analysts were blinded to group allocation, blinding of the proceduralist was not feasible because of the procedural nature of the intervention and preparation of the injectate. Finally, the study population included patients with chronic lumbosacral radiculopathy related to lumbar disc protrusion and/or lumbar canal stenosis, which may introduce clinical heterogeneity.

Future multicenter randomized controlled trials with larger sample sizes, longer follow-up periods, validated disability measures, and cost-effectiveness analyses are needed to determine the reproducibility, durability, and broader applicability of these findings and to identify patients most likely to benefit from the addition of hyaluronidase.

Conclusion

In this single-blind randomized clinical trial, adding hyaluronidase to fluoroscopy-guided caudal epidural steroid injection was associated with a greater reduction in pain intensity and improvement in selected functional outcomes compared with steroid injection alone in patients with chronic lumbosacral radiculopathy. The steroid-plus-hyaluronidase group showed greater improvement in NRS scores, neurogenic claudication, and sleep disturbance during the 3-month follow-up period.

These findings support further evaluation of hyaluronidase as an adjunct to caudal epidural steroid injection. Given the modest sample size, absence of a sham-procedure control, and limited follow-up duration, larger multicenter randomized trials with longer follow-up and validated disability measures are needed to establish the magnitude, safety, and durability of the observed effects.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board and Ethics Committee of the Neuroscience Institute, Tehran University of Medical Sciences (approval code: IR.TUMS.NI.REC.1403.010). The trial was registered in the Iranian Registry of Clinical Trials

(IRCT20240310060712N1). All participants provided written informed consent before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Authors' contributions

MN, AK, EE, HM, BE, and RA-Y contributed to the study conception and design. MN, AK, HM, BE, and RA-Y contributed to patient recruitment, intervention, and data collection. EE, HM, BE, and RA-Y contributed to data interpretation. MN and AK drafted the initial manuscript. BE and RA-Y critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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