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Research paper

Preliminary results in comparison of caudal epidural injection of hyaluronidase versus hypertonic saline in managing lumbosacral canal stenosis: A randomized clinical trial

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ABSTRACT

Background: Lumbosacral spinal stenosis (LSS) is one of the most common causes of back pain and disability. Its treatment varies from conservative and medical to surgical treatment, and the indications for its optimal management are not obviously defined. Epidural steroid injection is commonly used for pain relief in LSS. This study aims to compare the adjuvant efficacy of caudal epidural injection (CEI) of hyaluronidase with steroid versus hypertonic saline with steroid in patients with LSS.

Methods: This clinical trial was done in a prospective, randomized, double-blind approach; it was conducted among 30 patients aged between 45 – 75 years who suffered from low back and leg pain in recent 6 months due to LSS. The patients were randomly allocated to two groups. Group A included 15 patients who received fluoroscopically guided CEI containing steroid, local anesthetic, and hyaluronidase, and Group B consisted of 15 patients who received fluoroscopically guided CEI containing steroid, local anesthetic, and hypertonic saline. The outcome measures included the Visual Analog Scale (VAS), Oswestry Disability Index (ODI), and Quebec Back Pain Disability Scale (QBPDS), which were obtained from patients before the CEI as a baseline and after the second, fourth, and eighth weeks.

Results: Before injection, there were no statistically significant differences between the two studied groups, neither in demographic characteristics nor in VAS, ODI, and QBPDS parameters. After injection, the mean of ODI and QBPDS improved from the baseline to the 2^{nd}, 4^{th}, and the 8^{th} weeks in both groups ($p < 0.001$) without any superiority between the two groups ($p > 0.05$). However, there was a significant improvement of the mean VAS score through the second and fourth weeks in Group A ($p = 0.032, 0.050$). VAS score in the eighth week was equal without any superiority in both groups ($p > 0.05$). Additionally, the mean social life status was significantly improved in group A in the 4^{th} and 8^{th} weeks after the intervention.

Conclusions: In short-term follow-up, Caudal epidural injection of hyaluronidase, as well as hypertonic saline, seems to be effective in the management of LSS without any superiority in both materials. However, in the 2^{nd} and 4^{th} weeks after the procedure, better improvement of means VAS score was observed in the hyaluronidase group.

Keywords: hyaluronidase, hypertonic saline, clinical trial, epidural, steroid, lumbar, spinal stenosis

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INTRODUCTION

Lumbosacral spinal stenosis (LSS) is a condition that occurs when the spinal canal becomes compressed and is linked to a wide range of clinical symptoms. Additionally, it is considered a common source of lumbar back pain.[1] The incidence of LSS is reported to be 5 cases per 100,000 people.[2] LSS treatment includes conservative management, such as medications, physical therapies with or without caudal epidural injection (CEI) of steroid, and surgical treatment if decompression of the vertebrae is indicated.[3] These treatments vary in the degree of success based on the severity of symptoms, degree of stenosis, presence or absence of neurological defects, associated illness, and the time of treatment in the progression of the disease.[3] In patients with contraindication for surgery or those not willing to undergo surgery, CEI of steroids could be used for pain management. The main downside of this treatment is the short-term relief of pain.[4]

As the CEI alone showed inconsistent responses with a high possibility of recurrence followed by multiple injections, the pain physicians evaluated other materials as an adjuvant to improve the quality of analgesia.[5–7] Hyaluronidase mitigates the pain and edema and dissolves the bonds between hyaluronic acid and the connective tissues to relieve the fibroplasia in the tissues, so it sweeps the scar tissues and ameliorates the permeability of injection materials.[8]

As chronic inflammation plays a considerable role in inducing back and leg pain related to chronic LSS, CEI of steroids helps to reduce the inflammation, and additional hyaluronidase and/or hypertonic saline increases the efficacy of injections by reducing the adhesions.[9]

Due to the lack of sufficient and conclusive study on several protocols of CEI, significantly different cost of various injections, and variety of culture, lifestyle, and racial characteristics of our population, this research was designed to compare the efficacy of CEI of hyaluronidase with steroid vs. hypertonic saline with steroid in pain relief and improved function in LSS patients.

MATERIAL AND METHODS

Trial design

This clinical trial was conducted in a randomized, double-blind manner which was conducted following the checklist consort in 2018 on patients referred to physical medicine and rehabilitation clinics affiliated to Shiraz University of Medical Sciences. The study protocol was approved by the ethics committee of Shiraz University of Medical Sciences and registered as a clinical trial under registration ID of IRCT20171106037267N2 at the Iranian Registry of Clinical Trial. All patients were informed of the objectives, protocol, risks, and benefits of the study, and they signed informed written consent. Participation in the study was entirely voluntary and they were free to withdraw from the study whenever and for whatever reason with no explanation and they were ensured that it did not affect their care process.

The consort flowchart for selecting patients, distribution, and analysis of data is shown in Figure 1.

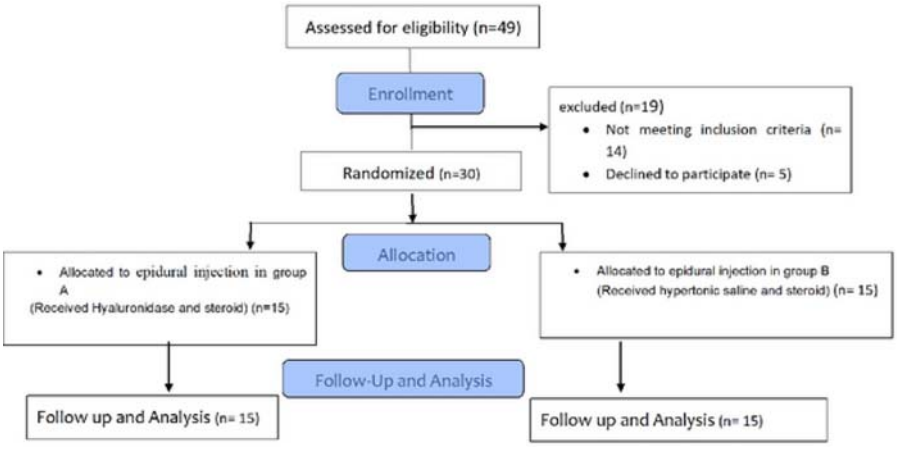

Figure 1. The consort flow diagram of the study.

Inclusion criteria

The inclusion criteria included confirmation of the LSS in patients by Magnetic resonance imaging (MRI) and electrodiagnosis; age between 45 to 75-year-old; suffering from persistent low back pain (LBP); the presence of pain and other clinical symptoms of LSS in the last six months; lack of response to conventional treatments like physiotherapy, exercises, as well as pharmacological therapies; Visual Analog Scale (VAS) pain score $>$ 4; and the patient's consent to participate in this trail.

Exclusion criteria

The exclusion criteria were the patients who had a previous history of all conditions resulting in peripheral neuropathy including diabetes mellitus (DM), collagen vascular disease, Lupus, brucellosis, or nerve injury, and history of knee arthroplasty ipsilateral to leg pain. Also, the pregnant patients; bleeding diathesis; infection at the site of injection; significant hepatic, renal or cardiovascular dysfunction; cancer or lack of communications ability; and the patients who had a history of allergic reaction to medication used in our protocol were excluded.

Procedure

The patients were transferred to the operation room, and they were asked to lie in the prone position, with the abdomen supported by a pillow to reduce the lordosis of the lumbar spine, and the legs placed in slight abduction and inward rotation to pull apart the gluteal fold for better palpation of sacral hiatus. The procedure was done under sterile condition proceeded with proper prophylactic antibiotics (IV Cefazoline 1gram); the patients were under monitoring (O_2 Saturation, blood pressure, and pulse rate) during the whole procedure. Fluoroscopic lateral imaging was used to detect the site of sacral hiatus. After anesthetizing the local skin and subcutaneous tissues with lidocaine 1%, several millimeters of contrast were injected into the sacral hiatus through a 22-gauge spinal needle. If the typical epidurogram view ("smoke up a chimney" in the lateral and "Christmas Tree" in AP view) was observed, the mentioned formulation was slowly administered into the epidural space and if a vascular pattern was seen, the needle was retrieved and rerouted. The patients were discharged when they were stable medically; they were advised to have a follow-up visit in 2 weeks and to call the physician if needed.

Randomization and blinding

In this work, 30 eligible participants were divided into two parallel groups at random. (Hyaluronidase and corticosteroid CEI: group A, and Corticosteroid and hypertonic saline 5% CEI: group B) by the clinic's supervisor, who had been taught using a block randomization listing. The computer-generated the list as a non-stratified list with a block size of six. Also, statisticians, patients, questionnaires, and statistical analyzers were blinded about the distribution.

Study Outcomes

Data on baseline characteristics, such as age, Body mass index (BMI), and sex were gathered. Pain intensity was measured using the Visual Analogue Scale (VAS), in which 0 means no pain and 10 represents maximum pain. The Oswestry Disability Index (ODI) was also used for the evaluation of the patients' disability levels. This questionnaire is divided into ten sections, each covering six statements. The patient chooses the one closest to what describes his limitation. Each section is scored from 0 to 5, with 5 showing maximum disability. The scores are summed up and then this equation can be expressed as a percentage: Total score (50 $\times$ 100).[10,11] The ODI validity has been verified in pain management in multiple studies. The final questionnaire was Quebec back pain disability scale (QBPDS). It is created to measure the degree of functional impairment in patients with back pain. It has 20 items which can be classified into 6 domains of activity impacted by sciatica: bed/rest (objects 1 to 3), sitting/standing (objects 4 to 6), ambulation (objects 7 to 9), movement (objects 10 to 12), bending/stooping (objects 13 to 16), and handling of large/heavy objects (objects 17 to 20). For each item, a 6 point Likert scale (0–5) to indicate the level of difficulty is used, where 0 = "not difficult at all, " 1 = "minimally difficult," 2 = "somewhat difficult," 3 = "fairly difficult," 4 = "very difficult," and 5 = "unable to do".[11] The walking ability and social life status were also compared between the two groups.

Sample size

The sample size was determined using SPSS.22 software based on analogous studies with an alpha error of 0.05, desired power of 90%, the dropout rate of 20%, and standard deviation (SD) of 1.2 based on the patients' demographic characteristics. Therefore, at least 15 patients in each group were required to meet the statistical significance.

Statistical analysis

The descriptive data were evaluated using the mean, SD, frequency, and frequency percent. The analysis of inferential statistics was done using the chi-square test (assessment of correlation of the two categorical data), independent T-Test (comparing mean of a quantitative factor between the two groups), Leven test (analysis of variance equation between the two groups), and the repeated measures ANOVA (RMANOVA) (to determine the trend of regression of pain scores over the time). A P value <0.05 was deemed statistically significant.

RESULTS

The mean age of group A was 57.07 ± 6.39 years and that of Group B was 58.50 ± 8.31 years. There was no statistically significant difference between both groups. Before the CEI, there was no statistically significant difference in demographic parameters, pain intensity (VAS), ODI, or QBPDS scores between the two groups ($p > 0.05$) (Table 1).

After injection, ODI, and QBPDS improved from the basic to the 2nd, 4th, and 8th weeks in both groups ($p < 0.001$) without any superiority between the two groups ($p > 0.05$) (Figures 2 and 3). The difference between the groups was statistically significant concerning the mean VAS score through the second and fourth weeks, which means a significant improvement in Group A, ($p = 0.032, 0.050$). However, the mean VAS score in the eighth week was equal without any superiority in both groups ($p > 0.05$) (Figure 4) and (Table 2).

Table 1. Baseline features of the patients

Variables	Group A (n=15)	Group B (n=15)	p- value
Age (year)[a]	57.07 ± 6.39	58.50 ± 8.31	0.518
Body weight (Kg)[a]	67.00 ± 10.60	67.73 ± 10.32	0.622
Gender (male/female)	2/13	3/12	0.50
VAS Scores (Before CEI)[a]	8.79 ± 1.18	9.44 ± 1.09	0.129
ODI Scores (Before CEI)[a]	35.86 ± 6.35	37.88 ± 8.80	0.474
QBPDS Scores (Before CEI)[a]	61.50 ± 10.24	61.63 ± 18.31	0.981

Notes: P-values of <0.05 were considered significant.
[a]Data was presented as Mean ± SD
Abbreviation: BMI, body mass index; CEI, caudal epidural injection; VAS, Visual Analogue Scale (0-10); QBPDS, Quebec back pain disability scale; ODI, Oswestry Disability Index

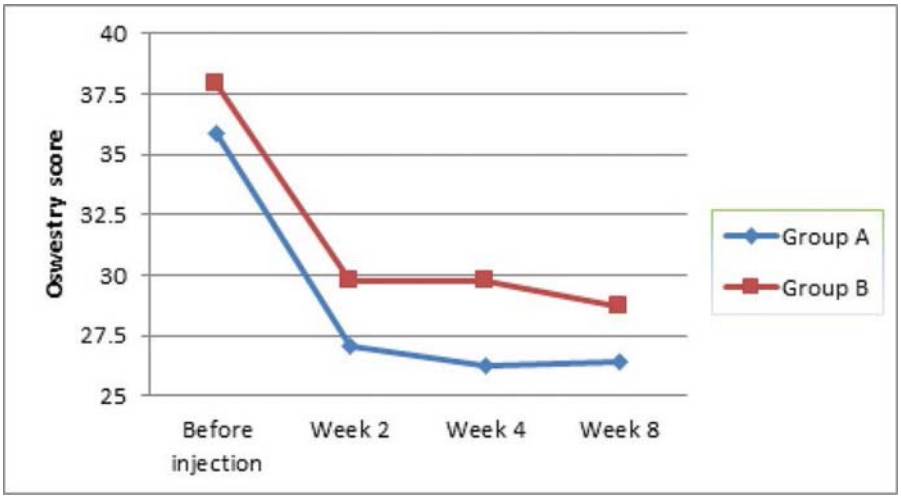

Figure 2. The changing trend in Oswestry Disability Index score in the two groups separately.

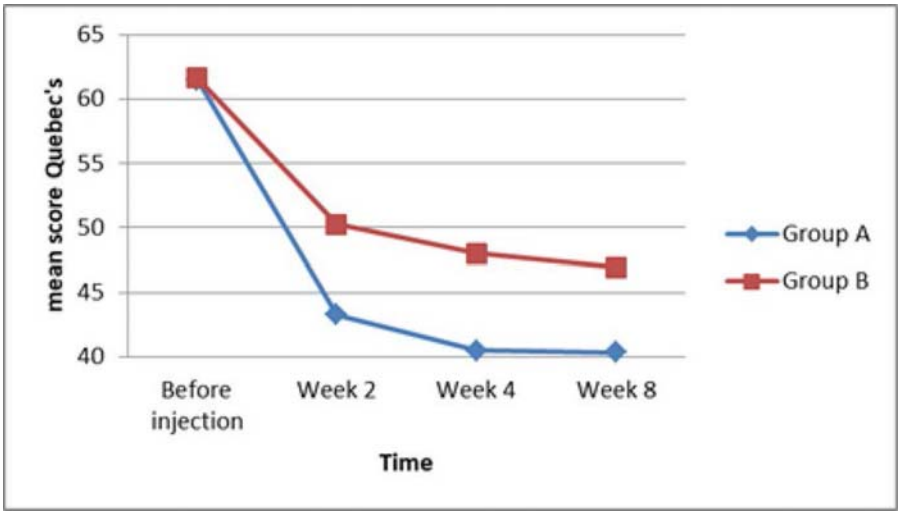

Figure 3. The changing trend in Quebec back pain disability scale score in the two groups separately.

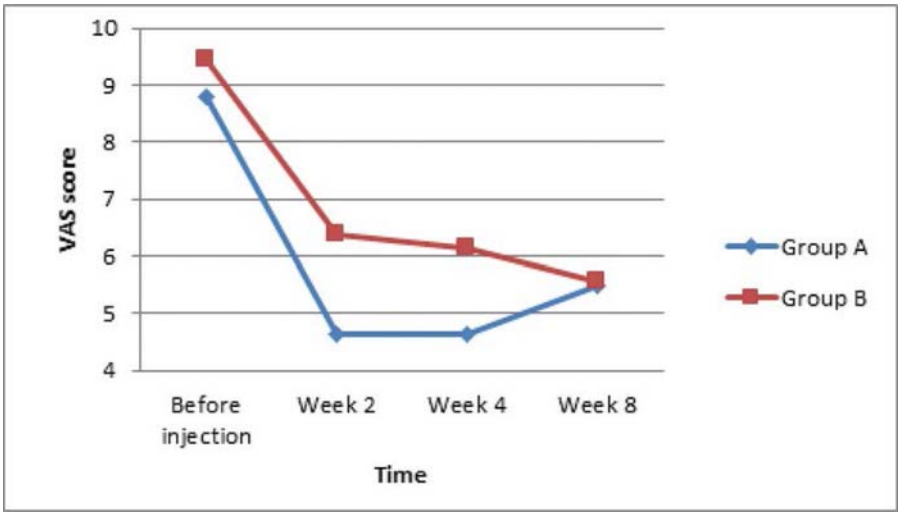

Figure 4. The changing trend in Visual Analog Scale score in the two groups separately.

Table 2. Comparison of VAS, QBPDS, and ODI in both groups

Scale	Time	Group (A)	Group (B)	p-value (Between Groups)
VAS[a]	Baseline	8.79 ± 1.18	9.44 ± 1.09	0.129
	2 Weeks*	4.64 ± 2.17	6.37 ± 2.02	**0.032**
	4thweek*	4.66 ± 2.17	6.13 ± 1.78	**0.050**
	8thweek*	5.50 ± 2.27	5.56 ± 1.67	0.982
ODI[a]	Baseline	35.86 ± 6.35	37.88 ± 8.80	0.474
	2 Weeks*	27.07 ± 5.26	29.75 ± 8.41	0.300
	4thweek*	26.29 ± 7.78	29.75 ± 7.1	0.213
	8thweek*	26.43 ± 6.47	28.69 ± 6.57	0.352
QBPDS[a]	Baseline	61.50 ± 10.24	61.63 ± 18.31	0.981
	2 Weeks*	43.29 ± 16.20	50.25 ± 15.75	0.243
	4thweek*	40.50 ± 16.50	48.06 ± 11.15	0.148
	8thweek*	40.36 ± 18.56	64.94 ± 9.56	0.224

Notes: P-values of <0.05 were considered significant.
[a] Data was presented as Mean ± SD
* After caudal epidural injection
Abbreviations: VAS, Visual Analogue Scale (0-10); QBPDS, Quebec back pain disability scale; ODI, Oswestry Disability Index.

Table 3. The intergroup comparison of walking ability and social life status before versus after treatment in 2, 4 and 8 weeks

Variables		p-value for Group A	p-value for Group B
Walking ability	Before vs. 2 weeks after treatment	**0.048**	**0.005**
	Before vs. 4 weeks after treatment	**0.031**	**0.005**
	Before vs. 8 weeks after treatment	**0.031**	**0.008**
Social life status	Before vs. 2 weeks after treatment	0.328	0.774
	Before vs. 4 weeks after treatment	**0.007**	0.317
	Before vs. 8 weeks after treatment	**0.017**	0.518

Notes: P-values of <0.05 were considered significant.

Walking ability was analyzed separately. According to relevant items evaluated in the ODI questionnaire, a significant improvement was found in all three visits after the CEI intervention without any superiority between the two groups ($p > 0.05$). Social life status was also figured out independently. Against lack of improvement in group B, amelioration of social life was demonstrated in groups A, 4, and 8 weeks after the intervention (Table 3).

DISCUSSION

LSS affects many adults annually and leaves a heavy burden on society. Walking limitations due to neurogenic claudication caused by LSS are considered the hall-mark of disabilities[12]. It is generally believed that mild and moderate symptomatic LSS should be treated with conservative therapy, and for patients with severe symptoms of LSS, surgery is the optimal option.[13]

Based on the literature on managing chronic pain of LSS, a Level II-1 evidence is reported for CEI that is more effective than both transforaminal and interlaminar approaches,[1] with the superiority of transforaminal to CEI after 6 months in the stenosis patients with sciatica and patients with disc herniation for pain management.[14]

A lysing enzyme, hyaluronidase, has supposedly the ability to disrupt the epidural scar tissue and adhesions, thereby facilitating the spread and efficacy of injected corticosteroids. It also reduces fibrosis, which may play a major role in pain related to LSS patients.[15] However, the effectiveness of hypertonic saline was due to the hypertonicity of the solution, instead of any thermal effect, decreased nerve conduction, selective C-fiber blockade in dorsal rootlets, and reduction of the spinal cord water content.[16]

According to a review of the available studies, the use of CEI of hyaluronidase in patients with chronic low back pain remains contentious and generally unconfirmed. Our study compared the effectiveness of CEI of hyaluronidase with steroid versus hypertonic saline with steroid injection in patients with LSS. Significant functional improvement was seen in both groups, and no intergroup statistical difference was observed in ODI and QBPD in the short term after the intervention. Although the VAS score showed more improvements in the hyaluronidase group in the 2^{nd} and 4^{th} weeks, it was comparable in 8 weeks post-treatment.

Thus, the addition of hyaluronidase to steroids rise to less pain and inconvenience in a short time follow-up. Thus, these patients could move to the active rehabilitation phase sooner to accelerate pain control and improve their quality of life. According to the economic expenses of hyaluronidase, it may not be applicable for all, so an individualized approach may be more acceptable.

The pain physicians evaluated different materials as an adjuvant to the epidural steroids to improve the quality of analgesia since the CEI showed inconsistent response with a high possibility of recurrence.[5] Comparing the effectiveness of various types of solutions following mechanical adhesiolysis in a 3-day procedure, by Heavner et al., showed no significant difference among hypertonic sodium chloride, isotonic sodium chloride, and hyaluronidase in terms of VAS although a lower proportion of patients in hypertonic saline and hyaluronidase groups needed additional treatments.[9,17] Devulder et al., demonstrated that administration of a corticosteroid in combination with hyaluronidase and local anesthetic via nerve root sheath injection was unable to provide a positive outcome and pain alleviation with either solution.[18] Although systematic review debated the role of sodium chloride (NaCl) hypertonic mixture with moderate evidence, no evidence for the effectiveness of additional hyaluronidase to percutaneous epidural lysis of adhesions was detected in refractory long-lasting lumbar back pain.[19]

To elaborate on the latter controversy, it can be said that the prolonged pain relief of CEI of steroid, which may continue up to 2 months, may mask the efficacy of CEI hyaluronidase in the same period.[20,21] Also, the patients were followed up for a short period (8 weeks) and this can mask the benefits of hyaluronidase in our study. Additionally, the administration route of our study was different from previous articles (caudal epidural versus nerve root sleeve and interlaminar epidural injection). Thus, it seems that pain control is affected by the administration method. The superiority of our study, when compared with previous studies, is single injection technique instead of 3 separate injections, the injection of lengthy local anesthetic, with the possibility for extended subarachnoid blocking in the event of a mishap, and the administration of a lower overall dose of hyaluronidase, with an accompanying cost reduction, may make it less onerous. It also eliminates the complexity of arranging for three days in a row in an outpatient setting, as well as the typically expensive price of the process in an inpatient setting.

Manchikanti et al., demonstrated the remarkable improvement of persistent sciatica, using adhesiolysis percutaneously alone or with additional hypertonic saline.[16] Additionally, Geurts, et al., showed that steroid and hyaluronidase injection significantly reduced recurrent radicular pain.[22] In the same vein, Yousef and associations showed that the addition of hyaluronidase to hypertonic saline-injected with CEI in patients suffering from unsuccessful back surgery syndrome increased the efficacy as measured by long-term pain reduction and enhanced lumbar spine range of motion.[23] Previous types of research support the results of our study. Additionally, further extensive trials with long-term follow-up are recommended to determine the efficacy of hyaluronidase treatment for LSS.

Comparison of the walking ability according to relevant items in the ODI questionnaire revealed a significant improvement in all the three visits after the intervention that was similar between the two groups. Against lack of improvement in the hypertonic saline group, amelioration of social life status was demonstrated in the hyaluronidase group 4 and 8 weeks after the intervention. Although the exact incidence of complication is controversial, CEI of steroid, hypertonic saline, and hyaluronidase is relatively safe and no serious adverse effect was reported by our patients.[24]

There were some limitations in this article. First, short-term follow-up due to a decline in the patient's compliance may be the most important limitation of this study, and long-term studies for determining the number of subjects in need of surgical interventions despite CEI are recommended. Second, the categorization of patients according to the severity of LSS may qualify the analysis of hyaluronidase and hypertonic saline effects. Thirdly, lifestyle modifications were recommended to all subjects, but regarding the differences in socioeconomic status and environmental factors, it was not possible to control the type and level of activity precisely; this may affect the outcomes. The heterogeneity of change in walking distance, as well as the value and change of VAS with motion, may be biased by selecting different assessment methods when compared to previous trials.

CONCLUSION

In short-term follow-up, Caudal epidural injection of hyaluronidase, as well as hypertonic saline, seems to be effective in the management of LSS without any superiority in both materials. However, the addition of hyaluronidase to steroids may ameliorate the efficacy of CEI in the social life status of LSS patients. This finding needs to be confirmed in large-scale cohort research with long-term follow-up.

Availability of data and materials

All related data are included within the article.

Ethics approval and consent to participate

The patient gave their written informed consent for participation in our study.

Consent for publication

Written informed consent for publication of this manuscript was obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

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Non.

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