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Original Article

Comparative Effectiveness of Caudal Epidural Steroid Injection Versus Mesotherapy of Calcitonin on Pain Reduction and Improving Function in Patients with Lumbosacral Canal Stenosis: A Randomized Control Trial

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ABSTRACT

Background: The use of epidural steroid injection in spinal stenosis pain management has expanded greatly. Calcitonin is also effective in relieving neuropathic pain in spinal canal stenosis through the mechanisms of arterial dilation, anti-inflammation, anti-edema, and rises in beta endorphin levels. The current study was designed to evaluate the effect of mesotherapy with calcitonin compared with epidural steroid injection for pain relief and functional improvement in patients with lumbosacral canal stenosis.

Methods: A total of 39 patients comparable in age and gender with signs and symptoms of lumbosacral canal stenosis participated in this randomized control trial. Group A comprised patients receiving mesotherapy of 100 IU Calcitonin+Marcaine 0.5% (4 mL) in three repeated injections in the lumbosacral area; group B received a single caudal epidural injection of Marcaine 0.5% (4 mL)+80 mg methyl prednisolone (2 mL) under the guide of a fluoroscope. Patients were evaluated before and 4 and 8 weeks after intervention using the visual analog scale (VAS), Oswestry Disability Index (ODI), Quebec back pain disability scale (QBPD), and Ronald-Morris Disability Questionnaire (RMDQ).

Results: Based on the VAS, ODI, QBPD, and RMDQ scales, a significant improvement in pain and functional disability was observed in both groups 4 and 8 weeks after intervention ($P<0.05$), which was comparable between the two groups ($P>0.05$).

Conclusion: Mesotherapy with calcitonin Marcaine is just as effective as caudal epidural steroid injection; considering its advantages, mesotherapy can be a proper alternative method for managing pain and functional impairment in patients with lumbosacral canal stenosis.

Introduction

Low back pain (LBP), with a lifetime prevalence of 84%, is a widespread complaint of patients who refer to musculoskeletal clinics [1]. Lumbar spinal stenosis is among the most prevalent causes of LBP with an annual incidence rate of five cases per 100,000 individuals [2, 3]. Anatomical narrowing of the lumbar spinal canal gives rise to vascular and neural structure compression followed by a plethora of clinical signs and symptoms [4], such as more pain in the legs than the back, restless leg syndrome, neurogenic claudication, weakness, and,

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albeit rarely, cauda equina syndrome [5-9].

The diagnosis of spinal stenosis is based on a combination of history, physical examination, radiologic findings (magnetic resonance imaging), and electrodiagnosis. Spinal stenosis symptoms can be managed either surgically or with non-surgical modalities like lifestyle modification, exercise, physical therapy, hydrotherapy, acupuncture, or pharmacotherapy. Given the expense and risks of surgery in elderly patients, pain physicians have propounded increasing the use of fluoroscopic- and sonographic-guided interventional techniques for managing chronic spinal pain, although meritorious case selection and the true effect of these invasive and non-invasive techniques are controversial [10-12].

The use of epidural steroid injections with three different approaches (caudal, transforaminal, and interlaminar) has advanced in spinal stenosis pain management by reducing inflammatory mediators such as NO2 and TNF-α and diminishing mechanical compression. Caudal epidural injection is the safest and easiest approach with the least risk of inadvertent dural puncture, although it is less specific in targeting the site of pathology [13-17].

Calcitonin is a polypeptide hormone secreted by the thyroid gland that has anti-hyperalgesic effects in addition to calcium homeostasis in vertebrates. There is no evidence of calcitonin receptor expression on normal peripheral nerve tissue or dorsal root ganglion; however, it is effective in relieving neuropathic pain in spinal canal stenosis, although the mechanism remains unclear [14]. Arterial dilation, anti-inflammation, anti-edema, and increased beta endorphin levels are various beneficial effects of calcitonin in lumbar spinal stenosis [8].

Mesotherapy is the intradermal or subcutaneous fat injection of active substances with local therapeutic effects. Slow diffusion, higher local concentration of drug compared with intramuscular administration, longer lasting effects, fewer systemic complications, synergic effects, and systemic therapies are the advantages of this route of administration [18-20]. Mesotherapy gained popularity in cosmetic medicine, but its expanded therapeutic indications have recently attracted the attention of pain physicians for the management of painful musculoskeletal conditions [21].

Though there is little evidence on mesotherapy in lumbosacral spinal stenosis, this study was designed to evaluate the effect of mesotherapy with calcitonin comparing epidural steroid injection for pain relief and functional improvement in patients with lumbosacral canal stenosis.

Methods

Trial Design

This single-blinded, randomized clinical trial was performed in 2018 on lumbosacral canal stenosis (L4, L5, and S1 levels) patients, who were randomly divided into two groups, A and B, using the random block method. The study protocol was registered in the Iranian registry of clinical trials (IRCT) with code number IRCT20171201037696N1 and approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1396.70). The consort flowchart is illustrated in Figure 1.

Participants

Lumbosacral canal stenosis (L4, L5, and S1 levels) patients who sought pain management by referring to the physical medicine and rehabilitation clinics affiliated with Shiraz University of Medical Sciences in 2018 were invited to participate in this study. First, the objectives, protocol, medications, risks, and benefits of the research were explained to all patients, and then participants signed an informed written consent form.

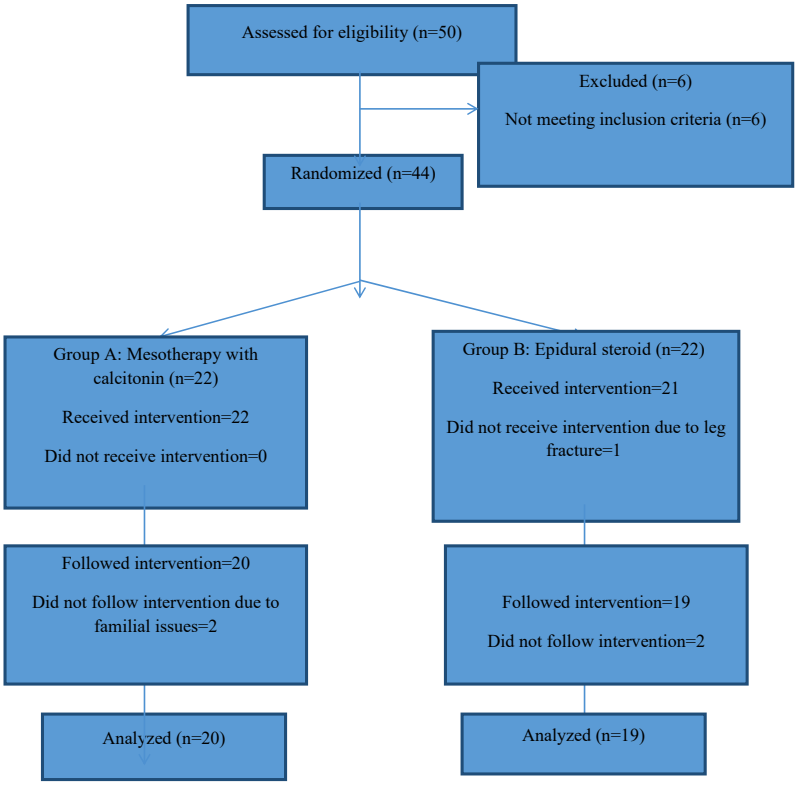

Figure 1: CONSORT flow diagram of the study.

Selection Criteria

The groups consisted of patients who had shown clinical signs and symptoms of lumbosacral canal stenosis (L4, L5, and S1 levels) during the previous month (documented by magnetic resonance imaging and electrodiagnosis). They were aged between 40 and 75 years. Provision of informed consent and the lack of any other disease involving the spinal column were the primary inclusion criteria. Conservative management consisting of lifestyle modification, pharmacotherapy, physical therapy, and exercise was tested prior to the interventional pain management.

The exclusion criteria were having a positive history of allergic reaction to the medication used in the protocol; pregnancy; peripheral neuropathy caused by collagen vascular disease; Lupus; gout; diabetes mellitus (DM); concomitant radiculopathy; trauma; vertebral fracture; spondylolisthesis; brucellosis; nerve injury; bleeding diathesis; infection at the injection site; history of injection in the affected joint in the previous 3 months; significant hepatic, renal, or cardiovascular dysfunction; cancer; or a lack of the ability to communicate.

Intervention

Mesotherapy Group

Group A received 100 IU calcitonin (2 ml)+Marcaine 0.5% (4 mL) in three repeated injections at one-week intervals. After proper skin sterilization, the drug was injected at 6 points including the inter-spinous area and paravertebral level 0.5 cun (half the width of the patient's thumb) lateral to the spinous process, gluteal area, and trigger points through specific needles (27 G) that were inserted at an angle of 30-45 and depth of 4 mm into subcutaneous tissue.

Caudal Epidural Injection Group

The drug regimen administered in group B was a single caudal epidural injection of Marcaine 0.5% (4 mL)+80 mg methylprednisolone (2 mL) under the guide of a fluoroscope. Caudal epidural injection was done in the operation room under sterile conditions and precise monitoring of O2 saturation, blood pressure, and pulse rate. Intravenous prophylactic antibiotic was administered prior to the procedure. Patients were in the prone position with legs apart and inwardly rotated and a pillow under the abdomen. After prep and drape, the sacral hiatus was palpitated, and the local skin and subcutaneous tissue were anesthetized using lidocaine 1%. The sacral hiatus was observed using an AP fluoroscopic image. A spinal needle gauge 18 was inserted into the sacral hiatus. After sensing the loss of resistance by the sacral ligament and needle progression in the hiatus before the level of the S3 vertebrae, several millimeters of contrast were injected into the sacral hiatus, which created a typical epidurogram "Christmas Tree" view. The contrast seemed "smoke up a chimney" in the lateral view. If the contrast injection presented a vascular pattern, the needle was quickly redirected. At the end of the procedure, the skin was cleaned and draped with sterile gauze. The patient was observed and monitored for an hour in the recovery room prior to discharge.

Both groups were trained to do abdominal and paravertebral strengthening and lower extremity stretching exercises, and proper lifestyle modification was explained to them. They were also advised to have follow-up visits 4 and 8 weeks later. Probable complications were also explained to them, and they were advised to call the physician at any necessary time.

Outcomes

The primary outcome measures, including pain and functional ability, were assessed using the visual analog scale (VAS), Oswestry Disability Index (ODI), Quebec back pain disability scale (QBPD), and Ronald Morris Disability Questionnaire (RMDQ). The questionnaire forms were patient-based with the physician involved in completing them during the first visit and 4 and 8 weeks post-intervention.

In the VAS questionnaire, the patients rated their pain severity between zero (no sense of pain) and ten (the most severe pain) at each visit. The trend was evaluated by drawing a curve, and a 50% reduction in VAS score was considered significant.

The Oswestry questionnaire consisted of ten questions on pain severity and effect of pain on activities of daily living (ADL), such as personal tasks, walking, sitting, standing, sleeping, lifting objects, sexual life, social life, and traveling. The scores ranged between zero and fifty (each item received a score from zero to five) which represented the best and the worst condition, respectively.

The Quebec questionnaire consisted of twenty items regarding the effect of pain on ADL. Each item was scored between zero (best ability of activity) and five (no ability of activity).

The Ronald Morris Disability Questionnaire (RMDQ) consisted of twenty-four items on the effect of low back pain on functional ability.

For the test-retest reliability of the Persian version of the Quebec questionnaire (QDS) and The Ronald Morris Disability Questionnaire (RDQ) in patients with low back pain, the Cronbach's alpha was reported to be 0.83 and 0.92, respectively. Both RDQ and QDS have shown excellent test-retest reliability (intraclass correlation coefficient=0.86, and 0.86, respectively) ($P<0.01$). The correlation between the physical functioning scales of the SF-36 and the RDQ and QDS was also reported as -0.62 and -0.69, respectively ($P<0.001$). Regarding pain scores, the correlation between the RDQ and the QDS and visual analog scale were reported as 0.36 and 0.46, respectively ($P<0.001$) [22].

Sample Size

The sample size was determined using the two independent samples formula. The mean difference (d=1.5), S1=1.1, S2=1.7, alpha error=0.05 with a desired power of 90% was used, so a total of 38 cases was estimated. By considering a dropout rate of 15%, the sample size was determined to be 44 (22 patients in each group).

Randomization and Blinding

Participants were randomly divided into groups A and

B using the random block method (group A: mesotherapy with calcitonin; group B: caudal epidural steroid injection).

Using the quadruple random permutation block method and the table of random numbers, a random list was formed with six possible quadruple permutations (AABB, ABAB, ABBA, BAAB, BBAA, and BABA), so that A represented the person receiving mesotherapy with calcitonin, and B represented the person receiving the caudal epidural steroid injection.

This method was based on 11 blocks in 4 permutations and assigning zero to nine (according to the random number table) to each of these permutations (i.e. AABB Code 0, BABA Code 1, AABB Code 2, BBAA Code 3, BAAB Code 4, and ABBA Code 5 to 9), and all 44 patients were assigned to groups A and B. The statistician was blinded to the method of treatment (single-blind study).

Statistical Method

Descriptive data was evaluated by frequency, frequency percentage, mean, and SD. The mean changes in VAS, QBPD, ODI, and RMDQ before and after the intervention were assessed using the chi-square test (assessment of correlation of two categorical data) and the independent t-test (comparison of the means of a quantitative factor between the two groups). The homogeneity of the groups was assessed using the Kolmogorov-Smirnov test, and the trend of quantitative factor changes during the time was evaluated using the Friedman test.

A P value<0.05 was considered statistically significant.

Results

A total of 39 participants, twenty patients in group A (mesotherapy of calcitonin+local anesthetics) and nineteen in group B (epidural steroid+local anesthetics), were enrolled in the study. Statistical tests showed that there was no significant difference in age or gender distribution between the two study groups (P>0.05) (Table 1). Pain scores (VAS) and functional disability (ODI and QBPD) were not statistically different between the two groups (P>0.05).

Following the trend of all mentioned scores revealed a significant improvement in pain and functional disability in both groups 4 and 8 weeks post-intervention (Figures 2, 3, 4, 5), but there was no intergroup statistical difference among the VAS, ODI, QBPD, and RMDQ scales. The VAS score was also decreased 4 weeks post-intervention in both groups, but no statistically significant decline was seen 8 weeks compared to 4 weeks after injection (Table 2).

Discussion

Lumbosacral spinal stenosis is a disabling disorder that mostly affects the elderly over 65 years of age. Pain and walking limitations are the essential troublesome symptoms that limit the activity of daily living, so they should be considered in treatment strategies [3-5].

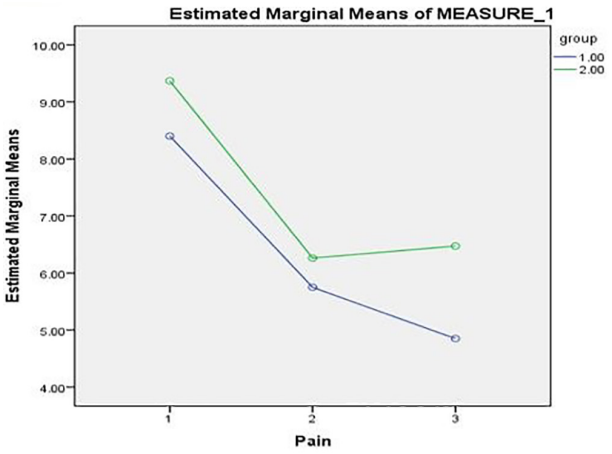

Figure 2: The trend of Visual Analog Scale score among groups A (mesotherapy, blue graph) and B (epidural steroid, green graph) in 8 weeks follow-up.

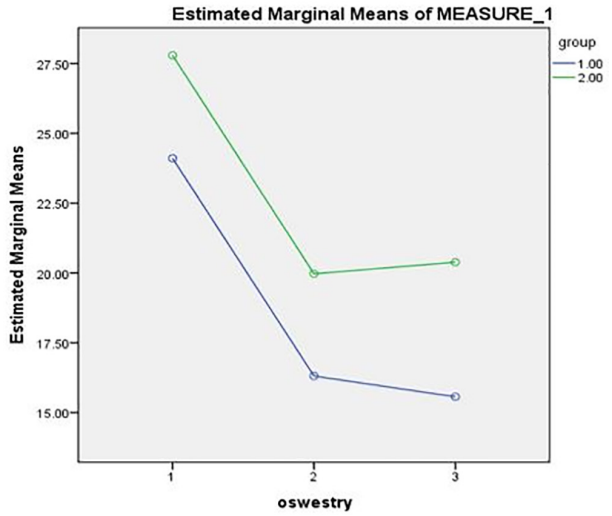

Figure 3: The trend of Oswestry Disability Index (ODI) score between the groups A (mesotherapy, blue graph) and B (epidural steroid, green graph) in 8 weeks follow-up.

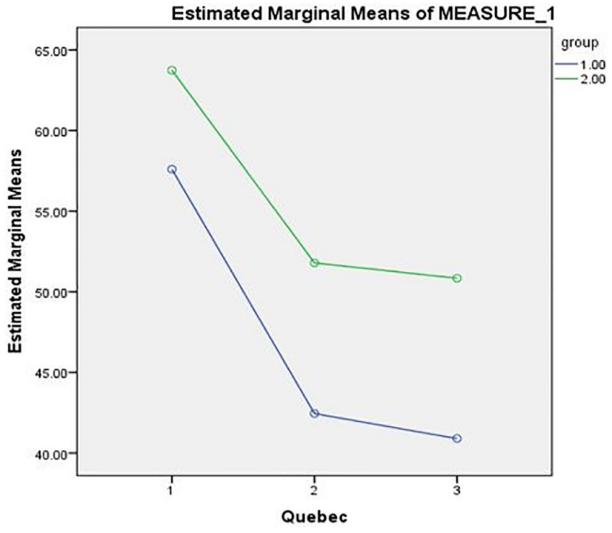

Figure 4: The trend of Quebec back pain disability scale (QBPD) score between groups A (mesotherapy, blue graph) and B (epidural steroid, green graph) in 8 weeks follow-up.

Table 1: Baseline characteristics of patients

	Group A (n=20)	Group B (n=19)	P value
Mean age (years)±SD	57.0±8.4	56.2±6.9	0.486
Sex (male/female)/%	2/18 (10/90%)	5/14(26.3/73.7%)	0.693

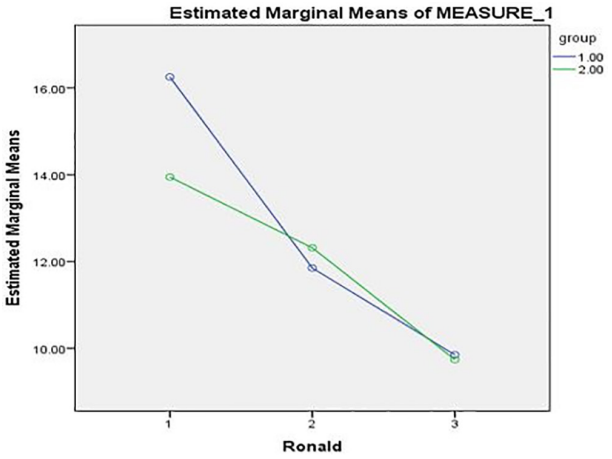

Figure 5: The trend of Ronald-Morris score between the groups A (mesotherapy, blue graph) and B (epidural steroid, green graph) in 8 weeks follow-up.

Controversy exists regarding epidural steroid injection, although a moderate to high level of evidence of short-term and long-term relief of lumbar disc herniation has been reported [13]; some randomized controlled trials have reported the efficacy of epidural steroid injection in improving function and pain among elderly adults with lumbar spinal stenosis [17]. Nonetheless, meta-analysis claimed minimal or no improvement in walking ability or pain in lumbosacral spinal stenosis patients by using various methods of epidural injection [23]. On the other hand, all studies have confirmed the safety of epidural steroid injection. Caudal epidural injection is the safest and easiest approach, with the least risk of inadvertent dural puncture, although it is less specific in targeting the site of pathology [13-17, 23].

Additional effects of epidural calcitonin+steroid compared with steroid alone in spinal stenosis patients regarding walking distance, pain and paresthesia perception, analgesic consumption, and the Oswestry scale suggest calcitonin as a new option for spinal stenosis management [24].

Ashraf et al. reported the beneficial effects of intramuscular injections of calcitonin (50 IU weekly for one month) in severe and very severe low back pain induced by lumbar spinal stenosis [25]. Intranasal calcitonin was also advantageous in spinal stenosis [26], although opposing evidence is also reported [27-29].

The possibility of recurrent symptoms, the inconsistent response to epidural steroid injection alone [28-31], and some evidence on the beneficial effects of calcitonin in spinal stenosis management through arterial dilation, anti-inflammation, anti-edema, and rise in beta endorphin levels [8, 24, 27] have been reported.

Rapid musculoskeletal pain relief was reported with three sessions of mesotherapy, which also resulted in better pain control in combination with transcutaneous electric nerve stimulation, laser and physical therapy, and also induced synergic effect with systemic pharmacotherapy [18].

The current investigation revealed significant pain control and improvement in functioning assessed by ODI and QBPD with three sessions of mesotherapy with calcitonin+Marcaine as well as caudal epidural steroid+Marcaine injection. Acupuncture point mesotherapy has been claimed to be more effective than trigger point mesotherapy, although the true role of the injection site should be further evaluated in future studies [18]. The current study focused on patients' trigger points in the bilateral paravertebral muscles and interspinous area. Patients' discomfort; local reaction such as itching, hypersensitivity, and irritation; and, rarely, subcutaneous infection have been reported by previous research [8, 18-21, 31-33]. The only complication reported in mesotherapy of calcitonin by the current cases, however, was transient nausea; in five patients, pain was well controlled with one to two ondansetron tablets (4 mg).

Although fluoroscopic-guided epidural steroid injections are safe and effective [34, 35], even with one

Table 2: Intergroup and intragroup comparisons of VAS score, ODI and QBPD at baseline and 4 and 8 weeks post-treatment (VAS: visual analog scale, ODI: Oswestry Disability Index, QBPD: Quebec back pain disability scale)

Variables	Group A (n=20)	Group B (n=19)	P value
VAS score (0-10)			
Pre-injection	8.40±0.30	9.16±0.30	0.43
4 weeks after injection	5.75±0.57	6.16±o.58	0.05<
8 weeks after injection	4.85±0.53	6.27±0.55	0.05<
P value before comparing after injection	<0.05	<0.05	
ODI (0-100)			
Pre-injection	24.1±9.6	27.7±8.5	0.13
4 weeks after injection	16.30±1.20	19.90±7.80	0.05<
8 weeks after injection	15.50±11.00	20.30±6.30	0.05<
P value before compared with after injection	<0.05	<0.05	
QBPD (0-100)			
Pre-injection	57.6±19.1	63.7±18.0	0.45
4 weeks after injection	42.40±25.10	51.70±16.00	0.05<
8 weeks after injection	40.90±23.90	50.80±13.10	0.05<
P value before compared with after injection	<0.05	<0.05	
Ronald-Morris low back pain and disability scale			
Pre-injection	16.20±5.58	13.94±5.20	
4 weeks after injection	11.80±5.99	12.30±4.30	0.05<
8 weeks after injection	9.85±3.36	9.70±4.71	0.05<
P value before compared with after injection	<0.05	<0.05	

*VAS: visual analog scale, ODI: Oswestry Disability Index, QBPD: Quebec back pain disability scale

session, the patients and medical team are exposed to X-rays, and an operating room and high level of dexterity are required. Mesotherapy of calcitonin has a similar level of pain relief and functional improvement and can be well performed in an outpatient clinic with no need of an operating room or X-ray exposure, though it requires several sessions. Therefore, mesotherapy can be an alternative method of pain management in patients with lumbosacral spinal stenosis, if a good patient selection has been done.

Generally, all pain interventions are employed to attain the active rehabilitation phase so as to promote the activity of daily living, functional independence, and quality of life. Thus, none of them is the final goal; they are ways to a better rehabilitation program. The short-term follow-up and subjective patient assessment through the course of the study using the questionnaire rather than objective lab marker or radiologic evaluation were the important limitations of this study.

It is recommended that long-term studies with more objective assessment strategies be conducted to compare the efficacy of mesotherapy with calcitonin and epidural steroid injection in patients with lumbosacral canal stenosis.

Conclusion

Mesotherapy with calcitonin+Marcaine is as effective as caudal epidural steroid injection. Thus, considering the advantages, mesotherapy can be a proper alternative method for managing pain and functional impairment in patients with lumbosacral canal stenosis.

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