

## Randomized Trial

# Adjuvant Hyaluronidase to Epidural Steroid Improves the Quality of Analgesia in Failed Back Surgery Syndrome: A Prospective Randomized Clinical Trial

Poupak Rahimzadeh, MD<sup>1</sup>, Vandana Sharma, MBBS<sup>2</sup>, Farnad Imani, MD<sup>1</sup>, Hamid Reza Faiz, MD<sup>1</sup>, Mohammad Reza Ghodratty, MD<sup>1</sup>, Ali Reza Nikzad-Jamnani, MD<sup>1</sup>, and Nader Djalal Nader, MD<sup>2</sup>

From: <sup>1</sup>Iran University of Medical Sciences, Tehran, Iran; <sup>2</sup>University of Buffalo, Buffalo, NY

Address Correspondence:  
Nader Djalal Nader, MD  
Professor  
University of Buffalo  
Dept of Anesthesiology  
VAMC, Rm 202C  
3495 Bailey Ave.  
Buffalo, NY 14215  
E-mail: nnader@buffalo.edu

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**Background:** Management of low back pain after spinal surgeries is one of the most challenging problems in pain medicine. Transforaminal lumbar epidural steroid injection has been used with inconsistent response. Most patients require multiple and frequent injections due to high recurrence of back pain.

**Objective:** To find out whether the addition of hyaluronidase to the epidural injectate affects the quality and duration of analgesia in patients with low back pain secondary to failed back surgery syndrome.

**Study Design:** Prospective randomized trial.

**Methods:** The study was registered in the Government Clinical Trial registry and the protocol was reviewed and approved by the institutional review board. After obtaining an informed consent, 25 patients with low back pain due to failed back syndrome were randomly assigned to receive a transforaminal epidural injection of hyaluronidase 1500 IU (HYL) or normal saline (NSL) to a mixture of bupivacaine 0.5% (1 mL) and triamcinolone 40mg (1 mL) in a double-blind fashion. An interventional pain specialist using fluoroscopic guidance performed all epidural injections. The patients received a comprehensive neurological examination by a non-interventional pain specialist who was blinded to the treatment during their follow-up visits, scheduled one, 2, and 4 weeks after the intervention. Numerical pain scores, analgesic requirement, and satisfaction scores were recorded during every visit.

**Results:** There was no difference in demographic data between the 2 groups. Pain scores and total analgesic requirement were significantly lower in the HYL group at 2 and 4 weeks after blockade ( $P < 0.01$ ). Patient satisfaction was higher in the HYL group.

**Limitations:** The study was limited by a relatively small sample size.

**Conclusion:** We conclude that adding hyaluronidase to the epidural injectate was effective in the management of chronic low back pain in patients with failed back surgery syndrome demonstrated over a period of 4 weeks.

**Key words:** Low back pain, lumbar epidural injection, steroid, hyaluronidase, bupivacaine

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**C**hronic low back pain is the second most common cause for seeing a physician in the United States and it alone is responsible for total or partial disability of at least 7 million Americans (1,2).

The lifetime prevalence of low back pain is estimated between 40% and 60% (3). The estimated direct and indirect cost of treatment for back pain exceeds \$50 billion in addition to 93 million lost workdays per year

(4). Annually, between 300,000 and 400,000 surgeries are performed for chronic low back pain; however, the success rate for this treatment modality is only 50% to 60% (5). Despite advances in surgical technology, the rates of failure for back surgery have not declined over past 2 decades. Failed back surgery syndrome (FBSS) is a chronic pain condition that has considerable impact on the patient and health care system (6). This condition may cause many social, occupational, and individual problems, so finding an effective, rapid, and less complicated method for pain control and treatment has been always desired.

Lumbar epidural injection of long-acting steroids is commonly used by interventional pain specialists to alleviate low back pain. The duration of analgesia varies among patients with FBSS and ranges from 15 days up to 180 days. Although there is not a consensus on the effect of steroids in reducing pain after epidural injection, the anti-inflammatory effects are the probable mechanism where the levels of tissue phospholipase and prostaglandins are decreased by steroids. In addition to anatomical impingement of the nerve roots by herniation and degeneration of the intervertebral discs, spinal canal stenosis, and spondylolisthesis, damage caused by inflammation of the surrounding tissues and swelling of the nerve roots may result in radiculopathy and related pain symptoms. Glucocorticoids are the most common medications administered epidurally for chronic low back pain due to their prolonged pain relieving effects (7).

Following surgical manipulation of the spine and surrounding tissues, significant changes occur in the epidural space that may attenuate pharmacological response to epidural steroids. Fibrosis and adhesion of the soft tissue generate multiple septations and eliminate the normal continuity of the epidural space. This continuity is required for homogenous spread of the medications injected into the epidural space. Hypertonic saline (10%) with or without fibrinolytic enzymes such as hyaluronidase have been clinically used to lyse the adhesion during percutaneous epidural neuroplasty to decrease the local tissue edema and improve the pain (8). The effects of adding hyaluronidase during epiduroscopy and during transforaminal epidural steroid injection were independently examined by Geurts et al (7) and Devulder et al (9) which showed inconsistent results with the addition of hyaluronidase.

In addition to the effectiveness of hyaluronidase, there is much controversy about the concentration and total dose of the enzyme with transforaminal epidural injection especially in patients with FBSS. The main

objective of this study was to compare the quality of pain relief and functional state in response to the addition of hyaluronidase in patients with FBSS who were treated with transforaminal lumbar epidural injection of steroids. We hypothesized that the patient who received hyaluronidase would have less pain, require lesser amount of analgesics, and have a more active lifestyle compared to those who did not.

## **METHODS**

The experimental design and protocol of the clinical trial were reviewed and approved by the Medical Research Ethics Committee at Tehran University of Medical Sciences. Additionally, the study was registered in the Iranian registry for clinical trials (IRCT201108137313N1). The study design was a double-blinded randomized control trial.

### **Inclusion and Exclusion Criteria**

FBSS is defined as persistent (at least 6 month) pain and or disability following laminectomy with or without sensory-motor neurological deficits or any form of urinary or bowel incontinence. Patients between the ages of 20 to 75 years old suffering from persistent (> 6 months) back pain following laminectomy for spinal canal stenosis and/or discectomy for herniated nucleus pulposus documented by magnetic resonance imaging (MRI) were included for screening and enrollment. Patients were excluded if they suffered from sacroiliac joint disease, facet joint arthritis, severe cardiopulmonary disease, uncontrolled diabetes, morbid obesity, addiction, infection, and coagulation disorders that prohibited lumbar epidural injections. None of the patients was on opioid medications for pain management before or during the study period.

### **Experimental Design**

A total of 33 patients with FBSS who were referred to the Tehran University outpatient pain clinic were screened, and 25 patients who were scheduled for elective transforaminal lumbar epidural steroid injection (TFESI) were enrolled in the study. After obtaining an informed consent, using robust (pseudo-) random number generation software, the patients were randomly assigned to receive one of the following formulations in the epidural spaces:

1. Bupivacaine 5 mg (1 mL) + Triamcinolone 40 mg (1 mL) + Saline solution 10% (2 mL) + Hyaluronidase 1,500 IU reconstituted in 1 mL distilled water (HYL)

2. Bupivacaine 5 mg (1 mL) + Triamcinolone 40 mg (1 mL) + Saline solution 10% (2 mL) + 1 mL distilled water (NSL)

Study drugs were compounded and prepared by a research pharmacist and the interventional pain physician who performed the procedure was blinded to the composition of the drug that was injected.

### **Patient Preparation and Technical Description**

The level and cause of neural compression and radiculopathy after surgery (disc herniation or spinal canal stenosis) were recorded. After transferring patients to the interventional pain procedure room, mild sedation was achieved using intravenous administration of midazolam 2 mg and fentanyl 100 mcg. Patients were placed in a prone position and the back was prepped with chlorhexidine 3% and local anesthesia was achieved by epidermal and subcutaneous administration of 3 mL Lidocaine 1% injectate. Under fluoroscopic guidance, a blunt Coude 22G (Epimed) needle was passed through an introducer and was advanced into the epidural space via a transforaminal approach. The position of the needle was confirmed by injecting 3 – 5 mL of contrast media Visipaque™ (iodixanol) and examining its epidural spread on antero-posterior and lateral views of fluoroscopy. The interventional pain specialist, who was blinded to the nature of the injectate, then injected the study drug into the epidural space. The patients were then transferred to the Peri-Anesthesia Care Unit (PACU) for monitoring vital signs, pain levels, and possible neurological adverse events for 60 – 90 minutes. They were then discharged home in care of a responsible adult and advised not to drive for 24 hours. The pain intensity was evaluated by visual analogue scale (VAS) scores.

### **Assessment and Treatment of Post-epidural Pain**

VAS pain scores from 0 = no pain to 10 as maximum pain were used to assess the intensity of low back pain and the numerical rating was recorded both without moving (static) and on movement (dynamic). In patients with pain scores more than 3, celecoxib 100 mg oral capsule was prescribed. The above criteria and the total daily dose of celecoxib were assessed as follows: 1 = no need for drugs, 2 = less than 200 mg/day, 3 = equal to or more than 200 mg/day. More than 50% reduction in pain scores was considered as significant clinical response to epidural injection.

### **Follow-up Visits and Pain Assessment**

Patients were advised to contact the treating pain physicians during administrative hours or the emergency medical care services in case of any adverse reaction or uncontrollable pain. All patients were reassessed for the location, intensity, and the nature of low back pain (whether the nature of back pain changed in comparison to the pre-procedure pain) one, 2, and 4 weeks after surgery. Focused neurologic examination (toe and heel walking; 2-point discrimination test; vibration test; sensation of touch, heat, and pressure; straight leg raising test (SLR); and deep tendon reflexes) (see Appendix I) was performed in addition to full documentation of static and dynamic pain using VAS scores during each follow-up visit and the results were recorded in a MS Excel-based data-sheet. Patients were asked to answer a single question satisfaction questionnaire regarding the quality of pain control (using Likert Scale) as follows: 1 = Extremely dissatisfied, 2 = Dissatisfied, 3 = Neutral, 4 = Satisfied, and 5 = Extremely satisfied.

### **Data Management and Statistical Analyses**

All data variables were entered in an MS Excel database and exported to SPSS 11.5 version (Chicago, IL) for statistical analyses. Numerical rating of the static low back pain was the primary endpoint for the study. A 50% decrease in pain scores was considered a clinically significant response to epidural injection. At least 2 point difference in VAS score between the groups was considered clinically significant. Assuming an alpha error of 0.05 and a beta error of 0.20, the power calculation was found to be 80% and therefore at least 10 patients in each group were required to detect statistical significance. Categorical data (the incidence of any adverse event) were analyzed using chi square test with Yate correction. Since pain and satisfaction scores did not follow a normal distribution, a non-parametric Mann-Whitney U test was used to examine continuous variables and data were presented as median (interquartile range). ANOVA repeated measures were used to assess the progress or regression of pain scores at various time points. A multivariate regression model including the cause of radiculopathy, type of surgery, type of treatment, and age was constructed to identify the factors that may have contributed to a favorable outcome. The null hypotheses were rejected when *P* values were < 0.05.

## RESULTS

Twenty-five patients ranging between 39 to 56 years old with low back pain due to FBSS were enrolled in this study (12 patients were in the HYL and 13 patients in the NSL group). The demographic distribution of the patients was similar in both groups. Similarly, there was no difference in the etiology, character, motion dependency, intensity, and duration of pain between the 2 groups. In 23 out of 25 patients (92%), SLR at an angle of between 30 and 70 degrees elevation induced severe pain (Table 1).

All patients in both groups, regardless of the etiology, demonstrated early complete pain relief (within 15 minutes) following TFESI. In fact, the reported numerical pain scores were 0 in 92% of the patients. Early local

anesthetic effect faded within 12 hours of TFESI as the anti-inflammatory mechanism became more of a player. Repeated measure analysis of the VAS pain scores over 4 time points demonstrated significantly longer lasting analgesia in the HYL group than NSL group,  $P < 0.001$  (Table 2). Additionally, the total amount of ingested oral anti-inflammatory medication use was significantly less in the HYL group when compared to the NSL group,  $P < 0.001$ . This increase in celecoxib intake occurred 10 days after epidural injection. More patients in the HYL group were satisfied with the level of pain control when compared to the NSL controls.

The nerve root originating between the fourth and fifth lumbar vertebrae was affected in 12 out of 25 patients (48%) which were followed by L3-L4 in 8 patients (32%) and L5-S1 in 6 patients (20%). There was no difference in the quality of pain relief and response to TFESI based on the involvement of any nerve roots. The cause of low back pain was due to a herniated disc in 15 patients while the remaining 10 patients suffered chronic low back pain because of spinal canal stenosis. The results of TFESI were more favorable in patients who presented with herniated disc rather than spinal stenosis,  $P < 0.01$  (Fig. 1).

Univariate analyses were performed to identify the association of pre-injection conditions with a favorable response to TFESI. Hyaluronidase addition, the cause of FBSS, age of 50 or higher, and the subacute versus chronic duration of low back pain were selected to build a multivariate logistic regression. The results of this analysis are depicted in Table 3. In summary,

Table 1. Demographic distribution and baseline pain characteristics.

	HYL (N = 12)	NSL (N = 13)	P Value
Age (year)	45.9 ± 3.0	48.0 ± 2.3	0.30
Gender (Female/Male)	5/7	6/7	0.23
Body Weight (Kg)	69 ± 13	72 ± 12	0.15
Duration of Pain (month)	7.1 ± 3.0	8.0 ± 3.2	0.23
Herniated Discopathy	8 (67%)	7 (57%)	0.21
Spinal Stenosis	4 (33%)	6 (43%)	0.21
Motion-related component	4 (33%)	4 (31%)	0.12
Positive SLR*	11 (91.7%)	12 (92.3%)	0.20
Pre-ESI VAS Pain scores	3.1 ± 2.0	3.4 ± 1.5	0.10

\* Pain induced by straight ipsilateral leg raising between 30 to 70 degrees; ESI=Epidural Steroid Injection

Table 2. Four-week follow-up responses to transforaminal epidural steroid injections and patient satisfaction.

	Groups	Day-0 TFESI	Week-1 s/p TFESI	Week-2 s/p TFESI	Week-4 s/p TFESI	P Values
VAS Pain Scores [Median (IQR)]	HYL	0 (0 - 0)	1 (0 - 2)	1 (0 - 3)	1.5 (1 - 4)	0.02
	NSL	0 (0 - 1)	1 (0 - 2)	1.5 (1 - 3)	2.5 (2 - 5)	
Number of Patients with > 50% decrease in NRS	HYL	12	11	11	10	0.01
	NSL	13	10	7	6	
Patients Satisfaction Score	HYL	4.9 ± 0.2	4.4 ± 0.3	4.2 ± 0.2	4.2 ± 0.2	0.001
	NSL	4.4 ± 0.5	4 ± 0.5	3.5 ± 0.5	3.4 ± 0.1	
Celecoxib Intake (mg/week)	HYL	700 ± 30	720 ± 70	750 ± 140	780 ± 140	0.01
	NSL	720 ± 40	950 ± 180	1,350 ± 160	1,420 ± 250	
Number of Patients on High Dose Celecoxib	HYL	0	1	1	1	0.04
	NSL	0	1	2	3	
Number of Patients with negative SLR	HYL	12 (100%)	10 (87.8%)	9 (80.1%)	9 (80.1%)	0.01
	NSL	12 (93.3%)	8 (67%)	7 (53.8%)	6 (47.2%)	

TFESI: Transforaminal Epidural Steroid Injection; SLR = Straight Leg Raising between 30 to 70 degrees; NRS: Numerical Rating of Pain Score

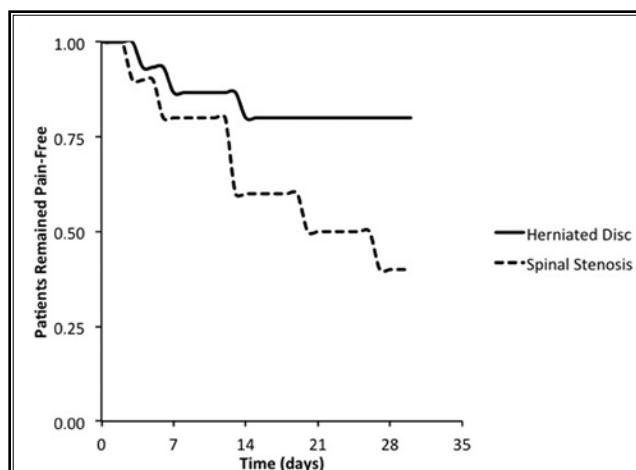


Fig. 1. Kaplan Meier curve depicting the fraction of the patients remaining pain-free over a follow-up period of 4 weeks. The most favorable results were seen among the patients who were treated for herniated disc ( $P < 0.001$ ).

the addition of hyaluronidase to the epidural steroid injection was the only independent factor which was associated with a favorable response, odds ratio = 0.12 (0.08 – 0.87),  $P = 0.04$ . There was a trend among the patients with herniated disc to have a favorable response to TFESI, odds ratio = 0.65 (0.54 – 1.20),  $P = 0.06$  despite of the fact these patients had significantly better responses than those with spinal stenosis in univariate analysis (Fig. 1). There was no difference with regards to the quality of pain control between patients 50 years or older and those younger than 50 years old, and between the patients who presented with subacute symptoms compared to those who presented with more chronic symptoms.

None of the patients in either group experienced any adverse event related to transforaminal injection of epidural steroid during one month follow-up period. They were specifically monitored for development of inadvertent subarachnoid injection, prolonged sensory-motor block, long-term weakness of the limbs, epidural hematoma, infection, bladder dysfunction, and arachnoiditis for 30 days following TFESI.

## DISCUSSION

Our study was an endeavor to analyze the effects of pharmacologic intervention alone using hyaluronidase in alleviating the back pain specifically associated with FBSS and has shown promising results over a short period of time. We studied the effects of the addition of hyaluronidase to epidural steroid injections in the

Table 3. Multivariate logistic regression analysis of factors associated with a favorable response to TFESI.

	OR	95% Confidence Interval	P Value
HYL/NSL	0.12	0.08 – 0.87	0.04*
Herniated Disc vs. Spinal Stenosis	0.65	0.54 – 1.2	0.06
Age $\leq$ 50 yr vs. age $>$ 50 yr old	1.23	0.75 – 3.78	0.65
Chronic vs. Subacute symptoms	2.12	0.89 – 6.67	0.52

“difficult to treat” back pain population, measured by the quality of pain relief and improvement in functional state. We demonstrated that adding hyaluronidase to the injection compound increased the effectiveness of transforaminal epidural steroids in alleviating the intensity of the pain, prolonging the duration of analgesia, and decreasing the total dose of non-steroidal anti-inflammatory drugs used to treat chronic low back pain over a 4 week period after failed back surgery.

The proteoglycan structure of cartilage tissue plays an important role in maintaining the consistency of intervertebral discs. The degenerative changes of the annulus fibrosus secondary to shearing forces results in protrusion of nucleus pulposus into the spinal canal with secondary impingement of the related nerve roots (10). These changes are associated local inflammatory responses that enhance the stress over the nerve roots and exacerbation of the sciatica symptoms. Local release of inflammatory mediators within the disc and surrounding epidural space is further promoted by surgical trauma such as laminectomy and development of posterior spinal instability (3,11).

The main explanation for this observation is the fact that following back surgery and periods of inflammatory processes involving the epidural space, fibroblastic activity increases as a part of repair mechanism (12). The chemical irritation and inflammatory reaction induced by leakage of the nucleus pulposus into the epidural space produces a significant degree of fibrosis and adhesion which contribute to low back pain and sciatica symptoms (13). Scar formation and local fibrosis of the dura matter following surgical manipulation of the epidural space during discectomy or laminectomy add to the underlying inflammatory process and exacerbate low back pain following back surgery (13). Low back pain caused by epidural fibrosis does not respond well to surgical decompression and some patients even report higher levels of pain following this intervention (8,14).

It is prudent that most of sciatica symptoms favorably respond to anti-inflammatory treatment measures. Although the systemic administration of non-steroidal anti-inflammatory drugs (NSAID) along with physical therapy alleviates a large component of low back pain, a local injection of corticosteroids in the vicinity of inflamed nerve roots reduces regional swelling and decreases the mechanical stress caused by herniated disc(s). The role of corticosteroids in the reduction of inflammation and tissue edema is already well known.

Pain control in FBSS remains a challenge and very few studies have been performed to show the efficacy of epidural steroids and hyaluronidase in the treatment of back pain. As described, adhesions and scar tissue play a major role in the evolution and pathophysiology of pain in FBSS. Mechanical lysis of adhesions using percutaneous epiduroscopy has been studied and has shown promising results in patients with back pain associated with and without failed back syndrome or spinal stenosis (15-17). In the post lumbar surgery patients, Manchikanti et al (18) showed that percutaneous adhesiolysis was effective in 73% of patients over a 12 months period. On the other hand, Heavner et al (19) showed that percutaneous lysis of adhesions in itself improves the pain intensity with effects lasting as long as one year, but did not show any improvement in pain scores when hyaluronidase was added to the epidural solution (20).

Hyaluronidase is a lysing enzyme, which supposedly has the ability to disrupt the epidural scar tissue and adhesions thereby facilitating the spread and efficacy of injected corticosteroids. It also reduces fibrosis, which plays a major role in pain related to FBSS (20). There are very few trials that have studied the effects of hyaluronidase in the epidural space during epiduroscopy (7), nerve root sleeve injections (9), and caudal injections (21). In each of these studies the addition of hyaluronidase improved pain relief. The anti-inflammatory effect of corticosteroids complements the effects of hyaluronidase in epidural neuroplasty (22). The results of the addition of hyaluronidase to the epidural space injectate in back pain have shown controversial results so far and mostly unproven. In addition, the effectiveness of hyaluronidase in producing pain relief in FBSS and spinal stenosis is largely unknown.

In a study by Geurts et al (7), they reported that mechanical lysis of adhesions with epiduroscope and targeted injection of steroid and hyaluronidase showed significant reduction in chronic radicular pain. In another study by Devulder et al (9), nerve root sleeve injection

of corticosteroid, local anesthetic, and hyaluronidase failed to show a good outcome and pain relief with any of the solutions. Heavner et al (19) compared the use of epidural saline plus hyaluronidase to saline alone and did not show a significant difference in the clinical outcome. A recent prospective trial showed that the addition of hyaluronidase to caudal steroid and hypertonic saline in patients with FBSS improves short-term pain control (21). The role of hypertonic saline is also of importance. Significant research and trials were done by Racz and colleagues showing the use of hypertonic saline in the epidural space for neurolytic purposes due to its osmotic action and anti-edema effects, hence reducing local pressure on the nerve roots(23).

In our double-blinded, randomized control trial, we used a transforaminal approach to lumbar epidural steroid injections. This is a more specific approach to the nerve root lesions compared to interlaminar epidural approach, especially in patients with radiculopathy associated with either herniated disc disease or spinal stenosis alone. Unlike the interlaminar method, the main volume of injected medication is spread in the anterior epidural space where the herniated discs are most affected (20). Therefore, the transforaminal approach is the preferred technique for injection of fibrolytic agents because of the needle's proximity to the target site providing higher concentrations of the hyaluronidase in the scarred area (21-22).

Based on the review of the existing literature, the use of epidural hyaluronidase in back pain still remains controversial and mostly unproven. We studied the effects of the addition of hyaluronidase to epidural steroid injections in the "difficult to treat" back pain population, measured by the quality of pain relief and improvement in functional state. We classified our study population based on the etiology and included only a subset of FBSS patients who had either herniated disc disease or spinal stenosis. In an attempt to reduce the confounding effects of other agents that may have an association with relief of pain, we tried to minimize the agents used to steroids and hyaluronidase alone. We performed univariate and multivariate logistic regression to identify the association of other factors which could have led to a favorable response and found that addition of hyaluronidase is an independent factor implicated in pain relief. Even though no significant association could be established between patients with herniated disc disease having a favorable response compared to spinal stenosis, there is a definitive trend. One possible explanation for this difference

could be that radiculopathy secondary to herniated disc involves inflammation and chemical irritation of nerve roots from the contents of the disc in addition to mechanical compression which responds to corticosteroids better in comparison to spinal stenosis where mechanical compression alone is involved.

One of the major limitations of the study was that, even though the patients had a better pain control and satisfaction level in the hyaluronidase group, the follow-up was limited to 4 weeks only, and therefore, whether there was a significant difference in pain relief over a long term is unknown. The number of patients enrolled was low. A higher number definitely would have increased the power of study and helped

to extrapolate the results to the general population to a better degree, but per the statistical analysis, this number was sufficient to minimize the alpha and beta errors.

### **CONCLUSION**

As pointed out, our study definitely strengthens the concept that addition of hyaluronidase has a positive impact on minimizing the pain scores, improving the quality of the analgesia and patient satisfaction, and decreasing analgesic requirements after epidural steroid injections, but in the future bigger randomized controlled trials are warranted to further verify this finding.

## **APPENDIX I**

### **Definitions of the pain evaluation tests used**

1. Straight leg raising test: With the patient lying down on his or her back on an examination table or exam floor, the examiner lifted the patient's leg while the knee was kept straight; if the patient experienced reproduction of back pain when the straight leg was at an angle of between 30 and 70 degrees, then the test was considered positive.
2. Toe and heel walking test: Ability of the patients to walk on their toes and then on the heels was tested separately to check for the plantar flexion and dorsiflexion of the feet respectively. The results were recorded as positive or negative.
3. Two point discrimination tests: The examiner alternated between touching the patient with one sharp point or with 2 sharp points on one of the toes and then repeated on the other toe. The patient was then asked to report back what s/he felt (one or 2 points). The smallest distance between 2 points at which the patient could still distinguish as 2 separate stimuli and not one, was recorded. The cut off used for normal discrimination was 30 mm.
4. Deep Tendon Reflexes: Checked using a reflex hammer and graded as follows:  
0: absent reflex  
1+: trace, or seen only with reinforcement  
2+: normal  
3+: brisk

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