Randomized Trial

Effect of Adding Calcitonin to Translaminar Epidural Steroid in Degenerative Lumbar Spinal Canal Stenosis

Nabil Ali Elsheikh, MD, and Yasser M. Amr, MD

From: Departments of Anesthesiology and Surgical Intensive Care, Faculty of Medicine, Tanta University, Egypt

Address Correspondence:
Yasser M. Amr
Tanta University Hospital
Anesthesia Department
Tanta University
Tanta 31257-Egypt
E-mail:
yasser.amr@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 06-19-2015
Revised manuscript received: 08-27-2015, 09-22-2015
Accepted for publication: 10-13-2015

Free full manuscript:
www.painphysicianjournal.com

Background: Spinal canal stenosis is one of the most common causes of low back pain and disability. Its management varies from surgical to conservative, and the indications for ideal management are not clearly defined.

Objectives: This study was conducted to evaluate the effect of adding calcitonin to local anesthetic and corticosteroid in epidural injection for patients suffering from degenerative lumbar spinal canal stenosis.

Study Design: Randomized double-blind clinical trial.

Setting: Hospital outpatient setting.

Methods: One hundred thirty-two patients with degenerative spinal canal stenosis were randomly allocated into 2 groups. Group I received C-arm guided epidural injection of local anesthetic and corticosteroid and Group II received 50 international unit calcitonin added to the mixture of local anesthetic and corticosteroid. Both groups received 2 sets of injections, one week apart. Visual analogue scale for pain during movement and walking distance until incidence of neurogenic claudication have been used for pain assessment, and Oswestry Low Back Pain Disability Questionnaire and analgesic consumption were evaluated for one year.

Results: Both groups showed comparable benefits regarding improvement in pain intensity, walking distance, Oswestry scale, and analgesic consumption during the first month follow-up period. These beneficial effects continued in calcitonin group for one year.

Limitations: The present study patients would be graded as having mild or at worst moderate stenosis. So, the present study did not examine the efficacy of epidural calcitonin in severe spinal canal stenosis and did not stratify the results according to degree of stenosis which would also have been useful in determining the validity of calcitonin in different degrees of stenosis.

Conclusion: Adding calcitonin to epidural steroid and local anesthetic injection seems to be more effective than epidural steroid and local anesthesia alone in management of spinal canal stenosis regarding increased walking distance, better Oswestry scale, diminished pain intensity and perception of paresthesia, and less analgesic consumption, all the above mentioned benefits continued up to one year. So, epidural calcitonin may be considered as a new therapeutic modality in the management of pain in spinal canal stenosis.

Key words: Calcitonin, epidural steroid, lumbar, spinal canal stenosis

Pain Physician 2016; 19:139-146

Lumbar spinal canal stenosis is the narrowing or stricture of the spinal canal, with possible subsequent nerve impingement (1). The canal components that contribute to its narrowing include facet joint hypertrophy, ligamentum flavum thickening, bone spurs, and multilevel disc bulge or protrusion (2).

Lumbar spinal canal stenosis is one of the most

common causes of spine pain and disability. The difficulty in diagnosis lies in the absence of clinical symptoms at rest, with pain and limitation of mobility described under physical strain (3,4).

Even though many studies demonstrated that surgery has better long-term results, a large number of people improved with nonsurgical intervention. Moreover, surgery is associated with high rates of complications relative to nonsurgical intervention (5). Epidural steroid injection has been increasingly employed for pain management in such patients who refuse surgery or for whom surgery was contraindicated. The main pitfalls of this procedure are patients' short-term relief of pain (6).

Porter and Hibbert (7) described the use of subcutaneous calcitonin for treatment of lumbar spinal stenosis in 1983. Since then, calcitonin administration either through subcutaneous (8,9), muscular (10), or nasal (11,12) routes has had conflicting results in spinal stenosis patients.

To date no clinical trial has been done to evaluate the validity of epidural calcitonin in such cases. This study was conducted to evaluate the effect of adding calcitonin to local anesthetic and corticosteroid in epidural injection for patients suffering from degenerative lumbar spinal canal stenosis.

Methods

The study was conducted from January 2013 to December 2014 in the pain relief unit at a university teaching hospital. After approval from the local institutional ethical committee, written informed consent was obtained from the patients.

Inclusion criteria was patients over 40 years old with a history of chronic low back pain with or without lower extremity pain ≥ 6 on a visual analog scale (VAS) of 0 – 10; pain for at least 3 months; with a diagnosis of central spinal stenosis with or without radicular pain (confirmed by computed tomography [CT] revealed anterior-posterior diameter < 12 mm at the level of the lumbar vertebrae). All patients failed to improve with conservative management, including physical therapy, exercises, and pharmacotherapy.

The following were the exclusion criteria: INR > 1.5; platelet count < 50,000; infection at the site of needle entry; congenital spinal canal stenosis; degenerative spondylolithesis, psychiatric disorders affecting co-operation of the patient, a history of spine surgery, previous chronic opioid use, peripheral vascular disease, uncontrolled medical illness (diabetes and/or hypertension), and patients with a history of adverse reaction to either local anesthetics, steroids, or calcitonin.

An intravenous catheter (20 G) was inserted in a peripheral line for crystalloid infusion and sedation. Patients were given intravenous midazolam 0.05 mg/kg before the procedure. Basic monitoring with noninvasive arterial blood pressure, electrocardiogram, and pulse oximetry were applied before the procedure. The patients were randomly assigned into 2 groups.

Group I, called the steroid group, received 2 sets of epidural injections one week apart, each injection contained 40 mg methylprednisolone (Depomedrol) with 8 mL lidocaine 0.5% under c-arm at the site of stenosis. Group II, called the calcitonin group, received 2 sets of epidural injections one week apart composed of 40 mg methylprednisolone (Depomedrol) added to 8 mL of 0.5% lidocaine plus 50 international units (IU) of calcitonin.

The patient was put in a prone position with a pillow under the pelvis to flatten the lumbosacral curve. The lumbosacral area was sterilized with bovine iodine and draped. The procedure was performed under fluoroscopy and the injectate was put at the level of maximum stenosis. The epidural needle pathway was anesthetized with 3 mL lidocaine 1%. Under anteroposterior view, an 18 gauge epidural needle was introduced. The epidural space was identified by the loss of resistance technique for saline and confirmed radiologically by the characteristic longitudinal spread of dye (2 mL of Omipaque 300 mg/mL) in the epidural space.

Study Team

The observer was a senior resident blinded to the randomization who performed all patient assessments and dosages of post procedure analgesics; the interventionist was a pain physician who performed the blocks and was blinded to group assignment or materials used. The randomization was performed using sealed envelopes indicating the group of the assignment at the time of the first visit to the pain clinic by a chief nurse, who read the number contained in the envelope and determined group assignments, but did not participate in patients' follow-up.

Measurements

The assessment times were pre-enrollment and second week, first, second, fourth, sixth, eighth, tenth, and twelfth month and the following were recorded:

1. Pain on movement was evaluated by VAS 0 – 10 (where 0 means no pain and 10 means the worst

possible pain).

2. Perception of paresthesia was evaluated as 0 – normal (no paresthesia), mild (1 – 3 points), moderate (4 – 7 points), severe (8 – 10 points) based on a patient's expression on VAS graded from 0 (no paresthesia) to 10 (maximum intolerable paresthesia) (13).
3. The Oswestry Low Back Pain Disability Questionnaire (ODI) was used for assessment before injection and at one 2, 4, 6, 8, 10, and 12 months after injection. This questionnaire is divided into 10 sections; each section contains 6 statements. The patient marks the one which most accurately describes his limitation. Each section is scored on a 0 – 5 scale, with 5 representing the greatest disability. The scores are added together and then interpreted as a percentage from this equation: Total score/50 × 100. The ODI has been utilized in multiple pain management studies with its validity established (14,15).
4. Walking distance using self-reported walking ability. We asked the patient to walk on level ground at their own pace, until forced to stop due to pain of neurogenic claudication.
5. Consumption of analgesics post procedure (oral acetaminophen was available as per request with a maximum daily dose of 4 g) and collected as a total amount and divided by the follow-up period to determine the daily request at each assessment value.

Statistical Analysis

For this study, the sample size calculation was based on detection of a 2 point difference after intervention for the outcome pain intensity, as measured by VAS (estimated standard deviation of 4). For achieving a 2-sided 5% significance level and a power of 80%, a sample size of 63 patients was necessary. To avoid potential errors and patients' loss during follow-up, 70 patients were included in the study.

Comparison of parameters was made using the Student t-test and Chi-square test when appropriate. Significance was considered if $P < 0.05$.

Results

The study population consisted of 140 patients, classified into 2 groups, 70 patients in each group. Three patients from (Group I) and 5 patients from (Group II) were missed during follow-up (Fig. 1). Both groups were comparable regarding age, gender, site

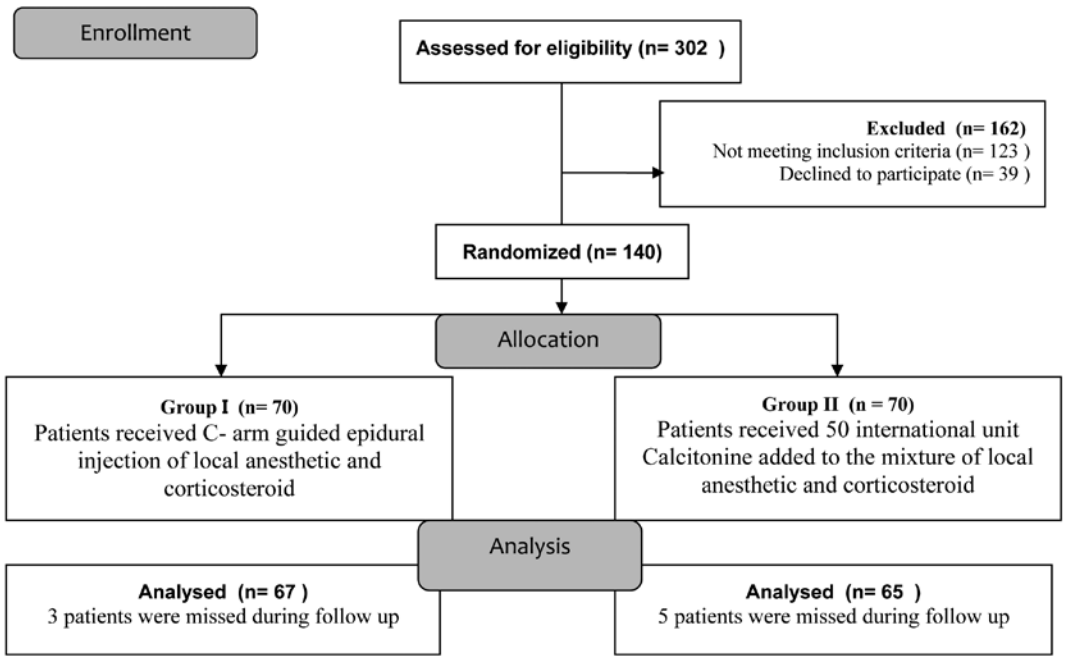

Fig. 1. *Flow diagram of patient progress through the phases of the randomized trial.*

Table 1. *Patient characteristics in both groups.*

	Group I N= 67	Group II N=65	*P*
Age (Years)	58 ± 15	56 ± 18	0.5
Male / Female	46/21	40/25	0.74
Duration of pain (days)	230 ± 37	219 ± 56	0.18
Site of pain			
Back pain > leg pain	15	10	0.4
Leg pain mainly	25	31	
Both back and leg pain	27	24	
Number of levels affected			
One level	3	1	0.3
Two levels	30	34	
Three levels	29	21	
Three levels<	5	9	
Severity of stenosis as classified by spinal canal AP diameter			
mm AP diameter ≥ 11.6 < 12 mm	32	21	0.07
mm AP diameter ≥ 11.2< 11.6 mm	30	32	
mm AP diameter ≥ 10.8< 11.2 mm	5	12	

AP = anterior-posterior

of pain, and duration of pain (Table 1). Although, the investigators did not determine a lower limit for canal anterior-posterior diameter for inclusion in the present study, the lowest diameter for spinal canal included in the present study was 10.8 mm and all the patients with different diameters in between (< 12 mm and ≥ 10.8) were comparably distributed among groups (*P* value 0.07). Also the number of levels affected were comparable in both groups (*P* value 0.3), Table 1.

Epidural injections were successfully performed in all patients. Most common symptoms were pseudoclaudication and standing discomfort (94%), followed by numbness in 63% of patients and weakness in 43% of cases. Discomfort was in both buttocks and thigh in 93% of patients and only below the knee in 7% of patients (these symptoms were comparably distributed among both groups).

Pain score was comparable in both groups at the initial assessment visit (7.3 ± 3.2 versus 7.5 ± 3.6 in both groups, respectively, *P* = 0.74) (Table 2). There was a significant decrease in VAS in Group II when compared with Group I from the second month onward after enrollment (*P* values were < 0.05). Pain scores were comparable in both groups at the second week and first month (*P* values were 0.19, 0.09, respectively).

Regarding comparison within groups; after the block in Group I VAS decreased significantly in comparison to baseline during the second week, first month, and second month (*P* values < 0.0001) and then it was comparable to the pre-enrollment values after that (*P* > 0.05). Meanwhile, in Group II pain intensity decreased significantly during the follow-up period in comparison to the pre study values (*P* values < 0.05) (Table 2).

Regarding walking distance, there was a dramatic improvement after injection in both groups at the second week and first month. This improvement in walking ability continued to be statistically significant in calcitonin group, Table 3.

The Oswestry scale was comparable in both groups at pre-injection and the first month (*P* values were > 0.05). The Oswestry scale decreased significantly in Group II versus Group I from the second month onwards (*P* values were < 0 .05), Table 4.

Severe paresthesia was reported in both groups at pre-procedure assessment. Then it improved to a moderate degree at the the second week and first month post procedure assessment. However paresthesia was reported severe in patients of Group I from the second month onward. It was reported as mild in the other group from the second month onward.

Analgesic consumption was comparable in both groups at 2 and 4 weeks after injection (*P* > 0.05). It was significantly less in Group II from the second month onward (*P* < 0.0001), Table 5.

Table 2. *Pain scores before and after block during follow-up period for both groups expressed as mean ± SD.*

Time	Group I N = 67	Group II N = 65	*P*	*P*1	*P*2
Before Block	7.3 ± 3.2	7.5 ± 3.6	0.74		
2 weeks	3.3 ± 2.4	2.8 ± 1.9	0.19	< 0.0001*	< 0.0001*
One month	3.5 ± 3.1	2.7 ± 2.1	0.09	< 0.0001*	< 0.0001*
2 months	4.6 ± 4.1	2.9 ± 1.8	0.003*	< 0.0001*	< 0.0001*
4 months	6.7 ± 2.9	4.1 ± 3.3	< 0.0001*	> 0.05	< 0.0001*
6 months	7.4 ± 5.2	4.2 ± 2.6	< 0.0001*		< 0.0001*
8 months	7.2 ± 4.5	4.5 ± 3.7	< 0.0001*		<0.0001*
10 months	7.5 ± 4.8	4.6 ± 2.9	<0.0001*		<0.0001*
12 months	7.6 ± 5.3	5.1 ± 3.9	0.003*		0.0004*

* Significant difference. *P* = comparison between groups. *P*1= comparison within group I to the pre-enrollment values. *P*2= comparison within group II to the pre-enrollment values.

Table 3. *Walking distance (in meters) before and after block during follow-up period for both groups expressed as mean ± SD.*

Time	Group I N = 67	Group II N = 65	*P*
Before Block	130.6 ± 63.6	128.5 ± 65.6	0.85
2 weeks	253.3 ± 112.4	266.8 ± 121.9	0.51
One month	263.5 ± 94.1	282.7 ± 132.8	0.34
2 months	164.6 ± 74.9	302.5 ± 171.5	< 0.0001*
4 months	166.7 ± 62.5	350.4 ± 233.5	< 0.0001*
6 months	156.4 ± 65.6	344.8 ± 270.4	< 0.0001*
8 months	127.2 ± 74.3	370.7 ± 266.5	< 0.0001*
10 months	135.5 ± 54.5	344.4 ± 176.6	< 0.0001*
12 months	137.6 ± 65.4	284.4 ± 185.4	< 0.0001*

Table 4. *The Oswestry score before and after block during follow-up period for both groups expressed as mean and range.*

Time	Group I N = 67	Group II N = 65	*P*
Before Block	75 (66 – 85)	72 (62 – 84)	0.7
One month	15 (10 – 18)	17 (9 – 19)	0.6
2 months	31 (24 – 35)	14 (9 – 17)	< 0.0001*
4 months	34 (25 – 39)	17 (12 – 22)	< 0.0001*
6 months	40 (32 – 46)	16 (12 – 23)	< 0.0001*
8 months	49 (35 – 55)	21 (16 – 26)	< 0.0001*
10 months	56 (45 – 62)	33 (22 – 48)	< 0.0001*
12 months	64 (57 – 72)	42 (36 – 50)	< 0.0001*

* Significant difference in group II versus group I

There were no reported side effects in the steroid group. However, nausea was reported in 12 patients in the calcitonin group, persistent vomiting lasting up to 48 hours occurred in 3 patients in the same group. Also, diuresis for 24 hours was noticed in 16 patients in the calcitonin group.

Discussion

Spinal canal stenosis is acknowledged as a major health problem, although it is not a life-threatening disease. It has the potential to seriously affect the quality of life of patients. The main aim of the nonsurgical treatment modalities is to control pain and improve quality of life in cases with spinal stenosis.

Amongst the patients who have had spinal stenosis, there are multiple factors deemed to affect the se-

Table 5. *Analgesic consumption (mg/day) before and after block during follow-up period for both groups expressed as mean ± SD.*

Time	Group I N = 67	Group II N = 65	*P*
2 weeks	772.8 ± 232.5	750.5 ± 222.7	0.57
One month	775.5 ± 354.5	771.4 ± 240.5	0.9
2 months	2967.5 ± 964.4	756.6 ± 288.5	< 0.0001*
4 months	3203.7 ± 892.6	735.4 ± 215.4	< 0.0001*
6 months	3982.5 ± 455.4	842.8 ± 222.3	< 0.0001*
8 months	3977.2 ± 664.5	943.5 ± 327.5	< 0.0001*
10 months	3935.5 ± 654.5	838.6 ± 267.6	< 0.0001*
12 months	3937.6 ± 65.4	942.4 ± 28.7	< 0.0001*

verity of patients' symptoms, varying between vascular factors including venous engorgement during ambulation thus intrathecal pressure rise which causes neuroischemia and neurogenic claudication (16). Arterial insufficiency is another proposed theory for incidence of claudication by defective dilation of radicular arterioles during ambulation which may limit nutrition to the spinal nerve root (17,18). Furthermore, mechanical compression of a nerve root may launch a subsequent inflammatory cascade including cytokines, nitric oxide, lactate, phospholipase A2, and immune cells, which in the end causes radiculopathy. This may be a cause for acute flares of symptoms in chronically stenotic patients (19,20).

Comparison of both arms showed improvement of pain VAS at the initial 2-months assessment. This initial improvement in VAS was sustained in subsequent visits for one year in calcitonin group. While improvement of quality of life and walking distance was noticed in the first month of assessment in the steroid group, it was sustained in subsequent visits in the calcitonin group. Moreover, in the steroid group the amount of analgesics tripled during the follow-up period, whereas in the calcitonin group the analgesic consumption did not go up at all which may be attributed to improved walking distance and Oswestry scale in the calcitonin group during the follow-up period which limited the use of analgesics.

It is reasonable to assume that local anesthetics act through sympathetic blockade and vasodilatation, thereby increasing blood supply to compromised neural tissues (21), and inhibit neural sensitization and neurotransmitters release (22,23). However, prolonged pain relief for 2 months that extends beyond the local anesthetic effect in the steroid group is presumed to result from a reduction of inflammatory edema (24) and decrease of sensitization at the dorsal horn by steroids (25,26).

Some studies emphasize a longer benefit from epidural steroid injection, when combined with physiotherapy (27) or given several times by a transforaminal approach (28). Meanwhile, many studies (29,30) had demonstrated pain relief effectiveness in a modest proportion of patients after repeated caudal epidural injection.

Such behavior in the steroid group did not match previously published data (21), which demonstrated no beneficial effect of steroid over local anesthetic in symptom relief of spinal canal stenosis. This could be attributed to the inclusion of patients with severe spinal canal stenosis who complained of claudication at less than 20 meter. Moreover, the frustrating results might be attributed to the high benchmark of the authors as success was defined as improvement ≥ 75% in another study (31).

The exact mechanism of calcitonin is not well described, but the rationale of its use relies on its direct analgesic effect through release of B-endorphine (32), it decreases bone vascular supply by lowering its metabolic activity, and consequently improves blood supply to the compromised neural tissues (33). Moreover, it improves venous congestion and ischemia that occur in spinal stenosis and consequently diminishes the myelin loss in addition to assisting in re-myelinization (34) which may explain the significant improvement of paresthesia in the calcitonin group in the present study.

Transient diuresis for 24 hours was the most common adverse event in the calcitonin group, occurring in approximately 25% of the procedures performed. Nausea was reported in 12 patients. Three patients suffered from persistent vomiting lasting up to 48 hours. They had a good response to antiemetic. Some consideration must be given regarding these side effects. They should be thoroughly evaluated in further studies to delineate safety of epidural calcitonin. No adverse events were reported among patients treated in the steroid group.

Although the investigators did not determine a lower limit for canal anterior-posterior diameter for inclusion in the present study, the lowest diameter for spinal canal included in the present study was 10.8 mm and all the patients with different diameters in between (< 12 mm and ≥ 10.8 mm) and by some radiologists' criteria (35), the present study patients would be graded as having mild or at worst moderate stenosis. So, the present study did not examine the efficacy of epidural calcitonin in severe spinal canal stenosis and did not stratify the results according to degree of stenosis which would also have been useful in determining the validity of calcitonin in different degrees of stenosis.

The present study concluded that adding calcitonin to epidural steroid and local anesthetic injection seems to be more effective than epidural steroid and local anesthesia alone in management of spinal canal stenosis regarding increased walking distance, better Oswestry scale, diminished pain intensity and perception of paresthesia, and less analgesic consumption, all the above mentioned benefits continued for up to one year. So, epidural calcitonin may be considered as a new therapeutic modality in management of pain in spinal canal stenosis. Continuing to look into the effect

of calcitonin epidural injection in more advanced cases of spinal stenosis is essential to see if the benefit the authors detected in the current cohorts of mild cases remains true.

References

1. Johnsson KE, Rosen I, Uden A. The natural course of lumbar spinal stenosis. *Clin Orthop Relat Res* 1992; 279:82-86.
2. Genevay S, Atlas SJ. Lumbar fspinal stenosis. *Best Pract Res Clin Rheumatol* 2010; 24:253-255.
3. Katz JN, Dalgas M, Stucki G, Lipson SJ. Diagnosis of lumbar spinal stenosis. *Rheum Dis Clin North Am* 1994; 20:471-483.
4. Barz T, Melloh M, Staub L, Roeder C, Lange J, Smiszek FG, Theis JC, Merk HR. The diagnostic value of a treadmill test in predicting lumbar spinal stenosis. *Eur Spine J* 2008; 17:686-690.
5. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Blood E, Hanscom B, Herkowitz H, Cammisa F, Albert T, Boden SD, Hilibrand A, Goldberg H, Berven S, An H; SPORT Investigators. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *N Engl J Med* 2008; 358:794-810.
6. Friedly JL, Comstock BA, Turner JA, Heagerty PJ, Deyo RA, Sullivan SD, Bauer Z, Bresnahan BW, Avins AL, Nedeljkovic SS, Nerenz DR, Standaert C, Kessler L, Akuthota V, Annaswamy T, Chen A, Diehn F, Firtch W, Gerges FJ, Gilligan C, Goldberg H, Kennedy DJ, Mandel S, Tyburski M, Sanders W, Sibell D, Smuck M, Wasan A, Won L, Jarvik JG. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014; 371:11-21.
7. Porter RW, Hibbert C. Calcitonin treatment for neurogenic claudication. *Spine* 1983; 8:585-592.
8. Eskola A, Pohjolainen T, Alaranta H, Soini J, Tallroth K, Slatis P. Calcitonin treatment in lumbar spinal stenosis: A randomized, placebo-controlled, double-blind, cross-over study with one-year follow-up. *Calcif Tissue Int* 1992; 50:400-403.
9. Onel D, Sari H, Donmez C. Lumbar spinal stenosis: clinical/radiologic therapeutic evaluation in 145 patients. Conservative treatment or surgical intervention? *Spine* 1993; 18:291-298.
10. Ashraf A, Khodadadi M, Sadraei A, Naseri M, Nasseri A. The efficacy of intramuscular calcitonin injection in the management of lumbar spinal stenosis. *Asian Spine J* 2015; 9:75-82.
11. Podichetty VK, Segal AM, Lieber M, Mazanec DJ. Effectiveness of salmon calcitonin nasal spray in the treatment of lumbar canal stenosis: A double-blind, randomized, placebo-controlled, parallel group trial. *Spine* 2004; 29:2343-2349.
12. Tafazal SI, Ng L, Sell P. Randomised placebo-controlled trial on the effectiveness of nasal salmon calcitonin in the treatment of lumbar spinal stenosis. *Eur Spine J* 2007; 16:207-212.
13. Sihoe AD, Lee TW, Wan IY, Thung KH, Yim AP. The use of gabapentin for postoperative and post-traumatic pain in thoracic surgery patients. *Eur J Cardiothorac Surg* 2006; 29:795-799.
14. Childs JD, Piva SR. Psychometric properties of the functional rating index in patients with low back pain. *Eur Spine J* 2007; 14:1008-1012.
15. Fritz JM, Irrgang JJ. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. *Phys Ther* 2001; 81:776-788.
16. Harrast MA. Epidural steroid injections for lumbar spinal stenosis. *Curr Rev Musculoskelet Med* 2008; 1:32-38.
17. Crock HV. The applied anatomy of spinal circulation in spinal stenosis. In: McNeill TW (ed). Lumbar Spinal Stenosis. Mosby, St. Louis, 1992.
18. Ooi Y, MIta F, Satoh Y. Myeloscopic study on lumbar spinal canal stenosis with special reference to intermittent claudication. *Spine* 1990; 15:544-549.
19. Akuthota V, Lento P, Sowa G. Pathogenesis of lumbar spinal stenosis pain: Why does an asymptomatic stenotic patient flare? *Phys Med Rehabil Clin N Am* 2003; 14:17-28.
20. Goupille P, Jayson MI, Valat JP, Freemont AJ. The role of inflammation in disk herniation-associated radiculopathy. *Semin Arthritis Rheum* 1998; 28:60-71.
21. Fukusaki M, Kobayashi I, Hara T, Sumikawa K. Symptoms of spinal stenosis do not improve after epidural steroid injection. *Clin J Pain* 1998; 14:148-151.
22. Katz WA, Rothenberg R. The nature of pain: Pathophysiology. *J Clin Rheumatol* 2005; 11:S11-S15.
23. Melzack R, Coderre TJ, Katz J, Vaccarino AL. Central neuroplasticity and pathological pain. *Ann N Y Acad Sci* 2001; 933:157-174.
24. Winnie AP, Hartman JT, Myers HL Jr, Ramamurthy S, Baragan V. Pain clinic. II. Intradural and extradural corticosteroids for sciatica. *Anesth Analg* 1972; 51:990-1003.
25. Coderre TJ. Contribution of protein kinase C to central sensitization and persistent pain following tissue injury. *Neurosci Lett* 1992; 140:181-184.
26. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. *Acta Anaesthesiol Scand* 1990; 34:335-338.
27. Koc Z, Ozcakir S, Sivrioglu K, Gurbet A, Kucukoglu S. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine* 2009; 34:985-989.
28. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Sanelli JT, Freeman ED, Slaten WK, Rao S. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: an outcome study. *Am J Phys Med Rehabil* 2002; 81:898-905.
29. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. *Pain Physician* 2012; 15:371-384.
30. Hoogmartens M, Morelle P. Epidural injection in the treatment of spinal stenosis. *Acta Orthop Belg* 1987; 53:409-411.
31. Cuckler JM, Bernini PA, Wiesel SW, Booth RE Jr, Rothman RH, Pickens

GT. The use of epidural steroids in the treatment of lumbar radicular pain. A prospective, randomized, double-blind study. *J Bone Joint Surg Am* 1985; 67:63-66.

32. Fraioli F, Fabbri A, Gnessi L, Moretti C, Santoro C, Felici M. Subarachnoid injection of salmon calcitonin induces analgesia in man. *Eur J Pharmacol* 1982; 78:381-382.
33. Delamarter RB, Bohlman HH, Dodge LD, Biro C. Experimental lumbar spinal stenosis. Analysis of the cortical evoked potentials, microvasculature and histopathology. *J Bone Joint Surg Am* 1990; 72:110-120.
34. Burnaz Ö, ÖzgÖnenel L, Karacan I. The efficacy of calcitonin treatment in patients with lumbar spinal stenosis. *Istanbul Tıp Dergisi* 2007; 4: 521-526.
35. Steurer J, Roner S, Gnannt R, Hodler J; on behalf of the LumbSten Research Collaboration, Zurich, Switzerland. Quantitative radiologic criteria for the diagnosis of lumbar spinal stenosis: A systematic literature review. *BMC Musculoskeletal Disorders* 2011; 12:175.