Effects of Calcitonin Addition on Epidural Injection in Patients with Degenerative Spinal Canal Stenosis: A Randomised Double Blind Clinical Trial

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Abstract

Objective: Back pain is reported to be the fifth most common reason for referral a patient to a Physician and the most common disability in modern society. The present study aimed to evaluate the effects of calcitonin addition on epidural injection in patients with degenerative spinal canal stenosis in comparison with epidural triamcinolone injection.

Methods: This clinical trial study was performed on 40 patients with degenerative spinal stenosis, referred to pain clinic of Rasoul Akram Hospital in 2018, who were randomly divided into two groups, intervention and control groups, including 20 individuals in each group. In the intervention group, 50 units of calcitonin were injected with 8 cc of ropivacaine 0.2%, whilst 80 mg of triamcinolone with 8 cc of ropivacaine 0.2% was injected in the control group. Functional disability was evaluated based on the Oswestry Disability Index and pain ratings were assessed using the Visual Analogue Scale.

Results: Pain at 4 and 8 weeks after the procedure was significantly different between the two groups. A significant difference in the patient disability index was observed between the two groups at 8 and 12 weeks after the procedure. On the other hand, the rate of analgesic consumption at 4, 8, and 12 weeks after the procedure was significantly decreased in the calcitonin group (P < .001).

Conclusions: Based on our results, injection of calcitonin into the epidural space can reduce the pain of the patients and their analgesic consumption compared to the group receiving steroids through the epidural space.

Keywords: Spinal canal stenosis, epidural injection, calcitonin, low back pain

Introduction

Back pain is the fifth most common cause of referral to a physician and the most common disability in modern society, leading to a decline in the efficiency and disability of patients as well as their need for care services.1,2 The lifetime prevalence of low back pain is estimated to be 39-70%.1 The origin of back pain can be due to spinal structures (intervertebral discs, vertebral bodies, facet joints, nerve roots, and spinal canal tissues such as ligaments and muscles) or adjacent structures (abdominal or pelvic organs). Spinal canal stenosis is one of the causes of spinal nerve involvement through sensory roots involvement.3 It is referred to a narrowing of the canal space to a degree that causes pressure on the spinal cord or nerve roots. The stenosis can occur at the central canal of the spinal cord, lateral recess, or intervertebral holes that are the place where the Cauda equine nerves pass through (gums). Spinal canal stenosis is a clinical syndrome that often affects patients in fifth and sixth decades of their life.3 The diameter of 10-13 mm is considered as relative stenosis since the diameter of the canal in the noted area is 13 mm. Symptoms appear in about 20-25% of people over the age of 40, who have significant stenosis only when the nerve...
elements are under pressure. Decrease in the height of the intervertebral disc in these patients results in increased mechanical pressure on the facet joints, which is one of the causes of low back pain in such patients.\(^5\)

Low back pain in these patients is a type of radicular disorder with clinical manifestations of neurogenic claudication and spreading pain. It may radiate to the hips and thighs. Pain is exacerbated by standing and walking, and it is alleviated by bending or sitting in 83-93% of patients. It is often accompanied by numbness, heaviness, or weakness in the lower extremities.\(^5\) Stenosis occurs in the spinal canal due to congenital or acquired reasons. Congenital types are rare and develop due to a short pedicle of the vertebrae and can be seen in Achondroplasia, bone dysplasia, or Down syndrome. Most stenosis are acquired, and they are secondary to degenerative changes. Other causes of less common acquired spinal stenosis are spondylolisthesis, iatrogenic, metabolic, and post-traumatic causes.\(^6\)

The treatment used for spinal stenosis is divided into three groups: conservative or medical treatment, drug injection into the epidural space, and surgical treatment. Most adults with low back pain and radicular pain recover with simple rest and passage of time, but a small number of mentioned patients will suffer from chronic pain that disables them partially or completely.\(^7,8\)

Surgery or epidural injections of the steroid may be used to control chronic spinal cord stenosis in case of failure of conservative treatment. Surgery is recommended if the patient who suffers from back pain experiences new weakness, bowel or bladder incontinence, spinal instability, or infection. In the absence of noted symptoms, steroids are injected into the epidural space.\(^7,8\) Although steroid injection in the epidural space is a useful treatment, its efficacy is limited and short term.\(^9,10\) Amongst the novel drugs, such as hyaluronidase\(^11\) calcitonin is increasingly used. Calcitonin is a polypeptide containing 32 amino acids that is secreted from the parafollicular cells (C cells) of the thyroid gland. Calcitonin plays an important role in regulating bone metabolism and acts as a hormone that inhibits calcium uptake from bone. It stops osteoclast activity and facilitates ossification by interrupting calcium uptake from bones and intensifying osteoblast activity.\(^7\) Calcitonin in the form of L-ketone and calcitonin salmon is mainly used to treat hypercalcemia and pain associated with osteoporosis. L-ketone was selected more frequently than NSAIDs in the treatment of acute low back pain in randomised controlled trials. Calcitonin has also been used to treat diabetic neuropathy and complex regional pain syndrome in a clinical setting.\(^7\)

In addition, studies have been reported on the efficacy of calcitonin in reducing pain without associated side effects.\(^12,13\) There are no empirical and clinical studies on the effects of calcitonin on radicular pain. The analgesic effects of calcitonin in diseases other than osteoporosis have been confirmed.\(^14,15\) However, these analgesic effects may be caused by a mechanism different from bone calcium uptake inhibitors. Calcitonin leads to creation of a slow outward current associated with a decrease in sodium conductance, which causes hyperpolarisation of the membrane in neurons.\(^16\) This study designed to evaluate the effects of epidural injection of calcitonin, the primary outcome of this study was to evaluate the effects on pain score and disability index, and the secondary outcome was analgesic consumption need.

### Methods

The present research is a double-blind clinical trial study that was carried out in the pain clinic of Rasool Akram Medical Complex of Iran University of Medical Sciences. The study population consisted of patients referred to the pain clinic of mentioned hospital in 2018 with a history of chronic low back pain due to spinal canal stenosis who underwent medical and physical treatment as well as activity modification for 3 months, but no improvement has been made. The ethical approval for this study was obtained from the Ethics Committee of Iran University of Medical Sciences (approval number: IR.IUMS.REC.1396.32670). This study was registered in Iranian Registration of Clinical Trial (IRCT20120814010599N24). Also, their clinical symptoms are such that they are not candidates for open surgery currently or do not desire to have open surgery. To collect the required information, a checklist was prepared in advance and during the study, all required information was entered into the checklist before the procedure and also 4, 8, and 12 weeks after that.

The functional disability was recorded based on Oswestry Disability Index (ODI), whilst the amount of pain was recorded through Visual Analogue Scale (VAS), and possible side effects as well as the need for medication at each visit were recorded in the information form containing all of the above-noted points. After the approval of the project by the University Ethics Committee and obtaining an informed consent, this study, which is a double-blind clinical trial, began. For double-blinding, both patient and pain specialist who collected the data were blinded to groups. Based on previous studies with an \( z \) coefficient of 0.5 and study power of

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### Main Points

- Injection of calcitonin into the epidural space can reduce the pain of the patients and their analgesic consumption compared to steroids.
- Calcitonin effectively reduces chronic pain caused by malignancy or benign conditions such as osteoporosis and Paget's disease.
- Epidural calcitonin may be considered as a novel treatment method for pain management in spinal stenosis.
80%, the sample size for each group was estimated to be 20 and in total 40 individuals.

Patients by using a randomised computer-generated sequence were randomly divided into two groups: one in between including caudal epidural injection of ropivacaine (Molteni, Italy) with calcitonin (Caspiantranin, Iran) and the control group of epidural ropivacaine injections with triamcinolone. It should be noted that pain and functional disability scores were recorded before the procedure.

Inclusion criteria consisted of following points: age range between 40 and 70 years, failure to respond to usual treatments within 3 months, ASA class I and II, and hemodynamically stable patients. Exclusion criteria included the following: diabetes mellitus, anxiety and depression disorders, coagulation and bleeding disorders, addiction to any narcotics or psychotropic drug, history of drug allergy, local infection at injection site or systemic infection, patient dissatisfaction, history of spinal surgery, existence of traumatic causes, congenital spine defects and progressive neurologic deficits, and progressive neurologic deficits. Hemodynamic symptoms including blood pressure and ECG were monitored in both groups; pulse oximetry was also monitored after admission of patients to the operating room, and appropriate peripheral vein was obtained.

The patient was placed in the prone position. Oxygen was administered to the patient through a nasal cannula with the flow of 4 L min<sup>−1</sup>. Under aseptic and sterile conditions, the Prep and Drep were carried out. Patient was sedated with 50 μg of fentanyl and 1-2 mg of midazolam.

To perform the caudal epidural procedure, a fluoroscopic-guided procedure was performed using a marker of needle insertion in which needle path was anesthetised with lidocaine 1% and a 1.5-in. and subcutaneous 25-gauge needle tip.

Then, the TUOHY needle no. 18 was inserted into the epidural space, and the location of the needle was identified by contrast injection in the postero-anterior and lateral view of radiology with fluoroscopy. After negative aspiration of blood and cerebrospinal fluid, 50 units of calcitonin were injected with 8 cc of ropivacaine in the case group, and 80 mg triamcinolone plus 8 cc of ropivacaine 0.2% were injected in the control group. After cleaning the injection site and dressing, the patient was transferred to recovery room and monitored for 2 hours. They were discharged in case of the persistence of condition and vital signs. For patients under treatment, oral meloxicam 15 mg and 75 mg pregabalin were given as analgesics need. Patients were re-examined in the pain clinic after procedure as well as 4, 8, and 12 weeks after the procedure. The ODI, VAS, and analgesic use were recorded. In addition, possible complications and the need for medication at each visit in the information form containing all of the above points were recorded. After complete data collection and completion of checklists, statistical analysis was performed. Sample size was determined based on Altman nomogram. After collecting data, the data were entered into Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS Corp.; Armonk, NY, USA) for statistical analysis. Quantitative descriptive data were reported on average and confidence interval of 95%. Moreover, qualitative data were reported as frequency and frequency percentage.

Significance level was considered to be less than 5%, and T-test and chi-square tests were used. All information extracted from the patient records were kept confidential. The results of the research will be published, in general, in the form of the information of study group.

Results

Amongst the 40 subjects with a mean age of 67.95±4.03 years, 20 individuals were positioned in the intervention group and 20 were placed in the control group. The CONSORT flow chart is shown as Figure 1. The data obtained from this study show that eight individuals (20%) had unilateral low back pain and 32 individuals (80%) had bilateral low back pain (Table 1 and Figure 2a). The results indicated that there was a significant difference between the two groups in terms of VAS2 (4 weeks after procedure) score (P = .006) and VAS3 (8 weeks after procedure) score (P = .049) (Table 2).

According to the results, there was no significant difference between the two groups based on OD 1-4 questionnaire scores (Table 2 and Figure 2b). There was a significant difference between the two groups in the number of patients needed analgesic drug 1 (4 weeks after procedure) (P = .006), 2 (8 weeks after procedure), and 3 (12 weeks after the procedure) (P < .001) (Table 2 and Figure 2c), and the analgesic need was lower in the case group.

Discussion

Spinal canal stenosis is one of the most common problems with the spine that severely affects the quality of life of patients. The most important nonsurgical treatment of these patients is to reduce pain and improve their quality of life.7

According to the results of this study, adding calcitonin to epidural injection can diminish pain in patients with spinal stenosis. One of the logical reasons is that local anaesthesia is caused by sympathetic and block stimulation. Vasodilation of vessels causes increase in blood supply to vulnerable nerve tissue and inhibits nerve sensitivity and secretion of neurotransmitters. However, prolonged pain relief for 2 months, which is beyond the local anaesthetic effect in the steroid group, can be due to the reduction of inflammatory oedema and reduced sensitivity in the dorsal horn by steroids.7,17
Epidural steroid injection was given in combination with physiotherapy or with one transforaminal approach multiple times. Meanwhile, many studies indicated the efficacy of pain reduction in a small proportion of patients after repeated epidural injections. Calcitonin was discovered and developed in 1961 to treat diseases. The effects of calcitonin analgesia were discovered in 1983. It was specified that calcitonin can be used as an injection in the epidural and subarachnoid space. Calcitonin effectively reduces chronic pain caused by malignancy or benign conditions such as osteoporosis and Paget’s disease. However, its antinociceptive mechanism appears to be independent of its peripheral activity on the bone. The precise mechanism of calcitonin in reducing pain through epidural injection is not well recognised. Involvement of the opioid system with beta-endorphin release and the effects of serotonergic and catecholaminergic stimulation are some of effects of calcitonin. Also, calcitonin increases blood supply to damaged nerve tissue with decreased blood flow to the bone due to its reduced metabolic activity. In addition, it improves venous congestion and ischemia caused by spinal stenosis, thereby increases myelin through helping to remyelination. This may justify the improvement of paresthesia in patients receiving calcitonin in the present study, which overlaps with the study of Sheikh and Omar.

In a study by Eichenberger et al., it was shown that ketamine infusion alone had a greater effect on phantom pain control of the extremities rather than calcitonin infusion, but infusion of both drugs had a significant effect on pain control.

| Variable   | Case   | Control |
|------------|--------|---------|
| Age (years)| 67.9±3.6| 68.1±4.5|
| Sex        | Male   | 7 (33%) | 13 (65%) |
|            | Female | 13 (65%)| 7 (35%)  |
| Height     | 168.3±8| 173.8±6.6|
| Weight     | 72.2±7 | 78.7±8.9|
Based on a study by Papadokostakis et al., it was observed that nasal injection of calcitonin can have an effect on the control of chronic low back pain in patients with osteoporosis. It was indicated in a study by Karsdal et al. that the use of oral calcitonin may not have significant clinical benefits in reducing pain, function and stiffness in patients with knee osteoarthritis, but it was found out in a study by Elsheikh and Amr in 2016 that adding intrathecal calcitonin to epidural injection can significantly reduce pain and improve function in patients with low back pain.

**Figure 2.a-c.** (a) trend of VAS (b) trend of ODI (c) trend of analgesic consumption since 12 weeks of followup.

**Table 2. Table of Descriptive Statistics of the VAS, ODI, and Analgesic Consumption**

|                        | VAS (mean±SD) | ODI (mean±SD) | Analgesic Consumption (mean±SD) |
|------------------------|---------------|---------------|---------------------------------|
|                        | Case (n=20)   | Control (n=20) | Case (n=20) | Control (n=20) | Case (n=20) | Control (n=20) |
| Before procedure       | 7.5±0.76      | 7.4±0.60      | 39.7±4.05 | 39.60±3.38     | –            | –              |
| 4 weeks after procedure| 1.83±1.34     | 2.35±0.58     | 11.95±3.99 | 12.40±2.82     | 0.75±2.31 | 3.75±3.85     |
|                        | \(P = .775\)  | \(P = .589\)  | \(P = .117\) | \(P = .301\)  | \(P = .006*\) | \(P < .001*\) |
| 8 weeks after procedure| 2.30±1.26     | 2.75±1.02     | 11.5±4.98 | 14.75±3.17     | 0.37±.168 | 6.75±5.39     |
|                        | \(P = .003*\) | \(P = .301\)  | \(P = .301\) | \(P < .001*\) | \(P < .001*\) | \(P < .001*\) |
| 12 weeks after procedure| 2.15±0.75     | 2.90±1.25     | 11.20±3.65 | 15.85±3.66     | 0.375±1.68 | 9.37±5.90     |
|                        | \(P = .046*\) | \(P = .025\)  | \(P = .025\) | \(P < .001*\) | \(P < .001*\) | \(P < .001*\) |

VAS, Visual Analogue Scale; ODI, Oswestry Disability Index.
plus steroids was effective in managing trigeminal neuralgia.\textsuperscript{27}

According to the study of Elsheikh and Omar,\textsuperscript{7} transient diuresis was seen 24 hours after calcitonin administration and led to nausea and vomiting in 12 patients. Three patients had recurrent vomiting for up to 48 hours and responded well to antinausea treatment. These effects were not seen in the present study in patients receiving calcitonin.

This study had some limitation that was limited follow-up time and limited number of patients. We recommend performing multicentric studies with larger sample size for longer weeks.

Conclusion

The present study concluded that adding calcitonin to local anaesthesia injection could help in the management of pain caused by degenerative spinal stenosis, increased walking distance, better Oswestry scale, reduction of pain severity, perception of paresthesia, and effective and efficient consumption of medicine more than injecting anaesthetic and steroid drug alone through the epidural space. All of the above-mentioned benefits lasted for 12 weeks. Therefore, epidural calcitonin may be considered as a novel treatment method for pain management in spinal stenosis.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1396.32670).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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