

Original Article

Effects of calcitonin on lumbar spinal stenosis: a systematic review and meta-analysis

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Abstract: Background: To investigate whether calcitonin can improve walking distance (WD) and visual analog pain scale (VAS) in patients who suffer lumbar spinal stenosis (LSS). Methods: We performed a search on CENTRAL, PubMed, Embase and Cochrane databases up to July 2014; we finally found 19 original articles, of which only 6 were in full compliance with the RCT criteria. These full articles were carefully reviewed independent and in blinded way by two previously capacitated reviewers for the objective to extract data and score a quality of these articles by the criteria of Cochrane Handbook (5.1.0). Results: We accepted 6 studies with 232 participants. There is no evidence show calcitonin is better than placebo or paracetamol regardless of mode of administration. Conclusions: This meta-analysis suggest that calcitonin provide no significant improvement in pain symptoms or walking distance in LSS patients.

Keywords: Lumbar spinal stenosis, neurogenic claudication, pain, walking distance, calcitonin

Introduction

Lumbar spinal stenosis (LSS) is a degenerative disease which affects the lumbar spine. LSS can cause back and leg pain due to the compression of neuronal structures and intraspinal vascular by narrowed spinal canal. LSS is quite common in people older than 65 years, and causing the most significant clinical symptom intermittent neurogenic claudication. Neurogenic claudication is characterized by pain, paresthesia, and cramping in one or both legs [1]. It is caused suddenly by walking and prolonged standing, and can be relieved through sitting and bending forward [2, 3].

Neurogenic claudication is a main reason leading to disability and lost independence in elderly population [4]. The patients with symptomatic LSS not only suffer from back and leg pain but also are at high risk for developing serious complications. The disability and lost independence may lead to physical deterioration and obesity that may eventually lead to serious health problems [5]. Those affected have more serious walking limitations than individuals with knee or hip osteoarthritis [6]. Restricted ability to walk and stand leads to a significant decrease in quality of life [7-9].

Although the rate of surgery for LSS has risen dramatically, especially in the USA [10, 11]. Some good outcomes from surgery have been demonstrated, but literature has also suggested limited long-term benefits when compared to nonsurgical management [12, 13]. Some conservative treatment is recommended prior to surgical intervention. Some researchers have focused on the use of calcitonin to treat pain due to LSS [14-22]. For the reason that past studies have shown calcitonin can relieve pain caused by osteoporotic vertebral compression fractures, bone metastases and Paget disease [23-26].

Because limited walking is the main impaired function for patients with LSS, improvement of walking ability become the primary goal for treatment [3]. Two systematic reviews into calcitonin for LSS are available [27, 28]. However, whether calcitonin can improve walking distance (WD) and visual analog pain scale (VAS) in patients with LSS is unclear. It is important to evaluate the role of calcitonin treatments to manage patients with LSS. Therefore we undertook a systematic review and meta-analysis of all published literature to evaluate the effectiveness of calcitonin interventions for the treatment of LSS.

Materials and methods

We conducted this systematic review and meta-analysis according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0, Oxford, UK) [29].

Search strategy

The Cochrane library, Google Scholar, PubMed and Embase databases were completely searched independently by two investigators (K.P. and Z.X.) to retrieve all possible relevant studies published before August 1, 2014. The search strategy was based on combination of medical subject headings (MeSH) and keywords “calcitonin”, “spinal stenosis”, “pain”, “claudication”, and “pharmacotherapy” were chosen. No restriction to specific languages or years of publication. The “related articles” function was also used by two reviewers to broaden the search. The reference lists of the selected studies were also manually examined to find possible relevant studies which were not searched or discovered during the database searches progress. The corresponding authors were contacted immediately by email when additional information was needed.

Study selection

We included randomized-controlled trials (RCTs) which evaluated the efficacy of calcitonin versus placebo for treatment of LSS patients. Inclusion criteria for the systematic review and meta-analysis were (1) randomized-controlled trials in adults with LSS with calcitonin treatment; (2) clinical or radiological diagnosis of LSS; (3) describe neurogenic claudication with back (leg) pain and gait assessment; (4) provide the dosage and route of calcitonin administration; and (5) outcomes measured such as: walking distance, pain intensity, quality of life, and global improvement. Studies evaluating radiculopathy caused by disc lesions were excluded. Studies with mixed populations were only included if data for neurogenic claudication due to lumbar spinal stenosis were provided.

Outcome measures

All eligible studies were reviewed for baseline data (such as age and sex), intervention (such as calcitonin administration way, dose and

duration) and outcome measures. Both objective and subjective functional outcome measurements were all used to evaluate the interest data. However, the primary key pooled outcomes were pain scale (such as VAS) and walking ability. Adverse effects of calcitonin were also examined. The quality of eligible studies was also planned.

Quality assessment

Titles and abstracts were reviewed using the above mentioned selection criteria by two readers (K.P. and Z.X.). Data extraction of all interest variables and outcomes and assessment of the methodological quality were performed independently by two investigators. Any disagreement was resolved by discussion and final consensus. The methodological quality of all the trials was assessed using the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.

Statistical methods

The statistical analysis progress was performed by Review Manager 5.3.3 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). The weighted mean difference (WMD) was measured with the 95% CIs for continuous variables. *P* values < 0.05 were considered statically significant as usual, and the 95% confidence intervals (CIs) were reported. Statistical heterogeneity among studies was evaluated by Q-statistic and quantified by the *I*² statistic. Both a fixed-effects model and a random-effects model were used to obtain summary WMDs. If the Q or *I*² statistic was significant then a random-effects model was used; otherwise, a fixed-effects model comparison was used. Funnel plots and Egger test (with *P* < 0.05 considered statistically significant as usual) were created to visually evaluate for the presence of publication bias. A sensitivity analysis was conducted in which the RCTs were excluded to thereby determine the stability of the combined WMDs.

Results

Literature search

The initial literature search retrieved 105 relevant articles (duplicates were discarded). After a careful screen of the titles by two reviewers,

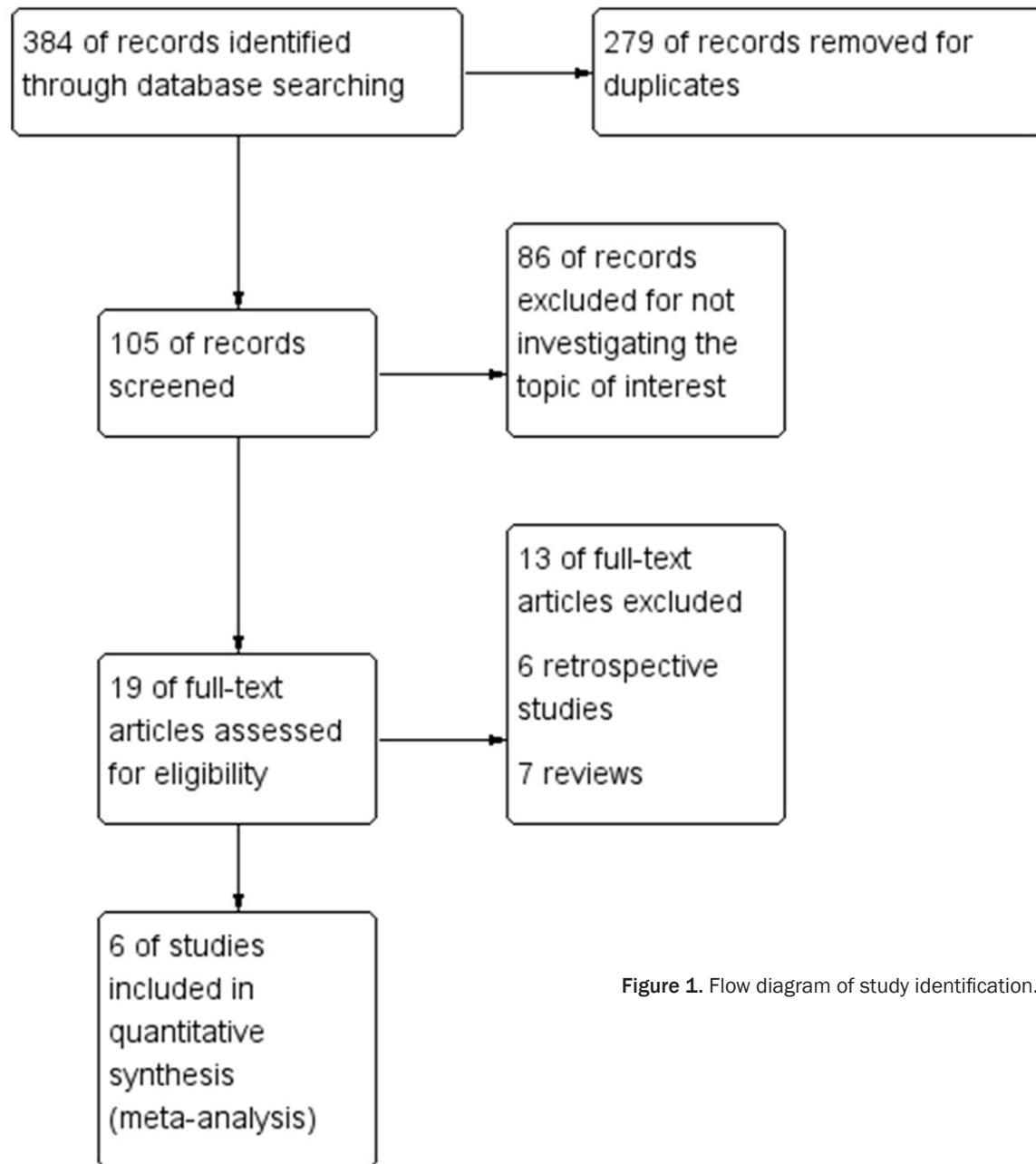


Figure 1. Flow diagram of study identification.

86 articles were excluded for not investigating the topic of interest. After two reviewers reviewing the abstracts, 13 more articles were excluded (6 retrospective studies and 7 review), leaving 6 studies for further full articles publication review. Therefore, 6 studies matched the selection criteria and were suitable for the meta-analysis [14, 15, 18, 20-22]; all were prospective randomized-control trials (Figure 1). A total of 232 patients (124 received Salmon calcitonin and 108 received Placebo) were enrolled in

these meta-analysis studies. The key characteristics of all the included studies are summarized in Table 1. All the studies involved patients who suffered LSS and follow-up for at least 6 weeks. Six level II studies from 1983 to 2009 were identified that compared salmon calcitonin with placebo for treatment of LSS prospectively and randomly. One of the studies included paracetamol as control group [22]. On review of the data extraction, there was 100% agreement between the two investigators.

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Table 1. Characteristics of included studies

Reference publication year	Design	Evidence-Level	Sample (n)	Drop outs	Symptoms duration (mean in years)	Radio-graphic inclusion criteria	Material (M/F ratio)	Administration route	Intervention	Observation times (Weeks/Months)	Mean Age (years)	Outcome Measures	Results	Adverse effects
Porter (1983)	Randomized, double-blind, placebo-controlled cross-over study	II	10	0	Not stated	Spinal stenosis by Metrizamide radiculography w/canal measured by ultrasound	1/9	Subcutaneous	100 IU 4/W for 4W (crossover to placebo)	4 weeks	55.5	Walking distance, ODI	8/10 assessed right their allocation to placebo or calcitonin; 10/10 walking Distance improved following calcitonin ODI results not stated	Not stated
Porter (1988)	Randomized, double-blind, placebo-controlled study	II	42	0	12.5	Spine assess by rad/CT/ultrasound	35/7	Subcutaneous	100 IU SQ 4/W for 8 W 100 IU SQ 4/W for 8 W	8 for all patients 16 for open SCT therapy	55.2	Walking distance	5 in Rx group and 1/22 in placebo group responded; difference was not significant	Nausea, flu-like symptoms
Eskola (1992)	Randomized, double-blind, placebo-controlled cross-over study	II	40	1	6	<10 mm SC diameter on myelography	20/19	Intramuscular	100 IU IM every 2 days 4/W 2 months wash-out then 4/W of placebo or calcitonin	12 months	56.6	Walking distance, performance improved in 41% VAS, performance test	Significant decrease in pain at rest, on jumping and walking; erythema, and 5 patients (13%) were able to walk unlimited	Nausea, headache, diarrhea
Podichetty (2004)	Randomized, double-blind, placebo-controlled study	II	55	12	2.8	At least one level of LSS within 1 yr on MRI/CT	33/22	Intranasal	400 IU NS daily 12/W	12 weeks	68.5	SF-36, VAS, walking time and distance	No significant difference in pain intensity (VAS), and walking time. Walking distance showed some improvement in both groups with SF-36 scores showing little improvement.	Nausea, erythema
Tafazal (2007)	Randomized, placebo-controlled study	II	40	4	2.9	13 mm/less mid sagittal stenosis	30/10	Intranasal	200 IU NS or placebo × 4W; 6W washout 200 IU NS × 6W	16 weeks	68.6	ODI; LBOS; VAS for back and leg pain; shuttle walking distance	ODI and LBOS showed marginal improvement; VAS for leg deteriorated in both groups; VAS for back showed improvement for control group and deterioration for placebo group. 23% of group reported good/excellent outcome	Runny nose

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Sahin (2009)	Randomized, II single-blind, controlled study	45	0	Not stated	Narrowest level or levels with an axial diameter be- low 10 mm, measured by lumbar MRI	31/14	Intranasal	200 IU NS daily 8/W;1500 mg paracetamol daily 8/W; Both groups took part in a physical therapy and exercise programme 5/W for 15 sessions	8 weeks	55	Walking distance, VAS; Range of motion; Functional status	Lumbar Schober was similar in both groups, while the finger-to-floor distance significantly improved in the calcitonin group. All other parameters showed significant improvement in both groups ,There was no significant differ- ence between the groups with respect to improved param- eters during the follow up period as well as their percent changes	Nasal irritation
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Eskola 1992	?	?	-	-	+	+	?
Podichetty 2004	?	?	-	-	?	+	?
Porter 1983	?	?	?	?	?	-	?
Porter 1988	?	?	?	?	?	-	?
Sahin 2009	?	?	-	+	+	+	+
Tafazal 2007	?	?	-	-	?	-	?

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 summarizes the methodological quality score of all the studies. Most of the studies were RCTs with a high level of methodological quality. Only one study was prospective randomized control trial on partly patients [14], and it also had a high methodological quality despite being partly patients. Thus, the methodological bias of this study was low.

Main analysis

Table 1 summarizes the outcomes of this meta-analysis. No significant difference was found

between the salmon calcitonin group and the placebo group for the gait assessment; walking distance (meters) (WMD, 41.04, 95% CI, -63.69-145.77; $P = 0.44$), change in walking distance (meters) (WMD, 17.56, 95% CI, -98.67-133.79; $P = 0.77$), change in walking time (seconds) (WMD, -42.20, 95% CI, -172.43-88.03; $P = 0.53$). Because significant heterogeneity was observed for the change in walking distance, the random-effects model was then used as no significant clinical heterogeneity was found between these studies.

For the leg or back pain assessment there was no significant difference between the salmon calcitonin group and the placebo group. VAS with motion (WMD, 0.71, 95% CI, -0.40-1.82; $P = 0.21$), change in VAS at rest (WMD, 1.76, 95% CI, -2.48-6.00; $P = 0.42$), change in VAS with motion (WMD, 0.11, 95% CI, -0.71-0.93; $P = 0.79$). Because significant heterogeneity was observed for the value and change of VAS with motion, the random-effects model was then used as no significant clinical heterogeneity was found between the studies.

With respect to placebo group, there was no significant difference for final outcome measures. Of the 6 RCTs, only Porter and Porter, recommended using calcitonin (subcutaneous, 100 IU 4/w for 16 weeks) for the reason that SCT may improve the outcomes for neurogenic claudication in patients with LSS. Eskola, found that calcitonin (subcutaneous, 100 IU for four weeks to one year) demonstrated so poor results for pain and gait assessment, and should only be recommended in few special selected cases. Podichetty concluded that calcitonin (nasal spray, 200 IU for activation followed by a 400 IU dose for six weeks) did not show more benefit than placebo in pain or gait assessment. Tafazal, using salmon calcitonin nasal spray 200 IU for four weeks, did not demonstrate

more benefit than placebo. Finally, Sahin, using 200 IU intranasal calcitonin daily for 8 weeks plus a physical therapy and exercise programme five times per week for 15 sessions, did not lead to a significant improvement in follow-up parameters than paracetamol.

Publication bias

We were failed to draw funnel plots because the trials was less than 10.

Discussion

Lumbar spinal stenosis (LSS) is a significant problem that affects a lot of elderly adults annually. Walking limitation due to neurogenic claudication of LSS is thought to be the hallmark of disability [30]. The walking ability is essential for almost daily living activities and has been identified as a quite important outcome in LSS [31, 32]. Despite LSS prevalence is raising, there are few studies investigating nonsurgical treatment modalities. This systematic review and meta-analysis of RCTs summarizes all available studies regarding the use of calcitonin for LSS patients. We were only able to identify six randomized, double-blind, controlled trials involving a total of 232 patients. Overall, the evidence described that calcitonin is not an effective analgesic and does not significantly improve walking distance in LSS patients, no matter whether the calcitonin administer way was intranasal or intramuscularly.

Overall, calcitonin treatment seems to be quite safe. There were so few adverse effects reported in these RCTs; however, the safety of calcitonin treatment also need to be further evaluated. Nausea was noticed in three calcitonin treatment group [15, 18, 20], whereas flu-like symptoms, headache, diarrhea and erythema were noticed in calcitonin treatment group. Due to the lack of significant adverse effects, calcitonin was thought to be a safe treatment for future clinical research.

It was very hard to perform a meta-analysis for the reason that the heterogeneity from diversity of criteria in patient selection, different ways of drug administration, doses, follow-up lengths, and difference in sample size. Other weakness was the different outcome measurements, such as pain and gait assessments were also measured in different ways.

In 2013, North America Spine Society's (NASS) Evidence-Based Clinical Guideline Development Committee has developed an evidence-based clinical guideline [33] on the diagnosis and treatment of degenerative lumbar spinal stenosis (LSS). They found insufficient evidence for this drug therapy, elaborating a I recommendation in favor of it use. However, However, this systematic review was based only in Eskola [18] trial.

The limitations of this meta-analysis were as follows. First, the calcitonin administration way, doses, frequency, and duration in each trial were not perfectly same, which may influence the outcomes of interest. Second, some parameters of interest demonstrated a large degree of heterogeneity. The heterogeneity of change in walking distance, the value and change of VAS with motion may be the result of bias from different assessment methods in the trials. Last but not least, this meta-analysis just requires a lot more patients for so little patients included, larger highest level studies are required to show superiority of calcitonin treatment for neurogenic claudication due to LSS.

On the basis of all the reviewed trials, when compared with placebo, we found no evidence to establish that calcitonin provide a statistically significant improvement in pain symptoms or walking distance in LSS patients. Also, the administration way appears to play no role in its efficacy for pain control. Further better and rigorous studies with long-term observation are required to elucidate the effectiveness of calcitonin treatment for LSS.

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KP conceived of the design of the study. LC and JP collected the data and contributed to the design of the study. FX prepared the manuscript. KP and ZX edited the manuscript. All authors read and approved the final manuscript.

Disclosure of conflict of interest

None.

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