Randomised placebo-controlled trial on the effectiveness of nasal salmon calcitonin in the treatment of lumbar spinal stenosis

Suhayl I. Tafazal · Leslie Ng · Philip Sell

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Abstract This is a double blind randomised controlled trial to assess the effectiveness of nasal salmon calcitonin in the treatment of lumbar spinal stenosis. The trial compared the outcome of salmon calcitonin nasal spray to placebo nasal spray in patients with MRI confirmed lumbar spinal stenosis. Lumbar spinal stenosis is one of the commonest conditions encountered by spine surgeons. It more frequently affects elderly patients and lumbar decompression has been used to treat the condition with variable success. Non operative measures have been investigated, but their success ranges from 15% to 43% in patients followed up for 1–5 years (Simotas in Clin Orthop 1(384):153–161, 2001). Salmon calcitonin injections have been investigated in previous trials and may have a treatment effect. Nasal salmon calcitonin has become available and if effective would have advantages over injections. Forty patients with symptoms of neurogenic claudication and MRI proven lumbar spinal stenosis were randomly assigned either nasal salmon calcitonin or placebo nasal spray to use for 4 weeks. This was followed by a ‘washout’ period of 6 weeks, and subsequent treatment with 6 weeks of nasal salmon calcitonin. Standard spine outcome measures including Oswestry disability index (ODI), low back outcome score, visual analogue score and shuttle walking test were administered at baseline, 4, 10 and 16 weeks. Twenty patients received nasal salmon calcitonin and twenty patients received placebo nasal spray. At 4 weeks post treatment there was

no statistically significant difference in the outcome measures between the two groups. The change in ODI was a mean 1.3 points for the calcitonin group and 0.6 points for the placebo group ($P = 0.51$), the mean change in visual analogue score for leg pain was 10 mm in the calcitonin group and 0 mm in the placebo group ($P = 0.51$). There was no significant difference in walking distance between the two groups, with a mean improvement in walking distance of 21 m in the calcitonin group and 8 m in the placebo group ($P = 0.78$). At the end of the trial the ODI had improved by a mean of 3.7 points in the calcitonin group and 3.8 points in the placebo group ($P = 0.44$). This randomised placebo controlled trial has not shown any treatment effect in patients with lumbar spinal stenosis treated with nasal salmon calcitonin.

Keywords Lumbar spinal stenosis · Neurogenic claudication · Nasal salmon calcitonin

Introduction

Lumbar spinal stenosis is one of the commonest conditions encountered by spine surgeons. Patients may have a range of symptoms of which neurogenic claudication is the cardinal dominant one. It may be primary and have a congenital component or secondary to age related degenerative changes. Surgery in the form of a lumbar decompression is one treatment option however in an elderly population co-morbidity may be a relative contra-indication. The success of surgery is variably reported. Non operative measures have been investigated, but their success ranges from 15 to 43% in patients followed up for 1–5 years [1]. It would be

S. I. Tafazal (✉) · L. Ng · P. Sell
Department of Orthopaedics,
University Hospitals of Leicester,
Leicestershire, UK
e-mail: stafazal@hotmail.com

clinically valuable to have a proven effective non-operative treatment.

The use of salmon calcitonin for the treatment of lumbar spinal stenosis was first described by Porter in 1983 [2]. He used subcutaneous calcitonin injections four times a week for 4 weeks and 11/41 patients had a dramatic response to salmon calcitonin. Nasal salmon calcitonin is currently indicated for the treatment of osteoporosis and Paget's disease. Our study is a randomised controlled trial to test the efficacy of nasal salmon calcitonin in the treatment of lumbar spinal stenosis.

Materials and methods

Forty patients with symptoms of neurogenic claudication and MRI proven lumbar spinal stenosis were enrolled into the study. The inclusion and exclusion criteria are listed in Table 1 below. All patients had unilateral or bilateral leg pain made worse by walking and prolonged standing and eased by resting or leaning forwards. The trial was given ethical approval by the Leicestershire Local Research Ethics committee (LREC; Ref No: 6007). At trial enrolment an information sheet describing the trial was given to the patients and informed consent was obtained from all patients prior to trial entry. Each patient had a full neurological examination as well as assessment of peripheral pulses and range of knee/hip movements prior to trial entry. Patients then completed a standard spine assessment questionnaire, including visual analogue score (VAS) for back and leg pain, Oswestry Disability Index (ODI) [3, 4] and Low Back Outcome

Score (LBOS) [5]. Psychological testing involved use of the modified somatic perception questionnaire (MSPQ) and the modified zung depression score (MZD). Subjective outcome was also assessed at each follow-up visit. Patients completed these questionnaires at enrolment and subsequently at 4, 10 and 16 weeks follow-up. All patients completed a shuttle walking test [3] at enrolment and then at weeks 4 and 10. A flow chart showing the trial design is shown in Fig. 1.

The patients were randomly assigned to use either nasal salmon calcitonin 200 i.u or placebo nasal spray (sodium chloride) for the first 4 weeks. Patients were given instructions to have one spray in alternate nostrils on alternate days to reduce the risk of irritation of the nostrils with prolonged treatment in the same nostril. We used the standard dose recommended for the treatment of osteoporosis. The randomisation code and the active/placebo nasal spray were produced by Nova laboratories, Leicester, UK. There was no funding or financial support for the trial from any companies or organisations. The trial code was held in the pharmacy department at Leicester General Hospital and was unblinded at the end of the trial once 40 patients had completed the trial.

At the end of the 4 weeks of initial treatment the patients were given a 6 week washout period, during which they received no further nasal spray and were instructed to continue with their normal analgesics. At the end of this period all patients received a further 6 weeks of active nasal salmon calcitonin, 200 i.u alternate nostrils on alternate days. This was to ensure that patients did not miss out on treatment as well as to investigate whether a further 6 weeks treatment in those who received the active spray initially had any additional benefit.

Table 1 Inclusion and exclusion criteria for the trial

Inclusion criteria	Exclusion criteria
Clinical symptoms and signs consistent with lumbar spinal stenosis	Vascular claudication
Pain including back/leg	Symptomatic hip/knee pathology
Standing leg discomfort	Previous lumbar spinal stenosis surgery
Weakness, Paraesthesia and absent reflex	Renal failure
Age > 50	Pregnancy
Radiographic evidence of relative/absolute stenosis- mid sagittal diameter 13 mm or less	Presence of other neurologic disease including peripheral neuropathy
Ability to complete shuttle walk test	Malignancy
	Prior use of salmon calcitonin

Statistical analysis

The data was analysed using SPSS statistical software version 11.5 (SPSS Inc, Chicago, IL, USA). Both active and placebo group outcomes were analysed using a Mann–Whitney *U* test.

Results

The results are summarised in Tables 3, 4, 5, 6 and Graphs 1 and 2 below. The results indicate that after the first 4 weeks during which patients received active/placebo nasal salmon calcitonin there was no statistically significant difference in the change in outcome

Fig. 1 Flow chart showing flow of patients through trial **Table 2** Baseline data for both active and placebo groups

Characteristic	Salmon calcitonin group (<i>n</i> = 20)	Placebo group (<i>n</i> = 20)
Male	15	15
Female	5	5
Age (SD)	67.0 (9.0)	70.2 (9.3)
Duration of symptoms in months (SD)	38.7 (50.4)	30.9 (16.7)
Mean score (SD)		
Oswestry disability index (%)	36.5 (16.0)	42.5 (13.3)
Low back outcome score	27.6 (10.6)	24.1 (9.9)
Visual analogue score leg (mm)	68 (17)	74 (20)
Shuttle walk test in metres	262 (217)	170 (120)
Modified somatic perception	4.8 (3.5)	7.8 (5.6)
Modified Zung depression	21.3 (9.9)	19.3 (9.4)

scores between the two groups (see Table 3). There is a minimal improvement in the mean ODI at the end of the trial of only 3.7 points in the calcitonin group and 3.8 points in the placebo group (Table 5). The LBOS also indicates similar changes to the ODI with only marginal improvements in score. The calcitonin group had received two courses of calcitonin by this point whereas the placebo group had only received a single

6 week course (see flow chart above). After the initial 4 weeks of nasal spray the VAS for leg pain improved by 10 mm in the calcitonin group and 0 mm in the placebo group, a difference which is not statistically significant ($P = 0.51$). At the end of the trial, the VAS score for leg pain actually deteriorated in both groups, by 15 mm in the calcitonin group and 11 mm in the placebo group. The only statistically significant difference between the two groups was for the VAS for back pain at the end of the trial with an improvement of 5 mm for the calcitonin group and a deterioration of 11 mm for the placebo group ($P = 0.03$). It was interesting to note that when looking at subjective global outcome measures three patients in the calcitonin group reported an excellent improvement in their symptoms whereas in the placebo group no patients reported an excellent outcome. Analysing the group as a whole at the end of the trial when both groups had received some calcitonin only nine patients (23%) reported either a good or excellent outcome, which is a poor response rate (see Graphs 1, 2 below).

Discussion

Lumbar spinal stenosis is a common condition affecting a predominantly elderly population in whom surgical intervention is associated with a high degree of risk. Conservative treatment strategies are desirable

Table 3 Change in outcome scores for active versus placebo groups pre-4 weeks post nasal spray treatment

Score change pre- 4 weeks	Calcitonin mean (SD)	Placebo mean (SD)	<i>P</i> value	95% confidence intervals
ODI (%)	1.3 (7.7)	0.6 (7.7)	0.51	-1.7–3.5
LBOS	3.6 (8.2)	0.6 (7.3)	0.49	-0.6–4.7
VAS for leg pain (mm)	10 (23)	0 (26)	0.51	-4–13
VAS for back pain (mm)	0 (27)	6 (27)	0.13	-6–12
Shuttle walking distance(m)	21 (76)	8 (44)	0.78	-7–35

Table 4 Subjective global patient rating at 4 weeks

Subjective rating at 4 weeks	Calcitonin	Placebo
Excellent	1	0
Good	1	1
Fair	4	5
Poor	11	13

Table 5 Score changes for calcitonin versus placebo groups at 16 weeks (end of trial)

Score change pre- 16 weeks	Calcitonin Mean (SD)	Placebo Mean (SD)	p value
ODI (%)	3.7 (16.2)	3.8 (12.1)	0.44
LBOS	3.6 (11.2)	2.9 (8.5)	0.93
VAS for leg pain (mm)	-15 (34)	-11 (32)	0.66
VAS for back pain (mm)	5 (26)	-11 (32)	0.03*
Shuttle walking distance (m)	-6 (126)	5 (51)	0.39

A negative value indicates deterioration in score. The Calcitonin group have received two separate courses of nasal salmon calcitonin and the placebo group have received a single 6 weeks course of treatment

Table 6 Subjective global patient rating at the end of the trial period

Subjective rating at 16 weeks	Calcitonin	Placebo
Excellent	3	0
Good	2	4
Fair	2	4
Poor	8	9

and salmon calcitonin has previously been shown to improve the outcome in such patients. Salmon calcitonin was previously administered by intramuscular or subcutaneous injection, but now a nasal form of the treatment is available and indicated for the treatment of osteoporosis [6] and Paget's disease [7, 8] in the UK. Our study investigated the efficacy of nasal salmon calcitonin treatment for lumbar spinal stenosis and found at the doses used it did not provide any significant benefit for patients with the condition. There was only a minimal improvement in the outcome measures after treatment both in the calcitonin and placebo group of patients, which was not statistically significant.

There has been only one previous randomised controlled trial looking at the efficacy of nasal salmon calcitonin treatment for lumbar spinal stenosis. This study by Podichetty et al. [9] also failed to show any

therapeutic benefit in patients after receiving 6 weeks of nasal salmon calcitonin treatment. These findings would concur with the findings in our study. One possible reason cited for failure of calcitonin treatment in the trial by Podichetty was the increased severity of symptoms in their patient's who had a mean walking distance of only 130 m, but in our study the mean baseline walking distance was greater, 262 m in the treatment group. This would indicate that despite having a greater initial walking distance (less severely affected), patients in our study still failed to show a positive response to treatment with nasal salmon calcitonin.

The first study by Porter in 1983 [2] seemed to show a possible benefit of salmon calcitonin treatment in some patients with spinal stenosis. He used calcitonin injections in patients with neurogenic claudication not associated with Paget's disease after a study [7] showed a dramatic improvement in the paraparesis of eight patients with Paget's disease treated with calcitonin. This then lead to further studies and Porter himself carried out a randomised double-blind trial [10] of salmon calcitonin subcuticular injections and found that there was no statistically significant difference in the response rate to salmon calcitonin compared to placebo in a group of 42 patients (5/20 patients in the salmon calcitonin group and 1/22 in the placebo group

Graph 1 Global patient rating after the first 4 weeks of treatment **Graph 2** Global patient rating at the end of the trial

responded). Another study [11] also showed promising results of salmon calcitonin injections administered to patients with lumbar spinal stenosis with five out of six patients responding markedly to treatment. They found that the walking distance of the patients improved considerably after a 4 week course of injections with a mean improvement of over 900 m. A further randomised cross-over study of calcitonin injections by Eskola et al. [12] found that there was a slight increase in walking distance in the calcitonin group, but this was noted 2–4 months after the start of treatment. They also noted that those patients with mild pain (baseline VAS < 30–40 mm) and walking distance limited to < 200–300 m derived no particular benefit from calcitonin. In our study the baseline VAS was 68 mm and so patients did have significant pain, but their walking distance was limited to 262 m in the calcitonin group, which may be a possible explanation for their lack of response to calcitonin treatment. As lumbar spinal stenosis is a condition frequently encountered in elderly patients, surgical intervention is considered to be high risk in these patients. Conservative treatments are desirable as part of a hierarchical cascade of treatments, but the success rate of such treatments has been rather variable in the literature. Salmon calcitonin has shown some benefit in these patients and one study in particular [13] has shown that 1 months treatment with calcitonin injections produced improvement in pain in 91% of patients, lumbar spine functional capacity (regaining of normal spine extension) in 55% and improvement in walking distance in 89% of patients. There were some significant confounding variables in this study, with patients receiving physical therapy, consisting of infrared heating, ultrasonic diathermy and active lumbar exercises along with salmon calcitonin injections. Therefore, the actual treatment effect of calcitonin injections alone may be less than that reported in this study.

The proposed mechanism of action of salmon calcitonin is through a direct analgesic effect [14, 15], although its true mechanism of action in spinal stenosis is unknown. Another proposed theory is that the effects of salmon calcitonin in spinal stenosis are due to its effect on lowering the metabolic activity of bone and consequently its blood supply, which may permit more blood to reach the deprived neural tissues [8, 12].

Our study has failed to show any benefit of nasal salmon calcitonin, but this may be because the bio-availability of the nasal formulation of calcitonin is only around 3% (range 0.3–30.6%) compared to intramuscular injection. This would mean that less of the drug is absorbed into the systemic circulation, which may account for the lack of efficacy of the nasal

spray observed in our trial. Another problem with our study was the differences in baseline scores between the groups, with the calcitonin group having a lower baseline ODI and VAS for leg pain (see Table 2) as well as a greater mean walking distance. This would have biased the results in favour of the calcitonin group, but there were still no significant differences detected in this study. We may also have a type 2 error, that is an insufficient sample size to detect a difference between the groups. During this study the lack of efficacy of the drug was clearly evident and it was felt that pursuing the trial further would not be of further benefit. The main side effect reported by patients in our study was a runny nose, which is a common side effect of the nasal spray.

Conclusion

Nasal salmon calcitonin does not seem to have a role in the conservative treatment of patients with lumbar spinal stenosis based on this randomised, placebo controlled clinical trial.

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