

# A Randomized Open Label Study to Assess Analgesic Efficacy of Salmon Calcitonin in Painful Bone Diseases

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## INTRODUCTION

Calcitonin, a polypeptide hormone secreted by the parafollicular cells of the thyroid is presently indicated for the treatment of postmenopausal osteoporosis and Paget's disease. In addition to its role in regulation of functions involving calcium equilibrium, which plays a vital role in bone metabolism and functions of other systems, it also has an intrinsic analgesic action at CNS levels and may also play a role in neuro modulation<sup>1,2</sup>.

Both animal and experimental data suggest that the analgesic action of calcitonin is related to central and peripheral mechanisms<sup>1,3</sup>. Majority of the findings suggest that analgesic action of calcitonin is due to its central effect on endorphin system. It is shown that beta endorphin levels rise administration of calcitonin<sup>4</sup>. Use of calcitonin for management of osteoporosis has shown that its analgesic effects appear much earlier than its effect on bone mineral density and is associated with rapid improvement in mobility<sup>5</sup>.

Pain associated with diseases like osteoporosis, lumbar canal stenosis, Paget's disease, osteonecrosis are usually managed with NSAIDs and methylcobalamin. Long term benefits of such conservative treatment is not well established and have not been very satisfactory leading to poor compliance.

Under such circumstances, salmon calcitonin offers a better alternative. Lack of serious side effects and beneficial effects on bone metabolism along with its central analgesic effect, make salmon calcitonin suitable for long term therapy in management of pain in a wide variety of chronic bone diseases. Some studies have shown that subcutaneous and intravascular calcitonin reduce pain and improve walking distance in lumbar canal stenosis patients. However, some studies especially with normal spray formulation failed to show any effect<sup>6</sup>.

This study was therefore, undertaken to determine the effectiveness of salmon calcitonin injection manufactured by M/s. Shreya Life Sciences Pvt. Ltd. (Brand Name Salmoncal) in improving the symptoms and functions in patients with chronic bone diseases when administered either alone or in combination with methylcobalamin.

## MATERIALS AND METHODS

### Patients:

Patients of either sex presenting to the orthopedic clinic for management of chronic painful bone disease were screened for inclusion in this study. The patients were

included if they suffered from any painful bone disease like osteoporosis, lumbar canal stenosis, had pain duration of more than 3 months and had pain at rest (VAS score >6). Patients were excluded if they had any neurological disorder like Parkinson's disease, arthritis, peripheral vascular disease, rickets or osteomalacia. Any patients with uncontrolled disorders of cardiovascular system, uncontrolled diabetes mellitus, uncontrolled neuropsychiatric disorder or any serious life threatening disease were also excluded. Patients with history of salmon calcitonin use and history of hyper-sensitivity to salmon calcitonin were not included in the study.

The study protocol was approved by the institutional EC and all the patients gave written informed consent before inclusion in the study.

Twenty sequential patients attending the orthopaedic clinic were included in the study. Thirteen female and seven male (total 20 patients) were included in the study. They were thermodynamically stable and there were no evidence of hepatic renal disease, neurological, vascular or hematological disease. Nineteen out of twenty had painful spine and 35% had pain at more than one site. In addition to pain in spine, 25% had pain in upper region of the body and 10% had in pelvic region. These patients had moderate to severe disorders with an average duration of 11.61±6.30 months of pain, were taking treatment for 9.00±3.74 months for pain relief and had pain intensity score on VAS scale of 7.35±1.63 at rest and 7.61±0.92 on movement in spite of treatment with anti inflammation drugs (95%) or corticosteroids (15%). After baseline assessment, the patients were put on Methylcobalamin 500 mg daily orally or by intramuscular injection. Salmon calcitonin (Salmoncal Shreya Life Sciences Pvt. Ltd.) was added at a dose of 50 IU daily for initial one week and then if tolerated well, increased to 100 IU once daily till significant pain relief was obtained and then every alternate day for the duration of study (45 days).

### Patient Assessment:

At the inclusion in the study all the patients underwent physical examination and biochemistry study. Their baseline pain intensity at rest and on movement were evaluated using visual analogue scale (0 = no pain; 10 = severe pain). Ambulation was assessed by measuring time taken and distance covered by the patient before intolerable symptoms forced them to stop. At physical examination, spine, shoulder, hip elbow or ankle

evaluation, as applicable, was carried out by assessing range of pain free motions. The patients were assessed at 3, 15, 30 and 45 days intervals.

Therapeutic success was defined as more than 25% improvement in pain intensity and more than 25% reduction in time taken to walk. More than 25% reduction

in consumption of analgesic was also considered for evaluation of efficacy. Safety and tolerability was assessed by monitoring appearance duration. Outcomes were measured at each visit time point and analyzed using Wilcoxon Sign Rank test and Student t Test.

## RESULTS

A total of 20 patients completed the study and their data was available for evaluation. There were 13 female and 7 male patients. The average age was 48.25 years (range 30-76 years) with mean body weight of 60.42 kg (range 48-76 kg). (Table 1)

**Table 1: Demographical Characteristics of Patients**

Parameters	Mean Value $\pm$ SD
<b>Number of cases</b>	<b>20</b>
<b>Age (yrs)</b>	
Mean+ SD	48.25 $\pm$ 13.42
Range	30-76 yrs
<b>Weight (kg)</b>	
Mean $\pm$ SD	60.42 $\pm$ 8.30
Range	48-76 kg
<b>Sex (%)</b>	
Male	07 (35.0)
Female	13 (65.0)

Nineteen out of 20 patients had painful spine and 35% had pain at more than one site. In addition to pain in spine, 25% had pain in upper region and 10% had pain in pelvic region (Table 2).

**Table 2: Profile of Present Illness - Site Of Involvement**

Site	No. of Cases (N = 20)	Percentage
Multiple sites	07	35.0
Shoulder region	02	10.0
Upper arm	01	05.0
Forearm	-	-
Hand	-	-
Pelvic region & Thigh	02	10.0
Head & Neck	02	10.0
Vertebral Column/Spine	19	95.0

The patients included in the study had moderate (85%) to severe (15%) disorder of bone with an average duration of 11.61 $\pm$ 6.30 months, were taking prior treatment for an average duration of 9.00 $\pm$ 3.74 months and pain intensity on VAS, of 7.1.63 $\pm$ 1.63 at rest and 7.61 $\pm$ 0.92 on movement (Table 3 & Table 4)

**Table 3: Profile of Severity of Bone Pathology**

Severity	No. of Cases (N = 20)	Percentage
Minor	-	-
Moderate	17	85.0
Severe	03	15.0

**Table 4: Profile of Present Illness**

Duration	Mean Score ( $\bar{X} \pm SD$ )
Duration of Disease (mths)	11.61 $\pm$ 6.30
Duration of Pain (mths)	9.00 $\pm$ 3.74
Peak Pain Intensity at Rest	7.35 $\pm$ 1.63
Peak Pain Intensity on Movement	7.61 $\pm$ 0.92

Prior to treatment with salmon calcitonin, patients were oral and topical NSAID (95%), calcium supplement (60%), corticosteroids (15%) and physiotherapy (20%) for control (Table 5).

**Table 5: Profile of Current Treatment**

Drugs	No. of Cases (N = 20)	Percentage
Narcotic Analgesic	-	-
NSAID	19	95.0
Corticosteroid	03	15.0
Local Anaesthetic	01	05.0
Topical Analgesic	14	70.0
Physiotherapy Exercises	04	20.0
Calcium Supplements	12	60.0
Vitamin D Supplements	02	10.0
<b>Others</b>	<b>03</b>	<b>15.0</b>
Mecaforte	01	05.0
Seantal	01	05.0
Diathermy	01	05.0

The mean base line pain intensity at rest, measured as VAS score, was 7.68 $\pm$ 0.67. Calcitonin treatment gradually reduced the intensity and after 45 days treatment there was significance reduction. The mean VAS score at 45 days was 0.75 $\pm$ 0.46. (Table 6) After treatment at the end of 15th day mean score had significant fall i.e. 38.1% from basal. At the end of 30 and 45 days fall were 73.0% and 90.2% respectively from basal.

**Table 6: Changes in Mean Vas Score of Pain at Rest with the Treatment**

Duration in Days	Mean VAS Score ( $\bar{X} \pm SD$ )
Basal	7.68 $\pm$ 0.67
3	7.61 $\pm$ 0.61
15	*4.76 $\pm$ 1.03
30	*2.07 $\pm$ 1.14
45	*0.75 $\pm$ 0.46

By Wilcoxon Sign Rank Test

\* P < 0.05 Significant

The pain relief was associated with significant functional improvement. Pain free sitting time increased those mean of 20.00 $\pm$ 7.34 minutes to move than 40 minutes by 30 days of treatment and continued to improve beyond till end of study period. After the treatment at the end of 15 days mean time had significant increased by 95.0% of basal time. At the end of 30 and 45 days they were comfortable for longer time also (Table 7).

**Table 7: Changes in Mean Time for Pain free Sitting with Treatment**

Duration in Days	Mean Time (mins) ( $\bar{X} \pm SD$ )
Basal	20.00 $\pm$ 7.34
3	21.15 $\pm$ 6.82
15	*39.00 $\pm$ 15.06
30	-
45	-

By Student "t" Test

\* P &lt; 0.05 Significant

Table 8 shows that for upto 15 days of calcitonin treatment was not able to improve the duration of pain free walk. However, at 30 and 45 days evaluation, the patients were able to walk without pain for more than 30 minutes of observation period.

**Table 8: Changes in Mean Time for Pain free Walk with Treatment**

Duration in Days	Mean Time (mins) ( $\bar{X} \pm SD$ )
Basal	13.30 $\pm$ 7.35
3	13.11 $\pm$ 7.77
15	14.00 $\pm$ 11.86
30	-
45	-

By Student "t" Test

P &gt; 0.05 Not Significant

However, with calcitonin treatment these patients were able to tolerate pain better and cover longer distance before pain could become intolerable even at 15 days follow up and could cover 47.1% more distance before stopping. The pain tolerance improved with continued treatment (Table 9).

**Table 9: Changes in Mean Pain free Walk Distance with The Treatment**

Duration in Days	Mean Distance (Ft) ( $\bar{X} \pm SD$ )
Basal	18.13 $\pm$ 8.84
3	19.29 $\pm$ 8.86
15	*26.67 $\pm$ 8.16
30	-
45	-

By Student "t" Test

\*P &lt; 0.05 Significant

Consistent with reduction in pain intensity, there was significant improvement in functional parameters. Pain free flexion of affected part changed from 23.13+7.040 at baseline to 80.00+22.360, pain free bending from 17.14+9.060 to 30.0+0. At the end of 15 days treatment, the mean lateral bending had significant increase by 38.1% from the basal value. At the end of 30 and 45 days increase were 65.3% and 75.02% respectively from baseline. Pain free rotational movement improved from 29.38+18.600 to 38.57+22.68. After the treatment for 15 days, the mean pain free rotation movement increased by 43.60% from basal. At the end of 30 and 45 days mean pain free rotation was increased by 40.77 and 38.57 respectively from the base line. The pain free leg raising angle changed from 40.74<sup>0</sup>±20.09<sup>0</sup> to 90.00<sup>0</sup> showing considerable improvement (Table 10, 11, 12 and 13).

**Table 10: Changes in Mean Pain free Flexion with Treatment**

Duration in Days	Mean Flexion (°) ( $\bar{X} \pm SD$ )
Basal	23.13 $\pm$ 7.04
3	23.13 $\pm$ 7.04
15	*47.35 $\pm$ 17.15
30	*62.31 $\pm$ 20.78
45	*80.00 $\pm$ 22.36

By Student "t" Test

\* P &lt; 0.05 Significant

**Table 11: Changes in Mean Pain free Lat Bending with Treatment**

Duration in Days	Mean Lat Bending (°) ( $\bar{X} \pm SD$ )
Basal	17.14 ± 9.06
3	16.88 ± 8.43
15	*23.67 ± 12.74
30	*28.33 ± 7.49
45	*30.00 ± 0

By Student "t" Test

\* P &lt; 0.05 Significant

**Table 12: Changes in Mean Pain free Rotation with the Treatment**

Duration in Days	Mean Rotation (°) ( $\bar{X} \pm SD$ )
Basal	29.38 ± 18.60
3	29.38 ± 18.60
15	*42.19 ± 30.49
30	*40.77 ± 24.99
45	*38.57 ± 22.68

By Student "t" Test

\* P &lt; 0.05 Significant

**Table 13: Changes in Mean pain free st. Leg raising after the treatment**

Duration in Days	Mean Leg Raising (°) ( $\bar{X} \pm SD$ )
Basal	40.71 ± 20.09
3	42.50 ± 21.39
15	*61.67 ± 18.20
30	*82.50 ± 11.65
45	*90.00 ± 0

By Student "t" Test

\* P &lt; 0.05 Significant

The drug was well tolerated. The adverse effects were mild to moderate in nature and were seen 75% of the cases. Nausea (40%), anxiety (30%) and headache (15%) were commonly reported adverse effect, which resolved with continued treatment. Table 14 lists the adverse effect profile. According to the investigator headache, malaise, nausea, anxiety, and palpitation burning sensation in limbs were possible related to calcitonin treatment.

**Table 14: Adverse Events**

EVENTS	NO. OF CASES (N = 20)	PERCENTAGE
Malaise	01	05.0
Dyspnoea	01	05.0
Anxiety	06	30.0
Nausea	08	40.0
Vomiting	02	10.0
Dryness of Mouth	01	05.0
Vertigo	02	10.0
Warm feeling in palms/Ear Lobe	02	10.0
Loss of appetite	02	10.0
Pain in abdomen with Diarrhoea	02	10.0
Palpitation	01	05.0
Burning sensation in sole	02	10.0
Diarrhoea	01	05.0
Headache	03	15.0
Anorexia	01	05.0
<b>Total No. of Patients</b>	<b>15</b>	<b>75.0</b>

## DISCUSSION

Calcitonin has been used since late 1960's for treatment of osteoporosis and Paget's disease. Analgesic properties have also been described and is attributed to release of Endorphin<sup>7</sup>. While therapeutic effects of calcitonin are well studied and documented in osteoporosis and Paget's disease, its analgesic effects are not well studied<sup>8</sup>. Demonstration of analgesic effect of calcitonin in osteoporotic acute vertebral fracture is considered to be due to its effect on bone metabolism, though contribution of central effect was not ruled out.

This study was planned to evaluate use of calcitonin as an analgesic in painful bone diseases like lumbar canal stenosis and other conditions where there is likelihood of neurological involvement secondary to pathological changes in bone tissues. The results of this study indicate that calcitonin given along with methylcobalamin is effective in inducing significant pain relief and improving functional capacity in patients.

Methylcobalamin is biologically active form of vitamin B<sub>12</sub>. It is well known that being neurotropic factor, methylcobalamin may improve neurotic pain that may co exist with chronic painful condition of bone disease like lumbar canal stenosis. However, many studies have not shown any significant benefits with methylcobalamin alone.

As mentioned earlier, calcitonin is shown to have analgesic effect independent of its effect on bone metabolism. The 6 weeks duration of the treatment was designed to minimise analgesic effect due to changes in bone metabolism. Findings of our study indicate that salmon calcitonin has independent analgesic effect. Increase in walking distance in spite of pain suggest better pain tolerance and could be due to calcitonin's endorphin mediated analgesia, as suggested by some investigators.

Majority of our patients suffered from lumbar canal stenosis. The data shows that calcitonin is effective in providing symptom relief and improving the functional capacity of these patients. Our findings are consistent with previous reports. The magnitudes of improvement seen in our study have been better compared to those reported previously. It is likely that methylcobalamin acted in synergistic manner to potentiate analgesic effect of calcitonin. The sample size of the study is relatively small and hence, subjective bias also might have contributed to better results. However, benefits of calcitonin treatment was observed in all the parameters assessed and hence, it is unlikely that subject bias could have played a major role in these findings. A study in large population with well defined disease might help in establishing the analgesic usage of calcitonin.

## CONCLUSION

This open label trial with salmon calcitonin given by intramuscular route with oral or intramuscular methylcobalamin has demonstrated that 4 to 6 weeks treatment provides pain relief and improves functional

capacity of patient with painful bone disease like lumbar canal stenosis.

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