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Research Article

ASSESSMENT OF EFFICACY, SAFETY AND QUALITY OF LIFE IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS USING SALMON CALCITONIN NASAL SPRAY

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ABSTRACT

An open label, prospective, multicentric, single arm post marketing surveillance (PMS) study was carried out to assess the efficacy and safety of Calcitonin nasal spray in the treatment of osteoporotic back pain among postmenopausal women. Fourteen investigators across India in clinical & hospital settings participated in this study. A total of 52 female patients aged 45-65yrs were enrolled and prescribed one spray of nasal Calcitonin (200 IU) daily for 1 month. All of the patients also received daily dose of calcium (1000 mg) and vitamin D (400 IU) supplements orally. After initial assessment of post menopausal osteoporotic patients based on Bone Mineral Density (BMD), efficacy parameters viz. Numeric Pain Scale (NPS) score, on demand Analgesic consumption & Osteoporosis quality of life questionnaire score were compared at baseline (first visit), at 15 days (visit 2) and at 30 days (visit 3) of treatment. Results showed significant improvement in NPS score and osteoporosis quality of life questionnaire score. On demand analgesic consumption was significantly lowered after treatment with Calcitonin nasal spray. Hence it was concluded that treatment with Calcitonin nasal spray was associated with significant improvement in back pain and quality of life among post menopausal osteoporotic patients.

Keywords: Calcitonin, Osteoporosis, BMD, NPS, QOL, Back pain.

INTRODUCTION

Osteoporosis is characterized by bone loss and consequent structural failure resulting in bone fragility and fractures. In osteoporosis, reduction in bone mineral density (BMD), deterioration of bone micro-architecture and alteration of the amount and variety of proteins are hallmark features. Osteoporosis is defined by the WHO as a bone mineral density that is 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by dual-energy X-ray absorptiometry (DEXA). Many of the osteoporotic patients complain of back pain and physical disability but there is no clear evidence relating back pain to low bone mineral density (BMD)[1]. Fractures of the spine (vertebra) can cause severe "band-like" pain that radiates from the back to the sides of the body. Over the years, repeated spinal fractures can lead to chronic lower back pain as well as loss of height and/or curving of the spine due to collapse of the vertebrae. Therefore, the most apparent cause for back pain in osteoporotic patients is vertebral deformities resulting from fractures[2,3]. In postmenopausal women, other reasons may also contribute to back pain such as concomitant degenerative disorders of the spine, and other non-specific factors[4].

The goal of treatment in osteoporosis is to prevent bone loss and fractures and to minimize pain and physical disability. A number of medications are available that prevent bone loss or enhance bone mass and strength. Among the antiresorptive agents currently used are estrogens, selective estrogen receptor modulators, Calcitonin and bisphosphonates. It is generally accepted that Calcitonin is an effective treatment not only in preserving or increasing bone mass but also in reducing fracture risk[5,6]. It has a well defined antiresorptive action on bone, in addition, several studies have proven the analgesic effect of Calcitonin in patients with osteoporotic vertebral fractures[7,8].

Analgesic property of Calcitonin is not limited to be bone specific, it has also been shown in patients suffering from pain of extraskeletal etiology such as migraine[9], phantom limb pain syndrome[10] and reflex sympathetic dystrophy[11]. However, the effect of Calcitonin on chronic back pain and physical disability of patients suffering from reduced BMD, with or without fractures, has not been studied.

The aim of this study was to investigate the effect of nasal Calcitonin on chronic back pain and quality of life in osteoporotic postmenopausal women.

MATERIALS AND METHODS

This was an open label, prospective, multicentric, single arm post marketing surveillance (PMS) study. The study was conducted by independent Principal Investigator (PI) and co-investigators after obtaining IEC (Independent ethics committee) approval. Investigator team members were trained on protocol and protocol related procedures and whole study was conducted in comply with GCP guidelines.

The present study was multicentric, carried out at 14 different sites within India. Fifty two patients were enrolled into the study. Study population consisted of patients aged 45-65 yrs (mean age 62 yrs) suffering with osteoporosis. Strict inclusion and exclusion criteria for the study were followed during enrollment of the patients. The inclusion criteria were postmenopausal women between 45-65 years of age or surgical menopausal (oophorectomy) cases & bone mineral density (BMD) values - 2.5 SD in at least one region measured by Dual Energy X-ray absorptiometry (DEXA). Those patients were excluded who were having presence of secondary causes of osteoporosis and other possible causes of back pain (fragility fracture, bone metastasis or inflammatory spine disease such as spondyloarthritis) or who were using medications that can cause osteoporosis or those who had any contraindications for use of salmon Calcitonin or calcium and patients having history of taking anti-osteoporotic agents in the last month.

Written, informed consent (IC) was obtained from these patients after giving a thorough explanation of the purpose and potential benefits and risks of the study. Detailed history of the patients along with physical examination was performed at the first visit. Demographic characteristics and BMD of Lumbar spine (L1-L4) and hip were evaluated.

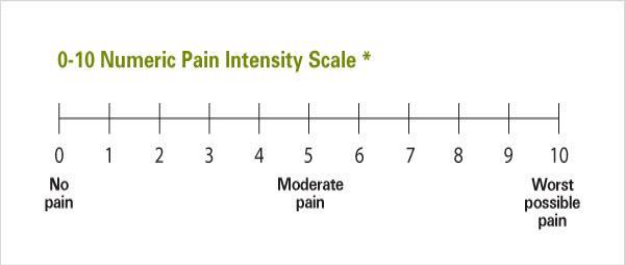
The patients enrolled for study were treated with Calcitonin nasal spray, one spray daily (containing 200 IU of Calcitonin) on alternative nostrils for a period of 1 month. During the treatment period, patients were instructed to take analgesic tablets, on as and when required basis. They were also instructed to maintain a weekly

record of analgesic dosage for a period of 1 month. All the patients received daily dose of calcium (1000 mg) and vitamin D (400 IU) orally. The patients were followed up twice on 15th day and 30th day. Statistical analysis was done using descriptive data and applying paired t-test.

At first visit, study patients were assessed for their initial BMD values. Mean BMD value for lumbar spine was -0.48 ± 2.91 (Between -4 to 3.4) and for femur was -0.10 ± 2.82 (Between -4.2 to 2.9). Patients were assessed at each of the visits by the investigators for the following:

1. Pain assessment scale (Numeric Pain Scale, NPS)

The levels of spontaneous pain are indicated by means of a 10 cm graduated scale, on which the patient could estimate the intensity of pain represented by a point between the extremes of "no pain at all" and "most severe pain." The patient rates his/ her pain on this line. This was done at the base line and at every follow up visits.



***Pain was scored on a scale ranging from 0 to 10 as follows: 1-4: Mild pain; 5-6: Moderate pain; 7- 10: Severe pain.**

According to the patient's self assessment, pain is graded and compared before, during and after treatment.

2. On demand Analgesic consumption

The investigator reported carefully in the Case Record Form the number of analgesic tablets used, if needed, for each patient from the patient's self recording of analgesic requirements. This was evaluated in terms of number of tablets of analgesics consumed during the treatment period with the study drug.

3. Osteoporosis quality of life questionnaire

QOL questionnaire was administered at every follow up visits. The various parameters in quality of life questionnaire like back pain, its severity, back pain disturbing the sleep and carrying out the household activities were evaluated at each visit.

The safety aspect of the study drug for any adverse events along with patient's quality of life was assessed by an osteoporosis quality of life questionnaire at each follow-up visits.

RESULTS

The mean pain score assessed by numerical pain scale (NPS) was found to be 7.96 ± 0.24 at visit 1 which was reduced to 5.04 ± 0.21 (p< 0.001) and 2.73 ± 0.17 (p< 0.001) at visit 2 and 3 respectively (Figure 1). The difference was found to be statistically significant.

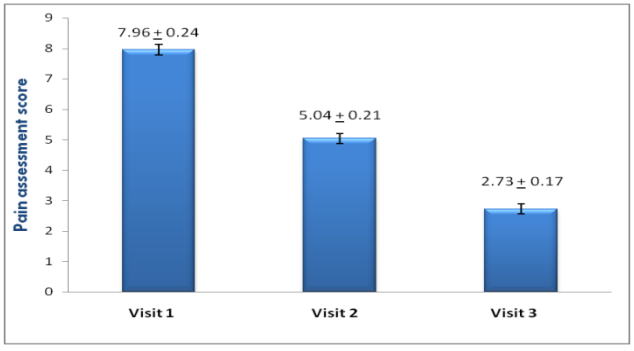


Figure 1: Pain assessment score at Visit 1, 2 and 3

The mean analgesic consumption of the tablets was 2.09 ± 0.15 at visit 1 which was reduced to 1.40 ± 0.13 (p< 0.001) and 0.86 ± 0.10 (p< 0.001) at visit 2 and 3 respectively. The difference was found to be statistically significant (Figure 2).

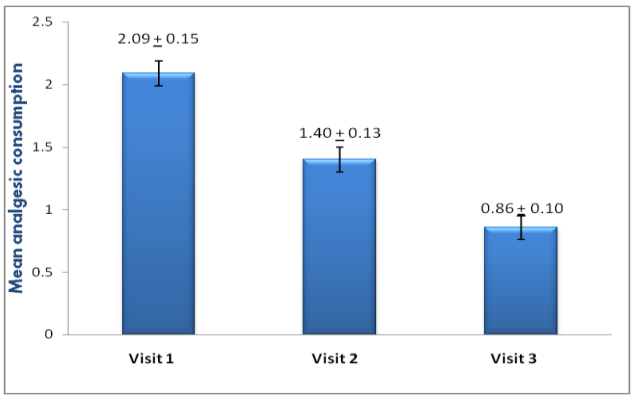


Figure 2: Analgesic consumption at Visit 1, 2 and 3

The various parameters in quality of life questionnaire like back pain, its severity, back pain disturbing the sleep and carrying out the household activities, showed the statistical significant improvement (p<0.001). Mean osteoporosis Quality of Life Questionnaire-Composite Score was 18.19 ± 0.68, 13.60 ± 0.47 and 9.18 ± 0.35 at visit 1, 2 and 3 respectively (Figure 3).

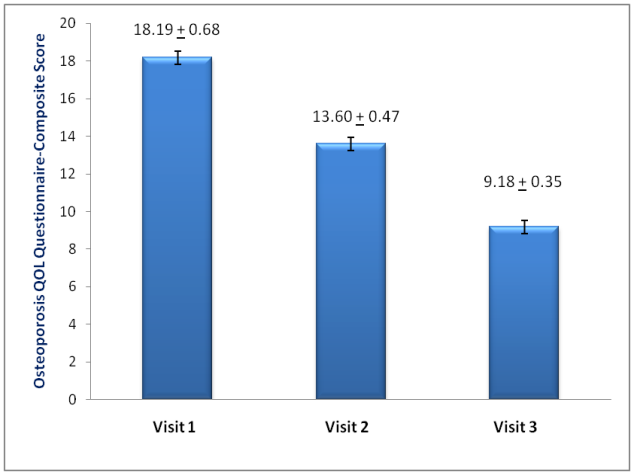


Figure 3: Osteoporosis Quality of Life Questionnaire-Composite Score at visit 1, 2 & 3

There was no adverse event reported except in one patient who complaint of nasal mucosa irritation.

DISCUSSION

Several studies have focused on the analgesic effect of Calcitonin in osteoporotic patients with vertebral fractures[7,12]. However, there are no data regarding the analgesic effect of intranasal Calcitonin on chronic back pain and disability in post menopausal women with osteoporosis, without vertebral fractures. Though mechanisms of the analgesic effect of Calcitonin are not yet fully understood, yet experimental studies have shown that Calcitonin may inhibit prostaglandins' synthesis or can interfere with the calcium flux between neural tissue and cerebrospinal fluid[13,14].

Experimental and preclinical evidences have supported the theory that Calcitonin may have a direct action on specific receptors in the central nervous system[15,16]. Calcitonin receptors are located in areas of brain responsible for pain transmission and modulation such as mesencephalon and periaqueductal gray matter[15]. Moreover rise in plasma levels of H-endorphins has been observed in patients who were given salmon Calcitonin[17]. Beta-endorphins belonging to the

family of endogenous opioids are produced by the pituitary gland[18]. The analgesic role of circulating Beta-endorphins is however uncertain[19]. Experimental studies in animals suggest that Calcitonin binding sites exist in the pituitary gland[20] also and might interfere with its secretory function. The treatment of osteoporotic women with back pain is usually focused on prevention of bone loss, fractures rates, and reduction of back pain and disability.

Nasal administration of Calcitonin is effective in preventing bone mass loss and decreasing the incidence of vertebral fractures[5]. Additional clinical evidences suggest that Calcitonin may have analgesic properties in acute and chronic back pain due to osteoporotic vertebral fractures. Intranasal salmon Calcitonin was shown to be equally effective as its intramuscular or rectal administration in decreasing acute pain and improving functional capacity in postmenopausal women with recent vertebral fractures[7,21,22]. In a randomized study of recent vertebral fractures, Calcitonin has shown a marked decrease in pain intensity accompanied by early mobilization and gradual improvement of functional status[23]. Furthermore, it has been claimed that Calcitonin is equally effective in chronic back pain due to osteoporotic vertebral fractures. *Peichl* and associates examined the effect of 200 IU intranasal salmon Calcitonin on bone density, fracture rate and chronic pain in a group of 24 postmenopausal women with established osteoporosis[8]. The authors administered the Calcitonin intranasally for 12 months and measured the pain intensity at baseline and at the end of the treatment using a Visual Analogue Scale. They found a 42% pain reduction in the Calcitonin group, and 23% in the control group ($P<0.05$). This finding was reflected by early restoration of sitting, walking and standing in the Calcitonin group.

The results from our study consolidated this observation. We examined the effect of 1 month treatment with intranasal salmon Calcitonin plus calcium on chronic back pain and daily activities in osteoporotic postmenopausal women. We found that Calcitonin combined with calcium had beneficial effect on chronic back pain in osteoporotic women with concomitant degenerative disorders or non-specific back pain, There was a significant statistical difference in chronic back pain intensity before and after treatment with Calcitonin nasal spray. These findings could be clearly attributed to the Calcitonin. However, the beneficial effect of Calcitonin in patients with acute pain, which has been reported by several authors, could be related to the different pathophysiological mechanisms governing the two entities of acute and chronic low back pain[24]. Further studies involving multiethnic population may be more conclusive and revealing with additional findings to investigate the role of Calcitonin in patients with chronic back pain if replicated on large multicentric samples.

Conclusion

Intranasal Calcitonin clearly appears to exert beneficial effect on chronic back pain and functional capacity in post menopausal women with osteoporosis regardless of the presence of fractures, degenerative disorders or chronic back pain of non-specific origin.

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