

A Comparative Study of Salmon Calcitonin and Zoledronic Acid in the Treatment of Osteoporosis

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Abstract: *Objective:* To compare increase in BMD following treatment with salmon calcitonin or zoledronic acid in osteoporosis and to compare the side effects of each drug. *Materials and method:* 50 patients (25 in each group) who attend the orthopaedics department of RIMS during October 2012 and September 2014 and who fulfil the inclusion criteria are included in the study. The subjects are distributed in two groups, on random basis, one treated with salmon calcitonin and the other group treated with zoledronic acid with equal amount of supplemental calcium and calcitriol combination. A BMD by DEXA scan was measured at the start of therapy, after 6 months of therapy and at the end of 1 year of therapy and the results compared. Statistical analysis was performed using independent T-test value. *Result:* Zoledronic acid causes better improvement of the bone mass as compared to intra nasal salmon calcitonin in my study.

Keywords: Osteoporosis, BMD, DXA scan, T-score, Salmon calcitonin, Zoledronic acid

1. Introduction

Osteoporosis is a systemic disorder of the skeleton characterized by a low total skeletal bone mass and micro-architectural deterioration of bone mass with a consequent increase in bone fragility and susceptibility to fractures. It is a preventable condition¹. The World Health Organisation (WHO) operationally defines osteoporosis as a bone density that falls 2.5 standard deviations (SD) below the mean for young healthy adults of the same sex-also referred to as a T-score of -2.5. World Health Organisation Diagnostic Criteria for woman without fragility fractures:

Diagnosics	BMD criteria
Normal	BMD value within 1 SD of the young adult mean.
Osteopenia	BMD value between -1SD and -2.5 SD below the young adult mean.
Osteoporosis	BMD value at least -2.5 SD below the young adult mean.

BMD stands for bone mineral density. It refers to the amount of mineral matter per square centimetre of bone. Osteoporosis is the most common metabolic bone disorder². It is a major global public health problem associated with significant morbidity, mortality, and socioeconomic burden³. The prevalence of osteoporosis increases with age for all sites and by World Health Organization (WHO) definition, up to 70% of women over the age 80 years have osteoporosis⁴. Based on 2001 census, approximately 163 million Indians are above the age of 50; this number is expected to increase to 230 million by 2015⁵. The total affected population at present would, therefore, be around 25 million⁶.

Several noninvasive techniques are available for estimating skeletal mass or density. They include dual-energy x-ray absorptiometry (DXA), single-energy x-ray absorptiometry (SXA), quantitative CT, and ultrasound (US)¹.

DXA is a highly accurate x-ray technique that has become the standard for measuring bone density in most centers. Though it can be used for measurement in any skeletal site, clinical determinations usually are made of the lumbar spine and hip. It is a standard practice to relate the results to "normal" values by using T-scores, which compare individual results to those in a young population that is matched for race and sex. Z-scores compare individual results to those of an age-matched population that also is matched for race and sex¹.

Treatment of a patient with osteoporosis frequently involves management of acute fractures as well as treatment of the underlying disease. Treatment includes risk factors reduction, nutritional therapy, exercise and pharmacological therapy. Pharmacological therapy includes Estrogen, Progesterone, Selective estrogen receptor modulators (SERMs), Bisphosphonate, Calcitonin, Denosumab and Parathyroid hormone¹.

Calcitonin is a polypeptide hormone produced by the thyroid gland. Calcitonin preparations are approved by the FDA for Paget's disease, hypercalcemia, and osteoporosis in women >5 years past menopause¹. Calcitonin is commercially available as salmon calcitonin. Salmon calcitonin and human calcitonin differ structurally at amino acids 2, 8, 11-13, 15-17, 19, 20, 22, 24, 26, 27, 29, and 31⁷.

The pharmacological properties of these calcitonins are the same, but salmon calcitonin is substantially more potent on a weight-by-weight basis (approximately 40-50 times that of human calcitonin) and has a longer duration of action⁸. There are approximately one million calcitonin receptors per rat osteoclast⁹. However, calcitonin is only approved by the US FDA for the treatment of established osteoporosis, not for the prevention of postmenopausal osteoporosis¹⁰. Salmon calcitonin (SCT) is administered either parenterally (intramuscular injection or subcutaneous (SC) injection) or intranasally. More recently, several microencapsulation techniques for oral administration of SCT are under development.

Intranasal SCT is indicated for the treatment of osteoporosis in women who are > 5 years postmenopause with low bone mass. Its clinical and biologic effects similar to those of the IM version. The mean bioavailability of the nasal spray approximately 3% of that of injectable calcitonin in normal subjects. It significantly increases the lumbar vertebral BMD as early as 6 months, with persistence up to 2 years. Although the increase in BMD is relatively modest compared with that of the other antiresorptive drugs, long term calcitonin therapy has been associated with a 30%-35% reduction in fractures. No effects on cortical bones of forearm or hip is demonstrated. Tolerance is better than with the parental route of administration. Rhinitis, epistaxis and sinusitis have occurred in 12%, 3.5% and 2.3% patients, respectively.

Zoledronic acid is a potent bisphosphonate with unique administration regimens (once yearly IV)¹. Zoledronic acid is a nitrogen-containing bisphosphonate. Its main structure has a phosphorus-carbon-phosphorus core with a hydroxyl group attached to the R1 position¹¹. Zoledronic acid is a potent inhibitor of bone resorption. It inhibits osteoclast proliferation¹² and induces osteoclast apoptotic cell death¹³. The data suggest that it is highly effective in fracture risk reduction. In a study of >7000 women followed for 3 years, zoledronic acid (5 mg as a single IV infusion annually) reduced the risk of vertebral fractures by 70%, nonvertebral fractures by 25%, and hip fractures by 40%. These results were associated with less height loss and disability. In the treated population, there was an increased risk of atrial fibrillation (2%) and arthralgia and a 15% risk of fever in comparison to placebo¹.

Zoledronic acid is the most potent bisphosphonate studied to date. Once-yearly zoledronic acid was initially approved for the treatment of multiple myeloma and for patients with metastases from solid tumors. However it is now approved by the FDA for the treatment of postmenopausal osteoporosis. The most frequent adverse events occurring in patients receiving zoledronic acid were pyrexia, myalgia, bone and musculo-skeletal pain. The rates of renal and cardiovascular adverse events, including atrial fibrillation were minimal. Zoledronic acid should be administered through a separate vented infusion line as a single 5 mg infusion once a year given over no less than 15 minutes. The solution should not come in contact with any calcium or divalent cation containing solution. Administration of Zoledronic acid is not recommended in patients with severe renal impairment (creatinine clearance < 35 mL per minute). Serum creatinine should be monitored before each dose. All patients should have a routine oral exam prior to treatment. Patients must be appropriately hydrated before the administration of zoledronic acid. Patients must be adequately supplemented with calcium and vitamin D. Zoledronic acid can cause foetal harm. Women of child bearing potential should be advised of the potential hazard to the foetus and avoid becoming pregnant.

2. Materials and Methods

A comparative randomised control study was carried out in Regional Institute of Medical Sciences, Imphal from October 2012 to September 2014. The patients who attend

the orthopaedics department during the study period and who fulfil the inclusion criteria will be taken as sample size. At least 50 patients (25 each) will be given either salmon calcitonin (intra-nasally 100 IU/day) or zoledronic acid (IV infusion 5 mg single dose) on random basis. The inclusion criteria included patients of primary osteoporosis with BMD score < 2.5 and 12 months follow up possible. The exclusion criteria included patients with secondary osteoporosis, 12 months follow up not possible and patients with other significant medical co-morbidity. Ethical approval shall be taken from RIMS- IEC before starting the study. Subjects shall be distributed in 2 groups, on random basis, one treated with salmon calcitonin and the other group treated with zoledronic acid with equal amount of supplemental calcium and calcitriol combination.

Informed consent will be taken from all participants and consent for minor will be taken accordingly all details of participating individuals will be recorded. Blood routine examination, urine routine examination, chest X-rays and BMD by DEXA scan shall be done routinely. Where indicated, X ray skull, pelvis, spine, liver function test, kidney function test and serum electrolytes, serum vitamin D, serum phosphorus, serum calcium, serum alkaline phosphatase, M band electrophoresis, urinary Bence-Jones proteins, USG whole abdomen and bone marrow biopsy will be done on selected cases.

Patient will be followed up after 3 months, 6 months, and 12 months. A BMD by DEXA scan will be done after 6 months and at 1 year of treatment and the results compared.

3. Results

A total of 50 patients were included in the study (25 patients for each group) from October 2012 to September 2014. Out of the 50 patients, the number of males is 10 and that of female is 40. Males and females ratio is 1:4.

The T-score of the salmon calcitonin group at the start of therapy ranges from -2.7 to -4.3 with a mean of -3.46 ± 0.46 whereas the T-score of the zoledronic acid group at the start of therapy ranges between -2.5 to -4.3 with a mean of -3.36 ± 0.50 . The T-score of the salmon calcitonin group after 6-months of therapy ranges from -2.0 to -3.5 with a mean of -2.76 ± 0.46 whereas the T-score of the zoledronic acid group after 6 months of therapy ranges between -1.7 to -3.0 with a mean of -2.45 ± 0.44 . The T-score of the salmon calcitonin group after 1-year of therapy ranges from -1.2 to -2.8 with a mean of -1.99 ± 0.45 whereas the T-score of the zoledronic acid group after 1 year of therapy ranges between -0.9 to -2.0 with a mean of -1.45 ± 0.41 . The independent T-test value at the start of therapy is 0.71, after 6 months of therapy is -2.41 and after one year of therapy is -4.39.

The degree of freedom at the start of therapy, after 6 months of therapy and after one year of therapy is 48. The p-value at the start of therapy is 0.48 which is not significant. The p-value after 6-months of therapy is 0.02 which is significant and the p-value after one year of therapy is 0.0 which is significant.

Table: The distribution and comparison of T-score in the two groups at the start of therapy, after 6 months of therapy and after 1 year of therapy.

Time points	Salmon calcitonin group (mean \pm SD) of T-score	Zoledronic acid group (mean \pm SD) of T-score	Independent 'T' test value	Degree of freedom	'p' value and inference
At the start of therapy	-3.46 \pm 0.46	-3.36 \pm 0.50	0.71	48	0.48(not significant)
After 6-months of therapy	-2.76 \pm 0.46	-2.45 \pm 0.44	2.41	48	0.02 (significant)
After 1-year of therapy	-1.99 \pm 0.45	-1.45 \pm 0.41	4.39	48	0.00 (significant)

In my study it is seen that the T-score of two groups are comparable at the start of therapy as the p-value is not significant. Also, it is seen that the T-score of the zoledronic acid group shows higher value at 6 months and at 1 year of therapy compared to the intra nasal salmon calcitonin group. Therefore it can be concluded that zoledronic acid causes better improvement of the bone mass as compared to intra nasal salmon calcitonin in my study.

In the salmon calcitonin group, the patients do not have any complaints regarding the drug on follow up. In the zoledronic acid group, the major complaint is fever on the following day after injection in 8 patients (32%) followed by myalgia in 4 patients (16%). No major adverse events or death were reported in both the study groups.

4. Discussion

Osteoporosis is a major global health problem associated with significant morbidity and socio-economic burden. It is a preventable condition. Most commonly it affects post-menopausal women reflecting a hormonal cause in the development of osteoporosis. Women are especially at risk if they have a premature or surgical menopause and have not received hormone therapy.

Osteoporosis can lead to a number of health problems with significant morbidity and mortality such as chronic backache, VCF, fracture neck of femur, trochanteric fracture, colles fracture etc.

Bone mass loss (osteopenia) must, therefore, be seen as a risk factor for fracture but not diagnostic of the disease itself (osteoporosis). Nevertheless, depending on the site measured, there is 1.5 to 2.5 increased fracture risk for every standard deviation below the norm for a given age group and bone site.

The results of this randomized study support the view that intra-nasal calcitonin and yearly zoledronic acid infusion increase the bone mass as reflected by improvement in T-score after 6 months and 1 year of therapy.

The results of these pooled randomised data support the view that salmon calcitonin decreases the risk of vertebral

and non vertebral fractures. It is unlikely that the calculated odds ratios would have arisen by chance. There are, however, a number of limitations to consider. Firstly, a large number of publications did not report the occurrence of fractures. It is possible, but unlikely, that no fractures occurred in these studies. It might also be the case that publication biases arose, in that studies with more fractures in the treated than control arm would be less likely to mention fractures in the report. Even if it is assumed that no publication bias occurred, but that some fractures occurred but were unreported, the degree of risk reduction of vertebral or other fractures cannot be computed from the present analysis. A second source of bias may have arisen because several of the studies, although randomised, were open rather than double blind. If patients on active treatment took additional steps to prevent fracture, a component of the effect could be due to contamination. Thirdly, the duration of studies was relatively short and in only two did it exceed 2 years. The long-term effects on fracture frequency can therefore not be derived.

The result of my study show that 100 IU of salmon calcitonin nasal spray per day significantly reduces the risk of fractures in osteoporotic patients and increase T-score after 6 months and 1 year of therapy. The effect on vertebral fractures was accompanied by a modest increase in lumbar spine bone mineral density and a decrease in bone resorption. In the present study, there was an improvement in the mean T-score by 1.47 \pm 0.01. This is comparable with the study of Reginster et al who reported a gain of 1.38 \pm 0.38¹⁴.

Previous studies with intra nasal salmon calcitonin suggested that resistance may develop with continued use because of antibody formation, down regulation of receptor sites or counter-regulatory mechanism. The result of this study, however, demonstrate a sustained effect in terms of reduction of fracture risk at the spine, maintenance of improved bone mineral density, and suppression of bone turnover during 1 year of observation.

Although vertebral fractures are the usual presenting manifestation of osteoporosis and are associated with substantial morbidity, fractures of the hip have greater morbidity, mortality, and cost. Although definite conclusions on the risk of hip fracture cannot be drawn from our study, we did observe a reduction in the risk of hip fracture in the salmon calcitonin nasal spray 100 IU. Further studies are indicated to determine the effect of salmon calcitonin nasal spray on the risk of hip fracture. Salmon calcitonin nasal spray was well tolerated by the elderly patients. The rate and reasons for discontinuation were distributed equally among treatment groups. Intolerance to the nasal group did not contribute significantly to study discontinuation. No patients discontinued for this reason. In my study, there was an improvement of 1.91 \pm 0.09 in the mean T-score of the lumbar spine after 1 year of therapy with zoledronic acid. This is comparable with the study of Recker et al who reported a gain of 2.05 \pm 0.32¹⁵.

The safety profile for zoledronic acid indicated few areas of concern. There were transient post infusion symptoms, as previously reported in patients of intravenous zoledronic

acid. We didn't find any incidence of renal adverse events. Although an increase risk of atrial fibrillation was unexpectedly observed in one zoledronic acid study involving postmenopausal women, but we found no increase risk no atrial fibrillation. My study has several limitations.

- 1) Sample size is small, 25 in one group.
- 2) Short duration of study.
- 3) Wide range of age variation.

5. Conclusion

The availability and effectiveness of annual zoledronate infusion for the treatment of osteoporosis heralds a new era in the management of osteoporosis, because it virtually eliminates the compliance problem.

Upper gastrointestinal adverse effects are one of the main factors limiting the use of oral bisphosphonates. Because zoledronic acid is IV administered, it bypasses the gastrointestinal tract, so these adverse effects are rarely seen. The positive effect of zoledronate in the prevention of fractures after the patient has sustained a hip fracture introduces the concept of administering it while the patient is hospitalised for an osteoporotic fracture. This will reduce the number of patients who sustain an osteoporotic fracture and are neither diagnosed nor treated for osteoporosis.

The need for an IV infusion may deter a few patients, particularly in geographic areas where IV infusion are not frequently administered and the patient may need to be referred to a secondary medical centre.

Daily administration of 100IU salmon calcitonin nasal spray over a period of 1 year was found to be an additional therapeutic regimen for routine use. Calcitonin is an alternative to Hormone Replacement Therapy (HRT) or bisphosphonates in the treatment of osteoporosis, while its central analgesic effect is of great benefit in advanced stages of osteoporosis associated with pain the locomotor system and reduced activity.

In conclusion, intranasal salmon calcitonin is well comparable to zoledronic acid in terms of efficacy as well as paucity of side effects. However, zoledronic acid is given once yearly but intra-nasal salmon calcitonin has to be given daily.

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