Original Research Article

# Role of intravenous zoledronic acid in treatment of osteoporosis

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## Abstract

**Background:** Zoledronic acid is used this to prevent or treat osteoporosis in men and post-menopausal women and patients on glucocorticoids. However, the clinical evidence in the effect of Zoledronic acid on osteoporosis and its complication is conflicting. **Aim:** To determine the increase in Bone Mineral Density among patients treated with Zoledronic acid using Dual X-Ray Absorbtiometryto track and document improvement. **Material and Methods:** A total of 30 subjects were recruited by simple random sampling. The baseline BMD of all the participants was measured using DEXA scan. Single dose of Zoledronic acid 5 mg by intravenous infusion is given over at least 15 minutes to all patients. The repeat BMD of all the participants was measured after 6 months of Zoledronic acid infusion to find its effect. **Results:** The mean BMD of lumbar spine increased significantly from pre-infusion value of 0.79 g/cm2 to post-infusion of 1.32 g/cm2. The T-score also increased from pre-infusion value of -2.367 ± 0.87 to -1.488 ± 0.06 in 6 months following the infusion. The increase is 37.13% higher than pre infusion values. There was a statistically significant improvement in the BMD values 6 months after infusion of Zoledronic acid. **Conclusion:** Over a short term period, the study concludes that Zoledronic acid has positive benefit in enhancing the T-Score values in osteoporosis and osteoporotic patients.

**Key Words:** Osteoporosis, Zoledronic acid, Body mass index, T-scan, DEXA scan.

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## INTRODUCTION

Osteoporosis is a skeletal disease that is characterized by compromised bone strength predisposing a person to an increased risk of fracture.[1] In the absence of fragility fracture, bone mineral density (BMD) is a proxy measure that accounts for up to 70% of bone strength. It is the clinical tool used to diagnose osteoporosis according to the classification of the World Health Organization. BMD is this a useful indicator to assess the fracture risk among patients with osteoporosis. Fractures associated with osteoporosis are a major cause of morbidity, disability, mortality, and costs.[2] Zoledronic acid is an anti-resorptive agent that acts by slowing down osteoclast mediated bone resorption, thereby increasing bone density and decreasing the amount of calcium released from the bones into the blood stream. Zoledronic acid is used this to prevent or treat osteoporosis in men and post-menopausal women and patients on glucocorticoids.[3] However, the clinical evidence in the effect of Zoledronic acid on osteoporosis and its complication is conflicting. So, this study was conducted to determine the increase in Bone Mineral Density among patients treated with Zoledronic acid using Dual X-Ray Absorbtiometry to track and document improvement.

## MATERIAL AND METHODS

This prospective study included was conducted over a period of two years in the Department of Orthopedics of Vinayaka missions kirupanandavariyar medical college

and hospital, Vinayaka missions research foundation (deemed to be university) Salem, Tamilnadu

**Pilot Study:** A pilot study was carried out to assess the feasibility in terms of collecting the baseline information on distribution of study subjects, time taken per participant, appropriateness of the questionnaire and subject cooperation. Due modifications were made to the questionnaire following this.

**Inclusion Criteria**

- Patients aged between 45 – 85 years, both male and female
- Bone Mineral Density (BMD) with T-Score ≤ -1.5
- Bone Mineral Density (BMD) with T-Score ≤ -2.5 with or without evidence of existing fractures.
- Informed written consent of the patients.

**Exclusion Criteria**

- Patients with hypersensitivity and contra-indication to Zoledronic acid.
- Patients with tumors and parathyroid diseases.
- Patients with any systemic illness, secondary diseases such as Diabetes mellitus, Hypertension etc.

**Study Tools:** The initial part of questionnaire has questions to provide information about demographic details of study subjects. The second part has details about anthropometric parameters like height, weight and BMI. The last part has details about risk factors of osteoporosis like smoking, alcoholism, glucocorticoid therapy, past history of cancer or fracture, menopause history of hysterectomy in case of females.

**DEXA Scan:** Bone Mineral Content (grams), projected bone area (square centimeters), and the derived areal BMD measurements (grams per square centimeters) at the LS spine and proximal femur were obtained by DXA using either GE Lunar Corp. (Madison, WI) or Hologic, Inc. (Waltham, MA) densitometers. LS measurements of L2-L4 (Lunar Corp.) or L1-L4 (Hologic, Inc.) were obtained, and vertebrae with fractures or artifacts were excluded. The stability of the DXA instruments was assessed by serial measurements of a local spine phantom. The variability of DXA measurements across clinical sites was assessed by measuring a spine phantom circulated among sites. The central site for bone mass measurements used the results obtained from the phantom measurements to adjust for drift in densitometric measurements, as necessary. The primary study outcome was change in BMD at the LS. DXA measurements at the LS were obtained in participants at baseline and at 6 months.

**Zoledronic acid treatment:** Single dose of Zoledronic acid 5 mg by intravenous infusion is given over at least 15 minutes to all patients.

**Sample Size:** Assuming a 95% significance level, 80% power, standard deviation of lumbar Bone mineral density37 0.756 g/cm2, and expected differences of 0.05g/cm$^2$, the required sample size was calculated to be 28.

**Data Collection Methodology:** A total of 30 subjects fulfilling the inclusion criteria, were recruited by simple random sampling. Data was collected by filling the pre-tested questionnaire by face to face interview. The baseline BMD of all the participants was measured using DEXA scan. Single dose of Zoledronic acid 5 mg by intravenous infusion is given over at least 15 minutes to all patients. The repeat BMD of all the participants was measured after 6 months of Zoledronic acid infusion to find its effect.

**Statistical Analysis:** Data were analyzed using Statistical Package for Social Sciences (SPSS) version 15.37 The analysis of data was carried out by entering the coded information on the computers and generating tables. The data are presented using descriptive statistics in form of tables and graphs. Results are expressed as proportions with 95% confidence interval. Univariate analysis was carried out using chi square test.

## RESULTS

All individuals both males and females, aged more than 45 years were included in the study. The minimum age recruited was 4 years and maximum was 79 years and mean age was found to be 54.6 ± 4.33 years. Majority of the participants were in the age group of 61-70 years (36.67%) and 51-60 years (33.3%) and the remaining below 50 years. The study included both males and females with a minimal female preponderance. Male subjects contributed to 43.33% and female subjects to 56.67% of the study population. Among the 17 female patients, 11 (36.67%) of them have attained menopause of whom 2 (6.6%) had undergone hysterectomy surgery. Among the 11 patients, 7 have attained menopause for less than 5 years and 4 for more than 5 years. According to WHO Classification of Osteoporosis, proportion of Osteopenia and Osteoporosis among study population were 13 (43.33%) and 6 (20.0%) respectively. Single dose of Zoledronic acid 5 mg by intravenous infusion was given over at least 15 minutes to all patients. The dual-energy X-ray absorptiometry (DEXA) were repeated in all the 30 patients at 6 months following Zoledronic acid infusion. The BMD values in g/cm$^2$ and the T- scores are measured at the lumbar spine and femoral neck to assess the osteoporosis. The lumbar spine BMD was considered as the final outcome. To find the association between the

infusion of Zoledronic acid and BMD, Paired T- test was used. The mean BMD of lumbar spine increased significantly from pre-infusion value of 0.79 g/cm2 to post-infusion of 1.32 g/cm2. The T-score also increased from pre-infusion value of -2.367 ± 0.87 to -1.488 ± 0.06 in 6 months following the infusion. The increase is 37.13% higher than pre infusion values. There was a statistically significant improvement in the BMD values 6 months after infusion of Zoledronic acid. Meanwhile the mean BMD of femoral neck also increased significantly from pre-infusion value of 0.53 g/cm$^2$ to post-infusion of 0.77 g/cm$^2$. The T-score also increased from pre - infusion value of -2.367 ± 0.87 to -1.488 ± 0.06 in 6 months following the infusion which is statistically significant (p-value <0.0001 and 0.0287 respectively).

**Table 1:** BMD and T-score values after Zoledronic acid infusion (n=30)

| | Baseline values | After 6 months of Zoledronic acid infusion | p-value |
|---|---|---|---|
| BMD Femoral Neck | 0.53±0.064 | 0.77 ± 0.09 | <0.0001 |
| BMD Lumbar spine | 0.79±0.140 | 1.32 ± 0.06 | <0.0001 |
| T-Score Femoral Neck | -2.367 ± 0.87 | -1.488 ± 0.06 | 0.0287 |
| T-Score Lumbar spine | -0.835 ± 0.07 | 0.453 ± 0.04 | 0.0343 |

## DISCUSSION

Osteoporosis is a skeletal disease that is characterized by compromised bone strength predisposing a person to an increased risk of fracture. Annual intravenous injection of Zoledronic acid 5mg has been approved by the Food and Drug Administration for the treatment of postmenopausal osteoporosis and treatment of male osteoporosis. In our study, 5 (29.41%) and 6 (35.29%) of the participants who were females had osteopenia and osteoporosis respectively while 8 (61.54%) of males had osteopenia. None of the males had osteoporosis. In a study conducted by Anburajan *et al*[4] at Chennai in a similar setting like ours, pDXA device-specific T-score threshold was used, it was found that 31.8% of female subjects aged 50 years or more were classified as having osteoporosis. No Indian male was found to have osteoporosis. In a study done by Agnes Rakel*et al*[5] in men, the Zoledronic infusion was shown to be non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline (Zol 6.1% vs alendronate 6.2%) Among the 17 female patients, 11 (36.67%) of them have attained menopause of whom 2 (6.6%) had undergone hysterectomy surgery. Among the 11 patients, 7 have attained menopause for less than 5 years and 4 for more than 5 years. About 3 (75.0%) of women who attained menopause for more than 5 years had developed osteoporosis and the rest (25%) had developed osteopenia. Among the Bangladeshi women, Hossain M *et al*[6] did an intervention study to find the effect of single dose intravenous Zoledronic acid on bone mineral density in post-menopausal osteoporosis. The mean BMD of lumbar spine increased significantly from pre-infusion value of 0.75695 g/cm$^2$ to post-infusion of 0.80216 g/cm$^2$. The T-score also increased from pre - infusion value of -3.567 +/- 0.77 to -3.158 +/- 0.08 in 12 months following the infusion (P<0.01). The increase is 5.026% higher than pre infusion values. After the menopause, the incidence of both osteopenia and osteoporosis rose significantly and the time since menopause was found to be a major risk factor in this regard. Mean height was 160±6 cms and mean weight was 59±2.2 kgs. The maximum BMI estimated was 31.8. BMD was higher in obese women, but the difference between this group. From our study results, it is evident that low BMI leads to increased osteoporosis and osteopenia when compared to normal BMI. Unni J *et al*[7] found that the mean BMI of the study group was 26.7. The findings of this study show an inverse relationship between BMI and BMD. With increasing BMI, the number of women with normal BMD score also increased. Acha *et al*[8] studied the relationship between BMI and hip fracture in 2653 individuals of 65 years or older which comprised of 57.9% females and found that individuals who were underweight were at greater risk for hip fracture and higher BMI was associated with lower risk of fracture. They found that each one-unit increase in BMI was associated with 9% decreased risk of hip fracture. The mean BMD of lumbar spine increased significantly from pre-infusion value of 0.79 g/cm$^2$ to post-infusion of 1.32 g/cm$^2$. The T-score also increased from pre-infusion value of -2.367±0.87 to -1.488±0.06 in 6 months following the infusion which is statistically significant (p-value <0.0001 and 0.0287 respectively). The increase is 37.13% higher than pre infusion values. Meanwhile the mean BMD of femoral neck also increased significantly from pre-infusion value of 0.53 g/cm2 to post-infusion of 0.77 g/cm2. Ma Chao *et al*[9] found that the BMD was significantly increased at femoral neck and total hip in ZOL group over three years when compared with placebo group. The mean difference of femoral neck BMD percentage change of ZOL versus placebo was 1.81 (1.54-2.26) at one-year follow-up, and was 3.65(3.31-4.04) at 3 years follow-up. Meanwhile, the mean difference of total hip BMD was 2.12 (1.78-2.45) at one year follow-up, and was 4.26 (3.80-4.81) at three years follow-up. A previous clinical HORIZON trail with 107 patients indicated that intravenous zoledronate therapy significantly increased BMD of lumbar spine

over 3 years.[10] The study by Sheila Anne Doggrell44 suggest that the 70% reduction in vertebral fracture rate observed with Zoledronic acid is greater than that previously reported for oral bisphosphonates (40-50%),[11,12] and one factor that may contribute to this, is the poor adherence to oral bisphosphonates. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Extension trial, used a design with a shorter treatment period (3 years of treatment followed by 3 years of placebo or active extension) and observed that Zoledronic Acid Once-yearly plays a major role in the prevention of non-vertebral Osteoporotic Fractures. Zhang *et al*[13] did a meta-analysis including 9 trials and its pooled effect showed that zoledronic acid could increase the bone mineral density by 2.98 times compared with placebo, and reduce the rate of fracture in patients by 32%. The longer term intervention, more than 12months intervention, could gain a better prevention effect for osteoporosis (OR, 95% CI for BMD was 3.35, 2.77-3.92; for fracture was 0.67, 0.54-0.82). They concluded that zoledronic acid could be effective approach in the prevention of osteoporosis, and could increase the bone mineral density and reduce the risk of facture.

## CONCLUSION

Single dose of Zoledronic acid 5 mg by intravenous infusion was found to be effective in increasing the BMD among individuals suffering from Osteopenia and Osteoporosis. There was a statistically significant improvement in the BMD values and T- score measured at femoral neck and lumbar spine 6 months after infusion of Zoledronic acid. Over a short term period, the study concludes that Zoledronic acid has positive benefit in enhancing the T-Score values in osteoporosis and osteoporotic patients.

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