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Original Research Article

Comparison of the Effect of 2 Mg & 4 Mg IV Zolendronate on Bone Mineral Density at the Lumber Spine on Menopausal Women with Osteoporosis

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Abstract

Background: Postmenopausal osteoporosis is a serious skeletal condition requiring immediate attention to improve the bone mineral density & preventing fractures. Zolendronate is currently most commonly used in the treatment of osteoporosis in postmenopausal women.

Aims & Objectives: To compare the effectiveness of 2 mg and 4 mg iv ZA on the change in the lumbar spine (LS) BMD in postmenopausal women with osteoporosis at one year.

Material & Methods: This randomized controlled clinical trial was conducted in Department of Orthopaedics from January 22 till January 23. The study recruited 60 postmenopausal women in age range 50 -80 yrs who had achieved menpause at least 5 yrs back. Patients were randomized into two groups: Group A- received a single IV infusion of 2 mg zolendronate in 100 ml of normal saline over 30 min & Group B- received a single IV infusion of 4 mg zolendronate in 100 ml of normal saline over 30 min.

Parameters analysed were serum calcium along with albumin, phosphorus, alkaline phosphatase, creatinine, 25(OH) D, plasma intact parathyroid hormone, and bone turn over markers & bone mineral density of lumbar spine (L1‑L4), nondominant FN, and TH were measured at baseline, 6 months, and at 12 months Adverse events were noted.

Results: This randomized controlled clinical trial included 60 osteoporotic postmenopausal patients, out of which 56(94%) had osteoporosis at LS, whereas osteoporosis at FN and TH was present in 15 (25%) and 13 (21%) patients, respectively. The BMD at both LS and FN were raised significantly at 12 months in both Group A & Group B which was statistically significant. But the percentage increment in BMD at 12 months was higher in Group 2 as compared to Group 1.The levels of β-CTX and P1NP showed a reduction at 6 months the effect of which was sustained at 12 months in both the groups. Mild adverse events like fever & flu were noted within 3 days of the drug administration which was symptomatically treated.

Conclusion: The study concludes the better efficacy of 4mg dose over 2 mg dose of iv zolendronate & supports its use in increasing the bone mineral density at lumbar spine at completion of one year.

Keywords: Osteoporosis, Postmenopause, Zolendronate, Bone Mineral Density, Lumbar Spine.

Introduction

Osteoporosis is a disease of the skeletal tissues with reduced bone mineral density (BMD) & distortion of the tissues of bone. Being asymptomatic, it hardly draws attention of the individual until the fractures occur. There is an estimated 61 million people in India with osteoporosis or osteopenia in 2022 out of which 80% are women. [1] The majority of them being postmenopausal women. After menopause, an imbalance occurs in the bone remodelling process, as a result resorptive processes exceed the formative processes resulting in osteoporosis. [2] According to Marwaha RK 2011, prevalence of osteoporosis among postmenopausal women in India ranged from 42.5% to 62%. [3]

Oral bisphosphonates have been used extensively in the treatment of osteoporosis with significant improvement in bone mineral density. [4] Some limitations exist in the long term usage of these drugs with respect to gastrointestinal upset, limited & variable absorption from the gut. Presently, 5 mg zoledronic acid (ZA) iv infusion once a year is used to treat the disease.2 Black DM et al 2007 concluded in their study that ZA 5 mg once in a year reduced both vertebral and nonvertebral fractures with improvement in BMD and bone turnover markers as compared to placebo. [5] In India, both 4 mg & 5 mg dose of ZA are used once in a year to treat postmenopausal osteoporosis depending on the availability. Reid IR et al 2002 [6] & Grey et al 2012 [7] used lower doses of ZA (1 mg, 2 mg, and 2.5 mg) with same results in BMD as the with standard doses of ZA (4 mg and 5 mg) in osteopenic postmenopausal women.

With being cost effective, lowering the dose of the drug would result in reduced adverse events. [8] Few studies are present in the literature comparing the efficacy of 2mg & 4 mg ZA in the treatment of osteoporotic postmenopausal women. [9] Thus this present randomized controlled clinical trial was conducted to compare the effectiveness of 2 mg and 4 mg iv ZA on the change in the lumbar spine (LS) BMD in postmenopausal women with osteoporosis at one year.

Material & Methods

This randomized controlled clinical trial was conducted in Department of Orthopaedics of our tertiary care hospital from January 22 till January 23. The study recruited 60 postmenopausal women in age range 50-80 yrs who had achieved menpa use at least 5 yrs back. An approval from the institutional ethics committee was taken. The participants were informed about the detailed nature of the study & written informed consent taken. Women having chronic infection, secondary osteoporosis, chronic kidney & liver disease, cancer, low serum 25‑OH Vitamin D level, on hormone replacement therapy or undertreatment with bisphosphonates, calcitonin were excluded from this study.

Using computer generated randomization technique the participants were randomly placed in either of the two groups:

1. Group A- received a single IV infusion of 2 mg zolendronate in 100 ml of normal saline over 30 min.
2. Group B- received a single IV infusion of 4 mg zolendronate in 100 ml of normal saline over 30 min.

At baseline, demographic, detailed medical history including smoking, alcohol intake, yrs since menopause were taken. Venous blood was collected & sent for laboratory

investigations i.e. serum calcium along with albumin, phosphorus, alkaline phosphatase (ALP), creatinine, 25(OH) D, plasma intact parathyroid hormone (iPTH), and BTMs. These tests were repeated at 6 months & 1 yr. Electrocardiogram was done for all participants. At baseline & 6 months, thoracic (Lateral and Anteroposterior view) & lumber spine(T4–L4) radiographs were taken to screen for prevalent vertebral fracture. Bone mineral density of lumbar spine (L1‑L4), nondominant FN, and TH were measured at baseline, 6 months, and at 12 months was measured by dual-energy x-ray absorptiometry. After injection participants were monitored for post infusion adverse effects like allergy, palpitations, carpopedal spasms or oliguria. Also each participant was prescribed oral daily calcium (1000 mg) and Vitamin D (500 IU/day).

Statistical analysis

The collected data was tabulated & analysed using statistical software SPSS version 22. Continuous variables were represented as mean ± SD. Categorical variables were expressed as a percentage and were analyzed using Chi‑squared test. Intra-group comparison at (baseline and 12 months) was done using student paired t test. $P < 0.05$ was considered significant.

Results

This randomized controlled clinical trial included 60 osteoporotic postmenopausal patients, out of which 56(94%) had osteoporosis at LS, whereas osteoporosis at FN and TH was present in 15 (25%) and 13 (21%) patients, respectively.

The baseline characteristics were comparable in both the groups with no statistically significant difference. (Table 1) The BMD at both LS and FN were raised significantly at 12 months in both Group A & Group B which was statistically significant. But the percentage increment in BMD at 12 months was higher in Group 2 as compared to Group 1.(Table 2)

The levels of β-CTX and P1NP showed a reduction at 6 months the effect of which was sustained at 12 months in both the groups. Serum calcium, serum creatinine, serum calcium, serum phosphorous levels, serum 25(OH) D, and plasma iPTH were in normal limits during the whole duration of study. Mild adverse events like fever & flu were noted within 3 days of the drug administration which was symptomatically treated.

Table 1 Baseline characteristics of Group A & Group B

Parameters	**Group A (n=30)**	**Group B (n=30)**	**P value**
Age	59±2.97	58±2.01	0.23
Years since menopause	15	13	0.51
Diabetes mellitus	10%	12%	0.64
Hypertension	14%	16%	0.5
Hypothyroid	9%	8%	0.72
BMI	24.8	23.6	0.43
Serum creatinine	0.8	0.83	0.57
Serum calcium	9.07	9.28	0.21
Serum phosphorous	3.73	3.92	0.37
Serum alkaline phosphatase	240±54.02	253±62.42	0.48
Serum 25(OH) D	25.05	26.53	0.74
Plasma iPTH	48.4±18.4	46.5±17.5	0.36
Plasma β CTX	0.64±0.27	0.67±0.56	0.55
Plasma P1NP	67.93	72.41	0.45
BMD –LS	0.698±0.03	0.68±0.06	0.66

BMD - FN	0.7	0.7	0.75
BMD - TH	0.724±0.058	0.755±0.041	0.52

Table 2: Comparison of percentage changes in various parameters at 12 months from baseline

Parameters	Group A	Group B	P value
Percentage change in LS-BMD	4.83±3.46	5.79±4.05	0.54
Percentage change in FN-BMD	1.21	2.43	0.62
Percentage change in TH-BMD	1.45	1.55	0.69
Percentage change in plasma βCTX	57.38	57.49	0.37
Percentage change in plasma P1NP	52.14	52.93	0.11

Discussion

This study was conducted to evaluate the efficacy of single dose administration of zoledronate in postmenopausal women with osteoporosis. Zolendronate like all bisphosphonates is a synthetic analogues of inorganic pyrophosphate. Pyrophosphate regulates bone metabolism & inhibits bone resorption in vitro. ZA has a high affinity for hydroxyapatite but, is resistant to attacks by phosphatases. [10]

In the present study, at baseline, the parameters in both the groups were comparable with no significant difference ($p>0.05$), thus minimising the selection bias.

In both the Groups, BMD showed statistically significant increment at 12 months. But the percentage change was more in Group B participants receiving 4 mg zolendronate than Group A participants receiving 2 mg zolendronate. Similarly, Durgia et al 2021 concluded that 2 mg ZA to be inferior to the 4 mg ZA in relation to BMD at lumbar spine by noninferiority analysis at 12 months. [9] Study conducted by Keegan et al 2004, showed that osteoporotic women with diabetes when treated with alendronate for 3 yrs presented with improvement in BMD at all sites with 6.6% increment at the lumbar spine and 2.4% increment at the hip as compared to placebo. [11] compared 4 mg & 5 mg dosing regimen of ZA iv annually in treatment of postmenopausal osteoporotic women. The study concluded that the BMD at lumbar spine BMD increased significantly from at baseline i.e. from 0.833 (0.132) g/cm^2 to 0.862 (0.132). No significant changes appreciated in BMD of total hip and femoral neck.[10]

Both Group A & B, observed reduced levels of serum alkaline phosphatase, CTX and P1NP at 12 months. Black DM et al 2007 & Grey A et al 2012 observed 50-60% reduction in the levels of these bone markers at 12 months. demonstrated significant decrease in β-CTX from 0.44 to 0.21 & P1NP levels from 55.57 (38.6) ng/ml to 27.26 (10.95) ng/ml from baseline till after treatment.[10]

Reid et al 2002 showed reduction of 49-52% in CTX levels at 12 months. [6] In a study by Grey et al higher the dose of zolendronate higher reductions noted in serum CTX levels. Also serum P1NP levels reduced to 58% with 2.5 mg ZA & 64% with 5 mg ZA in comparison to placebo. [7]

Black et al 2007 noted reduction of CTX levels by 59% & P1NP by 58% after completion of one year. [5]

Adverse events were noted in 25 % of the participants which were transient pyrexia, headache arthralgia, myalgia & flu-like symptoms. [12] Durgia et al study noted adverse events in 43% of the study subjects. [9] Other studies with similar results are Okimoto N 2020 [13], Reid 2010 [6]. Pro-inflammatory cytokines produced by T cells are responsible for the adverse events. [14] Prior prescription of

antihistaminic, anti-inflammatory drugs could reduce the incidence & severity of adverse events. [9]

Conclusion

Osteoporosis is a medical condition requiring daily treatment & thus sustaining compliance is difficult. Administration of IV treatment of Zolendronate annually would be more acceptable to patients & cost effective. 4 mg iv zolendronate have been shown to improve the bone mineral density at lumbar spine at 1 yr completion in postmenopausal osteoporotic women.

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