IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 3 Ser. 9 (March. 2019), PP 29-34
www.iosrjournals.org

Effect of Intravenous Zoledronic Acid on Bone Mineral Density in Geraitrics

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Abstract: *Osteoporosis is a systemic skeletal progressive disease with multiple factors involved in its causation. A huge prevalence rate, a substantial morbidity and a significant mortality risk, is of specific concern especially in elderly. Among the various modalities of evaluation, dual energy x-ray absorptiometry is the one used here for obtaining bone mineral density and T-scores of the patients. In this study the effect of zoledronic acid in improving bone mineral density over an year is seen, in elderly population of Rajasthan, and a significant improvement was seen with minimal side effects, which can be managed conservatively.*
AIM: To study the effect of Intravenous Zoledronic acid on BMD in Geriatric patients with the objective to present and compare the profile of BMD and T-score < 2.5 in geriatric patients attending at orthopedic department of S.M.S. hospital, Jaipur.
Material and methods: It is a hospital based prospective before and after interventional study. Sample size was calculated 81 subjects at 0.05 alpha error and power 80% assuming difference of means to be detected in BMD is 0.01 with SD 0.038.

Date of Submission: 27-02-2019 Date of acceptance: 14-03-2019

I. Introduction

Osteoporosis is "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures" (WHO 1994).[1]At 1993 concensus conference held in hongkong, a definition of osteoporosis was agreed upon which states that osteoporosis is characterized by low bone mass and micro-architectural deterioration of bony tissue, with a consequent increase in bone fragility and increased risk of fracture[2,3].Osteoporosis is operationally defined by WHO as bone density that falls 2.5 SD below the mean for young healthy adults of the same gender (t score < 2.5)[4].

The lifetime risk of an osteoporotic fracture is 13-22% in men and 40-50% in women. Even a small reduction in percentage in the incidence of fragility fracture can help save several thousands of lives and millions of rupees each year. At present times it is totally unacceptable that such a large number population should suffer fracture when these can be prevented by adequate measures[5].

In the pathophysiology of osteoporosis bone remodeling is a fundamental process, for the removal of old bone by resorptive action of osteoclast and osteoblast generating new bone matrix. It takes about 90-120days for one remodeling cycle to complete.At 25-30years of age, skeleton acquires maximum density 'peak bone mass', therefore at about 30years a negative bone balance sets in, so that an average 1% of bone is lost annually. Risk of developing osteoporosis dependson how much bone a person has as a young adult and the rate at which he or she loses it later in life. It is influenced by genetic and environmental factors[6].

Estrogen act as anti-resorptive factor and its deficiency causes bone loss by 2 inter-connected mechanisms, that is, activation of new bone remodeling sites and imbalance between bone formation and resorption is exaggerated.Marrow cells like monocytes, macrophages, mast cells, osteoclast precursor cells and also osteoblast, osteoclast & osteocytes express α & β receptors for estrogen.Also in estrogen deprivation, lifespan of osteoblast is decreased and that of osteoclast is increased. Loss of estrogen causes increased production of RANKL (receptor activator of nuclear factor kappa B ligand) and may reduce production of osteoprotegerin, increasing the recruitment of osteoclast.As the remodeling of bone is started at the surface of the bone, and trabecular bone has a larger surface area compared to the cortical bone. Therefore fracture occurs earliest at the sites where trabecular bone contributes most of the bone strength, so vertebral fractures are a common consequence.Re-modeling of bone is regulated by nerve derived signals like vasoactive intestinal polypeptide(VIP), Calcitonin gene-related peptide (CGRP), Pituitary adenylatecyclase activating peptides (PACAPs), neuropeptide Y (NPY) and substance P(SP) and also neuro-mediators like adrenaline, serotonin & glutamate.[7]

There is a rise in osteoporotic patientsupto 36 million. Prevalence of low bone mineral density is found in more than half the population. The peak incidence of osteoporosis occurs at the age of 50-60 years, which is 10-20 years younger than western nations. About 70% women in India above age of 80years are affected.[8]

Presently available treatment options for osteoporosis includes lifestyle modifications (such as quit smoking and alcohol, avoid sedentary lifestyle, improved protein & calcium rich diet), physiotherapy, drugs (calcium, vitamin-D, bisphosphonates, recombinant paratharmone, hormonal therapy, fluoride, calcitonin, denosumab).[9,10]

Bisphosphonates are potent inhibitors of bone resorption, a third generation highly potent bisphosphonate is zoledronic acid. It is a nitrogen containing bisphosphonate with an imidazole substituent, which has demonstrated more potent inhibition of osteoclast mediated bone resorption. It does not impair bone mineralization, with a better renal and intestinal tolerability therapeutic index[11,12]. It can be infused over 15-20 minutes because of less venous irritation. It is available in prepackaged bottle of zoledronic acid 5 mg/100 mL. After opening the bottle, it is usually stable for 24 hours at 2–8 °C (36–46 °F). If refrigerated, the solution should be allowed to reach room temperature before infusion. Its storage is recommended at 25 °C (77 °F) with excursions permitted to 15–30 °C (59–86 °F). Patients, especially those are on diuretics, should be hydrated prior to administration of zoledronic acid; drinking several glasses of water before leaving home is probably sufficient for most patients or a 250ml infusion of Ringer Lactate prior to drug infusion should be done.[12,13]Also to reduce the risk of hypo-calcemia and for the general bone health, patients should have an adequate intake of calcium and vitamin D. The NOF recommends a daily intake of at least 1200 mg elemental calcium with diet plus supplements, if needed, and vitamin D_3 800–1000 IU/day.[12,14]

Intravenous 5mg single dose of zoledronic acid can suppress resorption of bone for upto 12months, which causes significant reduction in osteoporotic fractures.[15]Zoledronic acid may cause side effects like: bone pain, myalgia, nausea, vomiting, constipation and flu-like symptoms like mild fever with malaise, chills, flushing & fatigue (due to cytokine release and can be managed by acetaminophen). Patient should also be monitored for renal toxicity as there maybe transient increase in serum creatinine in patients with impaired renal function.[13]

diagnosing osteoporosis various techniques are available: X-Rays (if bone density is >50%), 3D quantitative CT scan, bone mineral density by DXA (dual energy x-ray absorptiometry) scan, bone markers and bone biopsy are usually used. Bone marker assay and qCT are quiet costly.Dual energy x-ray absorptiometry is the current gold standard test for assessing the mechanical competence of the skeleton. It provides the bone mineral content and areal bone mineral density. It has been been experimentally seen that there is a strong co-linear correlation between DXA measurement and bone strength[9,10,,16].

CLASSIFICATION:

T-score	**Category**
-1 or above	Normal
Between -1 & -2.5	Osteopenia
-2.5 and below	Osteoporosis

II. Materials And Methods

Our study duration is from the time of approval of the Research Review Board till the follow up was completed (May2017 to December 2018, in patients above 60 years age group attending S.M.S. hospital, Jaipur during April 2017 to December2018. It is a hospital based prosptective before and after interventional study.Sample size was calculated 81 subjects at 0.05 alpha error and power 80% assuming difference of means to be detected in BMD is 0.01 with SD 0.038 (as per seed article). This sample size will validate change in T-score also (as per seed article). Descriptive and Inferential statistical analysis has been carried out in the present study using computer software (SPSS Trial version 23 and primer). The qualitative data were expressed in proportion and percentages, and the quantitative data expressed as mean and standard deviations. The difference in proportion was analyzed by using chi square test, the difference in means among the groups was analyzed using the Paired T Test for Significance level for tests were determined as 95% ($P< 0.05$). Outcome variable is bone mineral density assessed by t-score of hip/ lumbar spine/ radius

Study includes patients of both sex above 60years of age, giving an informed written consent with BMD T-score < 2.5 at hip/ lumbar spine/ radius. We have excluded patients with previous history of prior use of parathormone or bisphosphonate for more than three consecutive months (short term use was acceptable if washout period was there for an year or more), prior strontium treatment, hip replacement, kyphosis or scoliosis. Also excluded patients currently on thyroxine, steroids, immunosuppressive therapy, anti-epileptics, calcitonin, anti-tubercular treatment, hormone replacement therapy, gonadotropin releasing hormone.pre-existingVitamin-D deficiency, malignancy, stroke, hemi/paraplegia, chronic kidney disease, chronic liver disease, rheumatoid

arthritis, chronic pulmonary disease, organ transplantation or bed ridden patients and patients with history of allergy to bisphosphonates.

III. Results & Observations

In this study we are comparing the T-scores pre and post drug intravenous zoledronic acid administration with a follow up period of 1year, so to quantify the benefit.

Table No 1: Distribution of study population

Total number of cases at the beginning of the study	95
Mortality	4
Patients lost to follow up	10
Final study populations	81

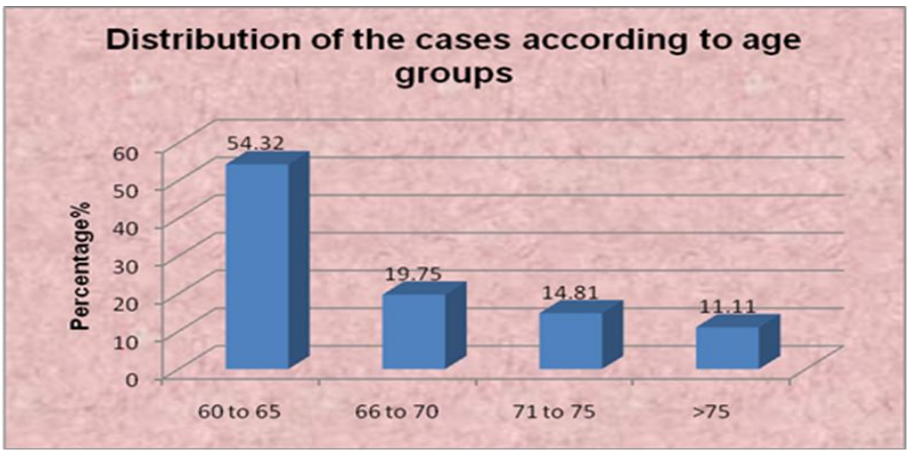

Figure1

Here we have conducted a study over a total of 95 patients as mentioned in table no 1. Out of 95, 10 patients were lost to follow up. 4 patients have expired during the study period, and a certain drug related cause couldn't be established as it could be age related mortality also. So, a total of 81 patients (69 females and 12 males) completed the study. Figure 1 shows the age was distribution of patients.

Table No 2: Paired Samples Statistics and Paired T Test of (T-score of Lumbar Spine Post –Pre injection)

Paired Samples Statistics						Paired Differences		t	df	Sig. (2-tailed)
POST –PRE T-score		N	Mean	Std. Deviation	Std. Error Mean	Mean	Std. Deviation			
Pair 1	Post T L1	70	-2.90	1.00	0.12	.23	.29	6.62	69	<0.001S
	Pre Spine T L1	70	-3.13	1.12	0.13					
Pair 2	POST T L2	70	-2.907	1.1739	.1403	.35	.60	4.79	69	<0.001S
	Pre T L2	70	-3.253	1.1472	.1371					
Pair 3	POST T L3	70	-2.93	1.32	0.16	.18	1.13	1.33	69	.189
	Pre T L3	70	-3.11	1.53	0.18					
Pair 4	POST T L4	70	-3.20	1.17	0.14	.33	.31	8.93	69	<0.001S
	Pre T L4	70	-3.53	1.24	0.15					
Pair 5	Post lumbar Total T-score	67	-2.997	1.0237	.1251	.31	.37	6.93	66	<0.001S
	Pre lumbar Total	67	-3.306	1.0501	.1283					
Pair 6	Post T femur neck	22	-2.59	0.80	0.17	.20	.35	2.73	21	.012
	Pre T femur neck	22	-2.80	0.93	0.20					
Pair 7	Post T Lower 1/3radius	10	-4.61	1.56	0.49	.52	.10	15.92	9	<0.001S
	Pre Lower 1/3 radius	10	-5.13	1.58	0.50					

The mean bone mineral density (T score) by DXA scan of total lumbar spine, femoral neck and lower one-third radius showing the mean value at the baseline was (-3.306+1.05SD), (-2.80+0.93SD) and (-5.13+ 1.58SD). The mean value of T-score increased to (-2.98+1.02sd) for total Lumbar spine, (-2.59+0.80sd) for femoral neck and (-4.61+1.56sd) for lower third radius as shown in the above table.

Table No 3: Report: Percent Improvement/ co-relation from pre-study data

	Total	femur neck	Lower 1/3radius
N	71	22	12
Mean	-103.009	-102.532	-104.642
Std. Deviation	1.0206	.7351	1.4126

The percent improvement in the pre-study data (table no 3). The percentage improvement or the correlation came out to be non-significant for the sites.

IV. Discussion

Osteoporosis in an elderly is of great importance in the present scenario in north-west Indian population. There are various drug treatment regime to cure and prevent this condition, since osteoporosis is a continuous ongoing process which later combines with senile osteoporosis so it cannot be cured completely but can be prevented and Zoledronic acid is one among them.

DXA scan was done at the beginning of the study before drug administration then after 12months. Patients were given single dose of intravenous Zoledronic acid stat 5mg/100 ml infused over 15-20minutes. To all these patients standard medical care with physiotherapy lifestyle modifications along with adequate calcium and vitamin D3 supplementation was given. Also levels of calcium, vitamin D3, serum creatinine, serum urea and serum alkaline phosphatase were checked routinely to rule out any deficiency or toxicity[15].

To the best of our knowledge this is the first study to assess the effects of zoledronic acid in North-west region of India. Demographic variables such as age, body mass index, geographical delineation like rural/urban, education status, death and other risk factors were analyzed. All these variables analyzed showed a p-value of more then 0.05, making them insignificant.

L.A.Gauri et al obtained similar results in their study on post-menopausal women over 1year[4]. By observing the results, we found that intravenous Zoledronic acid is helpful in treating and preventing osteoporosis in elderly population. After one year the results may be reversible if the drug is not given again.

Similar results were seen in many studies earlier also. Steven Boonen, M.D., Ph.D. et al conducted a study on fracture risk and zoledronic acid in men with osteoporosis in 2012. The modified intention-to-treat population comprised a total of 553 men who received the drug zoledronic acid and remaining 574 received placebo. Zoledronic acid was associated with significant and sustained increases in the bone mineral density at the lumbar spine, total hip, and femur neck over a 24-month period, irrespective of total testosterone levels[17]. Richard Eastell et al in 2009 conducted a study on postmenopausal women aged 65–89 yr with femoral neck T-score ≤ -2.5, with or without evidence of an existing vertebral fracture. There was a significant beneficial effect of zoledronic acid treatment on femoral neck BMD in all subgroups compared with placebo[18]. Kenneth W. Lyles, M.D., Cathleen S et al in 2007 conducted a study on zoledronic acid and clinical fracture and mortality after hip fracture. 1065 patients were randomly assigned to receive zoledronic acid, and 1062 patients received placebo; 71.3% of the patients completed the trial. Bone mineral density at the total hip and femoral neck increased in the zoledronic acid group. The differences in bone mineral density at the total hip and femoral neck between the zoledronic acid group and the placebo group were significant.[19].Dennis M Black et al in 2007, in their study on once yearly zoledronic acid in the postmenopausal osteoporosis. In this double-blind, placebo-controlled trial, 3889 patients (mean age, 73 years) were randomly assigned to receive a single 15-minute infusion of drug zoledronic acid (5 mg) and 3876 were assigned to receive the placebo at baseline, at 12 months, and at 24 months; the patients were followed at 36months[20].

Ian R Reid et al conducted a study in 2002 on intravenous zoledronic acid in 351 postmenopausal women 45 to 80years of age with low bone mineral density at 24 centers in 10 countries. All groups receiving zoledronic acid regimens had a progressive increase in bone mineral density in the lumbar spine throughout the 12-month study period, although the rate of increase tended to slow in the second half of the study. The mean lumbar-spine bone mineral density in the groups receiving zoledronic acid was 4.3 to 5.1 percent higher than the mean value in the placebo group, which remained stable[21].

In several clinical trials there is more change in bone mineral density for hip during second year of treatment, this may be a limitation of our study[7]. In the study population the drug is safe and well tolerated except transient acute phase reaction, experiencing acute flu-like symptoms of myalgia, fever and nasal congestion. 12 patients experienced acute phase reaction which subsided with acetaminophen[22,23,24].

In a study by Saag et al Transient, flu-like symptoms seen were the most common adverse effects with zoledronic acid and resulted in a higher frequency of adverse events in this group during first 3 days of treatment. After 3 days, adverse event rates were similar in both the groups. The majority of patients, including those had flu-like symptoms, expressed a preference for annual intravenous infusion (66.4%) compared with the weekly oral therapy(19.7%)[24].

In a study by black et al, Adverse events, like change in renal function, were similar in the zoledronic and placebo group. However, serious atrial fibrillation occurred more frequently in the zoledronic acid group (in 50 vs. 20 patients, P<0.001). But in our study, we didn't notice any ECG abnormality[15].

In a study by Lyles et al, the most frequent adverse effects in the patients receiving zoledronic acid were pyrexia, myalgia, and bone and musculo-skeletal pain. No cases of Osteo-necrosis of the jaw were reported, and no adverse effects on healing of the fractures were noted. The rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the placebo and the zoledronic group. These were similar to the findings in our study[22].

V. Conclusion

5mg/100ml single yearly dose of zoledronic acid is effective in preventing osteoporosis in geriatrics at vertebral as well as non-vertebral sites. All the patients were satisfied clinically from the baseline throughout the study. Zoledronic acid decreases the calcium level but not significantly below the normal range, hence safe. The drug is safe with minimal clinical side effects, which can be managed conservatively.

VI. Recommendations

Because the effect of zoledronic acid persist for about an year after the infusion and osteoporosis is a continuous process with significant morbidity, therefore further larger studies with longer duration of treatment are need to be conducted. Also research should be focused on other modes of treatment and prevention of osteoporosis in geriatrics.

Limitations: The duration of study is short and there is Insufficient power for fracture outcomes. There is lack of endpoints beyond the DXA based BMD (quantitative CT and fine element remodeling for bone strength, bone markers).

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Anurag Sharma. "Effect of Intravenous Zoledronic Acid on Bone Mineral Density in Geraitrics." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 3, 2019, pp 29-34.