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EFFECT OF INTRAVENOUS ZOLENDRONIC ACID ON BONE MINERAL DENSITY IN POST MENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY OF NORTH WEST PART OF RAJASTHAN

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ABSTRACT

Background : Menopause is the period during which systemic oestrogen level is reduced. During postmenopausal period, bone remodelling cycle is distorted and is occasionally associated with low bone mass which is the major determinant of bone strength. Zoledronic acid, a third generation bisphosphonates available as an alternative formulation approved for the treatment of postmenopausal women.

Aim : To study the efficacy of zolendronic acid in the post menopausal women with low BMD through change in BMD and to assess the adverse effects, compliance and adherence of the of zoledronic acid in the post menopausal women with low BMD.

Results : Mean BMD on day 1 was 0.438±0.039 while on 1 year it was 0.480±0.037 and the difference was found highly significant. Mean T-score on day 1 was -2.280±0.677 and on 1 year follow up it was -1.642±0.644 and the difference was found statistically highly significant ($p<0.001$). We divided T-Score into two groups i.e. >-2.50 and -1 to -2.5. Out of total 100 patients, on day 1 total 37 patients were found in T-Score group >-2.5 group and out of them 5, 25 and 7 belonged to ≤60, 61-70 and >70 years of age group and total 63 patients were found in T-Score group -1to-2.5group and out of them 20, 37 and 6 belonged to <60, 61-70 and >70 years of age group.

Conclusion : In conclusion zoledronic acid was effective drug for the treatment of the postmenopausal women with the low bone mineral density with a once yearly administration with only significant infusion related reaction, which can be managed conservatively. Zoledronic acid is also safe without effect on renal and hepatic function, and without any adverse serious reaction, though a large study and long follow up required to reach some definite conclusion.

Key Words : Zolendronic Acid, Bisphosphonates, Oestrogen, Menopause

INTRODUCTION

Zoledronic acid[1], a third generation bisphosphonates available as an alternative formulation approved for the treatment of postmenopausal women[2]. A once yearly intravenous zoledronic acid 5 mg is a more attractive therapeutic option in the management of osteoporosis than daily, weekly, or even monthly regimens of bisphosphonates. Zoledronic acid is the first intravenous therapeutic agent with documented protection against vertebral and non vertebral fractures, including the hip fracture.

The zoledronic acid has a higher binding affinity for hydroxyapatite and is a more potent inhibitor for farnesyldiphosphate synthese and bone resorption than other bisphosphonate[3]. Zoledronic acid increases BMD at the spine and hip and prevents bone loss in men, postmenopausal women, and patients treated with glucocorticoids. Intravenous administration of zoledronic acid can cause acute phase reactions in up to 30% of patient receiving their first dose. Subsequent doses administration in patients who have previously been treated with alendronate is associated with a much smaller incidence (less than 2%)[4].

These reactions are characterized by fever and muscle aches lasting several days. Acetaminophen given at the time of treatment may reduce the likelihood of this reaction, and it can also be given to treat the symptoms. Most of the work with zoledronic acid was done on white postmenopausal women where the incidence of osteoporosis is very high. Studies on Indian Postmenopausal women with osteoporosis are very less, where if any, were the comparison between two drugs.

India is a country of temperate zone, where the socio-economic condition is different from other parts of the world. Most of the people here are suffering from gastro-intestinal tract problems. So, comparison of oral drugs with IV preparations may not always be a true reflection of the drugs. Zoledronic acid is the only IV preparation available among the bisphosphonates group. Besides this, patients are reluctant to continue the drug as a daily therapy for a very long time.

MATERIAL AND METHODS

The present study was conducted in the Department of Medicine, Sardar Patel Medical College and Associate Group of Hospitals, Bikaner during July 2011 to December 2013 on post menopausal women.

We define the post menopausal women who were at least 50years of age where menopause has occurred at least five years previously. Patients were classified according The World Health Organization (WHO) criteria for osteoporosis on the basis of bone density[5,6].

Sample size : One hundred (100) patients with postmenopausal osteoporosis

Inclusion criteria : Woman of age 45 and above, who has attained menopause at least five years previously with a bone mineral Density of hand that was below t score of -1.

Method : After enrolment patients demographic data like age, occupation, locality, were collected as per the Performa. All the patients were to subjected detailed history and clinical examination.

Weight and height are measured to calculate the body mass index.

For all the patients data on baseline laboratory findings like CBC,UREA, CREATININNE, LFT, THYROID PROFILE, SODIUM, POTASSIUM CALCIUM, ESR CRP, ECG, X RAY CHEST,USG ABDOMEN AND PELVIS , LUMBOSACRAL X RAY were obtained .

All patients bone mineral density was measured on the plain radiograph of the right hand using digital x-ray radiogrammetry (Pronosco X-posure system2.0) a computerized version of the traditional technique of radiogrammetry. A standard x ray image of the hand was scanned by an x ray scanner into computer. In ordered to estimate the BMD value, the digitized image was analyzed via PRONOSCO SOFTWARE the mean surrogate bone

density value was calculated from cortical thickness from regions of interest measured at the center of the second , third, and fourth metacarpal. This bone density measurement (expressed as per grams per square centimeter) was based on measurement of the outer and inner diameter, measuring combined cortical thickness.

TECHNIQUE

With Pronosco X-posure V.2 based on DXR, a BMD estimate is obtained through a combined computerized radiogrammetric analysis and textural analysis of a digitised radiograph of the hand. Information from the middle three metacarpals is used by the system to generate a BMD estimate. This is referred to as digital X-ray radiogrammetry BMD (DXR-BMD). The DXR-BMD is corrected for porosity, which is assumed to reflect properties of the cortical bone micro-architecture.

In the Pronosco X-posure System V.1, the BMD estimate was obtained through the same technique as V.2 except that information from distal radius and ulna was also used.
A plain radiograph digitises the image. The initial computer processing identifies anatomical landmarks and automatically defines the 'Regions of Interest' (ROIs). The digitised image is displayed on the screen with the ROIs superimposed. There is no operator activity involved in placing the regions.

The system computes the DXR-BMD based on the cortical thickness of the ROIs. The cortical thickness is measured 118 times per vertical centimeter of the ROI in each cortex, giving a total of 236 measurements per centimeter when averaging over the two cortices. The DXR-BMD estimate is presented as i) an absolute bone mineral density estimate in g/cm^2 , ii) graphically, in a DXR-BMD versus age plot, together with a reference curve, iii) a T score and iv) a Z score.

A number of studies with the use of DXR have been initially done using the Pronosco X-posure System V.1. Recent studies have been with the Version 2. Several studies have confirmed that there is equivalence between the two versions of the Pronosco X-posure System. The regression analyses of DXR-BMD V.1 versus DXR-BMD V.2 measurements indicated that the slope of regression line was close to one (with a 95% confidence interval) and the intercept was close to zero (with a 95% confidence interval). These two observations indicate high degree of correspondence between DXR-BMD V.1 and DXR-BMD V.2 measurements

All patients were administered a 15-minute intravenous administration of zoledronic acid (5 mg). In addition, all patients received oral daily calcium1000mg per day and vitamin D 400IU. Safety of the patients was evaluated by clinical evaluation of adverse events and laboratory investigations with telephonic interview and hospital visits up to 1 year. Repeat bone mineral density was obtained after 12 months following the infusion. The effect the zoledronic acid was determined by comparing the pre and post infusion values of BMD and its score.

RESULTS AND DISCUSSION

Table 1
Distribution of Cases according to Age Group in relation to Bone Mineral Density

Age Group	BMD Group							
	On 1st day				On 1 year			
	≤0.400		>0.400		≤0.400		>0.400	
	No.	%	No.	%	No.	%	No.	%
≤60	1	6.3	24	28.6	0	-	25	25.0
61-70	12	75.0	50	59.5	0	-	62	62.0
>70	3	18.8	10	11.9	0	-	13	13.0
Total	16	100	84	100	0	-	100	100
Mean	67.63		64.32		-		64.85	
SD	6.13		5.37		-		5.60	
t	2.204				-			
p	0.030				-			

Table 2
Distribution of Cases according to Age Group in relation to T-Score

Age Group	T-Score							
	On 1st day				On 1 year			
	> -2.5		-1 to -2.5		> -2.5		-1 to -2.5	
	No.	%	No.	%	No.	%	No.	%
≤60	5	13.5	20	31.7	2	18.2	23	25.8
61-70	25	67.6	37	58.7	7	63.6	55	61.8
>70	7	18.9	6	9.5	2	18.2	11	12.4
Total	37	100	63	100	11	100	89	100
Mean	67.24		63.44		66.73		64.62	
SD	5.56		5.17		6.62		5.46	
t	3.451				1.181			
p	0.001				0.241			

Table 3
Statistical analysis of different parameters

Parameters	On 1st Day		On 1 year		t	P
	Mean	SD	Mean	SD		
BMD	0.438	0.039	0.480	0.037	38.912	<0.001
T-Score	-2.280	0.677	-1.642	0.644	23.415	<0.001

Table 1 shows distribution of Cases according to Age Group in relation to Bone Mineral Density. We divided BMD into two groups i.e. ≤0.400 and >0.400. Out of total 100 patients, on day 1 total 16 patients were found in BMD group ≤0.400 and out of them 1, 12 and 3 belonged to ≤60, 61-70 and >70 years of age group and total 84 patients were found in BMD group >.400 and out of them out of them 24, 50 and 10 belonged to ≤60, 61-70 and >70 years of age group. On Statistically analysis the difference was found statistically significant ($p<0.05$).

No statistically comparison was made on 1 years follow up because no patient was found in BMD group ≤0.400.

Table 2 shows distribution of Cases according to Age Group in relation to T-Score. We divided T-Score into two groups i.e. >-2.50 and -1 to -2.5. Out of total 100 patients, on day 1 total 37 patients were found in T-Score group >-2.5 group and out of them 5, 25 and 7 belonged to ≤60, 61-70 and >70 years of age group and total 63 patients were found in T-Score group -1to-2.5group and out of them 20, 37 and 6 belonged to <60, 61-70 and >70 years of age group. On Statistically analysis the difference was found statistically significant ($p<0.01$).

On 1 year follow up out of total 100 patients, only 11 patients had their T-score >-2.5 and out of them 2,7 and 2 patients belonged to age groups ≤60, 61-70 and >70 respectively. On statistical comparison the difference was found insignificant ($p>0.05$).
According to above table, mean BMD on day 1 was 0.438±0.039 while on 1 year it was 0.480±0.037 and the difference was found highly significant. Mean T-score on day 1 was -2.280±0.677 and on 1 year follow up it was -1.642±0.644 and the difference was found statistically highly significant ($p<0.001$).

Osteoporosis is defined as systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue with consequent increase in bone fragility and susceptibility to bone fractures.

Osteoporosis is common postmenopausal women and is associated with a high incidence of fractures. Because a low bone mass is the major risk factor for fractures, the treatment of osteoporosis focuses on agents that prevent bone loss or even increase bone mass Osteoporosis, however, is a multifactorial disease, and skeletal fragility results from various factors. The goals of therapy for osteoporosis are to reduce bone resorption and enhance bone formation, if possible.

There are many treatment options available, a once yearly intravenous infusion of zoledronic acid 5 mg is a more attractive therapeutic option in the management of osteoporosis than daily, weekly, or even monthly regimens of oral bisphosphonates. Moreover, the use of intravenous ZOL 5mg in preventing bone loss and reducing the risk of fractures is well established in postmenopausal osteoporosis.

The present study was a Prospective observational study conducted in the Department of medicine, Sardar Patel Medical College and Associate Group of Hospitals, Bikaner during July 2011 to December 2013 involving 100 post menopausal women.

In our study, as shown in the table no1, distribution of Cases according to Age Group in relation to Bone Mineral Density. We divided BMD into two groups i.e. <0.400 and >0.400. Out of total 100 patients, on day 1 total 16 patients were found in BMD group <0.400 and out of them 1, 12 and 3 belonged to <60, 61-70 and >70 years of age group and total 84 patients were found in BMD group >.400 and out of them out of them 24, 50 and 10 belonged to <60, 61-70 and >70 years of age group. On Statistically analysis the difference was found statistically significant ($p<0.05$).

In our study as shown in table 2, shows distribution of Cases according to Age Group in relation to T-Score. We divided T-Score into two groups i.e. >-2.50 and -1 to -2.5. Out of total 100 patients, on day 1 total 37 patients were found in T-Score group >-2.5 group and out of them 5, 25 and 7 belonged to <60, 61-70 and >70 years of age group and total 63

patients were found in T-Score group -1to-2.5group and out of them 20, 37 and 6 belonged to <60, 61-70 and >70 years of age group. On Statistically analysis the difference was found statistically significant ($p<0.01$). On 1 year follow up out of total 100 patients, only 11 patients had their T-score >-2.5 and out of them 2,7 and 2 patients belonged to age groups <60, 61-70 and >70 respectively. On statistical comparison the difference was found insignificant ($p>0.05$).

In the study conducted by Reid et al[7] studied intravenous zoledronic acid in postmenopausal women with low bone mineral density myalgia and pyrexia occurred more commonly in the zoledronic acid groups.

In a study by Saag[8] et al Transient, flu-like symptoms were the most common adverse events in the zoledronic acid 5 mg group and resulted in a higher frequency of adverse events in this group during the first 3 days of treatment. After 3 days, adverse event rates were similar in the 2 groups. The majority of patients, including those experiencing flu-like symptoms, expressed a preference for annual i.v. therapy (66.4%) compared with weekly oral therapy (19.7%).

In a study by black et[9] al Adverse events, including 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 recorded any ECG abnormality.

In a study by Lyles[10] et al the most frequent adverse events in patients receiving zoledronic acid were pyrexia, Myalgia, and bone and musculoskeletal pain. No cases of Osteonecrosis of the jaw were reported, and no adverse effects on the healing of fractures were noted. The rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the in the placebo and the zoledronic group. These were similar to our studies.

SUMMARY

The zoledronic acid significantly increased bone mineral density at 12 months (BMD with on day 1 was 0.438±0.039 while on 1 year it was 0.480±0.037). The zoledronic acid significantly increased T score at 12 months with Mean T-score on day 1 was 2.280±0.677 and on 1 year follow up it was 1.642±0.644. The zoledronic acid significantly decreased the risk of fracture. The most common adverse effects were the infusion related reaction. Fever being the most common, others were headache, myalgia, influenza like and arthralgia. Zoledronic acid was safe without significant effect on renal and liver function. Zoledronic acid decreases the calcium level but not significantly below the normal range, hence safe. There were no serious adverse effects found. No case of Osteonecrosis of jaw was reported on one year follow up. In comparison to other osteoporosis drugs zoledronic acid has good compliance due once yearly administration.

CONCLUSION

In conclusion zoledronic acid was effective drug for the treatment of the postmenopausal women with the low bone mineral density with a once yearly administration with only significant infusion related reaction, which can be managed conservatively. Zoledronic acid is also safe without effect on renal and hepatic function, and without any adverse serious reaction, though a large study and long follow up required to reach some definite conclusion.

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