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A randomised comparative study of zoledronic acid and teriparatide in post menopausal women with osteoporosis

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Abstract

Background: This study was undertaken to study and compare the effectiveness of zoledronic acid and teriparatide on bone mineral density in postmenopausal women with osteoporosis.

Methods: A hospital-based randomized comparative interventional longitudinal study concocted on patient suffering from post-menopausal osteoporosis attending in the dept. of Physical Medicine and Rehabilitation, SMS Hospital, Jaipur.

Results: The baseline mean value for Teriparatide group was -2.46 ± 0.58 sd and in the Zoledronic group was -2.52 ± o.58 sd (p =0.770 not significant) indicating both groups were comparable at baseline . The mean value in Teriparatide group increased to -2.2±1.15 sd at 3 month, -2.18±1.31sd at 6 month and increased to -2.28 ±0.62 at 9 month. In the Zoledronic group mean value increased to -2.23±1.05 sd at 3 month, further increased to -2.38±1.03 sd at 6 month and finally increased to -2.01±0.84 at 9 month.

Conclusion: Zoledronic acid 5 mg intravenous and Teriparatide 20 µgm subcutaneous daily, both are effective in prevention and treatment of post menopausal osteoporosis .

Keywords: Zoledronic acid, Teriparatide, Osteoporosis.

Introduction

According to the National Institute of Health consensus conference in 2000, osteoporosis is defined as a skeleton disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture [1]

WHO operationally defines osteoporosis as bone density that falls 2.5 SD below the mean for young healthy adults of the same gender (t score≤ 2.5)[6] Osteoporosis affects >10 million individual in United States. The lifetime risk of an osteoporotic fracture to be 40-50% in women and 13-22 % in men osteoporotic fractures are associated with substantial morbidity and a significantly increased mortality risk.[2]

The different pharmacologic groups available are: bisphosphonates—considered as first line therapy. These are etidronate, alendronate, risedronate and zoledronic acid, parathyroid hormone 1 to 34 (teriparatide), calcitonin— tibolone and new experimental therapies—strontium ranelate, parathyroid 1 to 84, bazedoxifene, lasofoxifene, denosumab.[3-4] This study was undertaken to study and compare the effectiveness of zoledronic acid and teriparatide on bone mineral density in postmenopausal women with osteoporosis.

Material and Method

Study Area: Patient suffering from post-menopausal osteoporosis attending in the dept. of Physical Medicine and Rehabilitation, SMS Hospital, Jaipur.

Study Design: A hospital-based randomized comparative interventional longitudinal study

Duration: From the approval of the Research Review Board till the desired sample size was obtained and their follow up completed. (Feb 2016 to Dec 2017)

Sample Size: To address this 105 patients suffering from post menopause osteoporosis were screened for eligibility and consent was taken for a randomized control study 75 eligible patients were assigned either to teriparatide or Zoledronic group according to computer-generated numbers .29 patients in teriparatide group and 26 patients in Zoledronic group completed the study.

Inclusion Criteria

1. postmenopausal osteoporotic elderly patients aged 50 to 80 years with BMD T scores of -2.5 or less at femoral neck / total hip /lumbar spine, in presence of 1 or more fragility fracture.
2. T score less than -3 and with 2 or more nonmodifiable risk factor for fracture(age>65 years, personal history of prior fracture, family h/o fracture, Caucasian or Asian race, poor health)
3. Those willing to give an informed written consent

Exclusion Criteria

1. Patients were excluded for any prior use of parathormone or bisphosphonate for more than three consecutive months, short-term use was acceptable if followed by a 1year washout
2. Prior strontium treatment, chronic use of systemic corticosteroids within the prior year.
3. Renal dysfunction ,hypocalcaemia /hypercalcemia
4. Any medical illness interfering with an infusion of Zoledronic acid or subcutaneous teriparatide or assessment of BMD
5. Pt with a ho allergy to bisphosphonate or teriparatide

Results

Table 1 : Age Statics of the study population

	Tereparatide Group			Zoledronic Group			
	N	Mean	SD	N	Mean	SD	P value LS
BMI	29	23.997	3.0563	26	26.119	4.9763	.059
Age	29	63.24	6.379	26	62.73	7.993	.793
PMP PERIOD(yr back)	29	15.17	6.798	26	16.42	6.592	.493

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Table no 1 showing the mean body mass index of the study population was 23.997±3.05 of the group Teriparatide and 26.119± 4.97 Zoledronic (P= 0.059NS) The mean Age of the study population was 63.24±6.379 of the group Teriparatide and 62.73 ± 7.99 Zoledronic (P= 0.79 NS) The mean duration of post menopause period of the study population was 15.17 ±6.798 of the group Teriparatide and 16.42 ± 6.59 Zoledronic (P= 0.49NS). This indicates both the groups are comparable regarding age, body mass index and postmenopausal duration at baseline.

Table 2: BMD Dexa T Score Lumbar Spine Statistics among the Groups

	Tereparatide Group			Zoledronic Group			
Gr	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P Value LS
BASE T SPINE	29	-3.70	0.94	26	-3.27	0.91	.090
1F/U TSPINE	29	-3.21	1.56	25	-3.14	0.85	.859
2 F/U T SPINE	29	-2.70	1.74	25	-2.34	1.75	.457
3 F/U T SPINE	29	-3.09	0.91	25	-3.80	5.22	.474

Unpaired t test

Table no 2 showing the DEXA scan BMD value for t score of spine for the two groups showing the mean value for baseline Teriparatide group -3.70±0.94 sd and that of Zoledronic group -3.27 ±0.91sd (p value =0.90 not significant). There was no significant difference observed in the two groups at baseline, so both groups were comparable at baseline. The mean value in t score increased to -3.21 ±1.56 sd during first 3 month, then increased to -2.70 ±1.74 sd during 6 month and finally reached upto -3.0.91 ±0.91sd at 9 month whereas in Zoledronic group the value increased to -3.14± o.85sd during first 3 month, increased further to to -2.34 ± 1.75sd at 6 month whereas decreased to -3.80 ±5.22 sd at 9 month.

Table 3: BMD Dexa T Score Hip Statistics among The Groups

Group	Tereparatide Group			Zoledronic Group			
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P value LS
BASE T HIP	29	-2.46	0.58	26	-2.52	0.58	0.770
1 F/U T HIP	29	-2.2	1.15	25	-2.23	1.05	0.927
2 F/U T HIP	29	-2.18	1.31	25	-2.38	1.03	0.548
3 F/U T HIP	29	-2.28	0.62	25	-2.01	0.84	0.177

Table no 3 showing the BMD DXA t score hip mean and standard deviation among the two groups at baseline at 1st follow up, 2nd and 3rd follow up period among the groups. The baseline mean value for Teriparatide group was -2.46 ± 0.58 sd and in the Zoledronic group was -2.52 ± o.58 sd (p =0.770 not significant) indicating both groups were comparable at baseline . The mean value in Teriparatide group increased to -2.2±1.15 sd at 3 month, -2.18±1.31sd at 6 month and increased to -2.28 ±0.62 at 9 month. In the

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Zoledronic group mean value increased to -2.23±1.05 sd at 3 month, further increased to -2.38±1.03 sd at 6 month and finally increased to -2.01±0.84 at 9 month.

Table 4: Comparative analysis of BMD DEXA T SCORE lumbar spine difference and % difference among the groups

Group	Tereparatide			Zoledronic			P Value LS
	N	Mean	SD	N	Mean	SD	
BASE DIFF TSPINE 1st f	29	0.25	0.19	25	0.15	0.13	.041S
% BASE DIFF TSPINE 1st f	29	-7.23	6.12	25	-4.89	6.79	0.191
BASE DIFF T SPINE 2nd f	29	0.5	0.2	25	0.24	0.16	<0.001S
%BASE DIFF T SPINE 2nd f	29	-14.1	6.06	25	-7.71	4.51	<0.001S
BASE DIFF T SPINE 3rd f	29	0.92	1.76	25	0.29	0.26	0.087
%BASE DIFF T SPINE 3rd f	29	-2.6	51.93	25	-.95	.74	0.122

Unpaired t test

Table no 4 showing the mean and standard deviation of change and the % change in t score of lumbar spine among the two groups

Significant difference was observed in T spine at difference and % difference from baseline to 1st follow up and 2nd period among the groups but no significant difference was observed at 3rd follow up period.

Table 5: Comparative analysis of BMD DEXA T score total hip Difference and % difference among the groups

Group	Tereparatide			Zoledronic			P value
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	
BASE DIFF THIP 1 follow up	29	.12	.14	25	.12	.12	.997
BASE DIFF THIP% 1f /u	29	-5.43	7.64	25	-4.74	4.69	.695
BASE DIFFTHIP 2sf	29	.21	.23	25	.32	.33	.178
BASE DIFFTHIP 2sf%	29	-9.46	11.45	25	-13.44	14.76	.270
BASE DIF THIP 3nd f	29	-.09	1.93	25	.39	.19	.218
BASE DIF THIP 3nd f%	29	4.75	8.79	25	-15.45	7.85	.258

Table no 5 showing the difference in mean and percentage difference of mean in change of t score total hip in Teriparatide and Zoledronic group.

No Significant difference was observed in T Hip at difference and % difference from baseline to 1st follow up 2nd and 3rd follow up period among the groups

Table 6 : Distribution of the cases according to complications

	Tereparatide		Zoledronic		Total		P Value LS
	No	%	No	%	No	%	
fever	0	0.00	3	11.54	3	5.45	>0.05NS
flu like rxn	0	0.00	5	19.23	5	9.09	>0.05NS
myalgia	0	0.00	3	11.54	3	5.45	>0.05NS

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skin rashes	4	13.79	0	0.00	4	7.27	>0.05NS
Vit D toxicity	0	0	0	0			NA

This table shows the Distribution of the cases according to complications.

No significant difference was observed according to complications among the groups. As slightly few complication were observed that were found only in Group Zoledronic like. Flu like rxn in 5 cases myalgia in 3 cases fever in3 cases while skin rashes in 4 cases in group Teriparatide

Discussion

Postmenopausal osteoporosis is of great concern in the current scenario in Indian population. There are various drugs treatment regime to cure and prevent this condition, since postmenopausal osteoporosis is an ongoing process which lately combines with senile osteoporosis so this condition is preventable but cannot be cured completely. Both Zoledronic and teriparatide are established treatment options for treating post menopausal osteoporosis

In this study we compare both the drugs with respect to efficacy and cost-effectiveness, since India is developing country with the treatment options are costlier with longer duration of therapy

To address this 105 patients suffering from postmenopausal osteoporosis were screened for eligibility and consent was taken for a randomized control study, 75 eligible patients were assigned either to teriparatide or Zoledronic group according to computer-generated numbers. 29 patients in teriparatide group and 26 patients in Zoledronic group completed the study.

DXA scan was done to measure the bone mineral density at the hip and lumbar spine at baseline, 3, 6, and 9 months. Patients received single intravenous Zoledronic acid infusion and teriparatide group received 20 micrograms subcutaneous injection daily for 6 months. In both the groups standard medical care with physiotherapy ,lifestyle modification along with adequate calcium and vitamin D3 supplementation was provided and levels of vitamin D3 ,calcium ,serum urea ,serum alkaline phosphatase, serum creatanine were checked every 3 months to rule out any deficiency or toxicity.

The bone mineral density value (T score) by DXA scan of lumbar spine for the two groups showing the mean value at baseline , in Teriparatide group was (-3.70±0.94 sd) and that of Zoledronic group was(-3.27 ±0.91sd) (p value =0.90 which is not significant).

There was no significant difference observed in the two groups at baseline indicating both groups were comparable at baseline.

In the Teriparatide group the mean value T score of lumbar spine increased to -3.21 ±1.56 sd during first 3 month, then further increased to -2.70 ±1.74 sd during 6 month and finally decreased up to -3.09 ±0.91sd at 9 month, whereas in Zoledronic group the value increased to -3.14± 0.85sd during first 3 month, increased further to -2.34 ± 1.75sd at 6 month whereas decreased to -3.80 ±5.22 sd at 9 month.

In the Teriparatide group the mean change of difference in bone mineral density of lumbar spine group from baseline was increased to 7% at 3 month, 14 % during 6 month, 2.6 % during the 9 month while in the Zoledronic group the change in lumbar spine bone mineral density in was 4.9% at 3 month, 7.7 %during the 6 month and .95 % during 9 month.

This change in bone mineral density of lumbar spine in the two groups was more in the teriparatide group although in both groups there was an increase in bone

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mineral density, .at no point of time during the study period the bone mineral density reached the baseline value.

In the Teriparatide group mean change of difference in the bone mineral density in lumbar spine was significant during first follow up 0.49 ± 1.268 (p = 0.047) and second follow up 1.0 ±1.43 (p=.001) but the difference was not significant statistically during the third follow up.

The change in BMD is highly significant in the second follow up period of 6 months, in both the group and this may be attributed to one remodeling cycle duration of 90 to 120 days. Jean Jacques et al,[5] Esworr et al[6] get similar results in their study in which teriparatide increased BMD significantly at 3 months and increased lumbar spine BMD by 5.2 %, further lumbar spine BMD increased to 12.2% at 6 months and change was significant in both the groups .

Felicia Cosman et al[3] obtained similar result regarding change in lumbar spine BMD with teriparatide but the magnitude of change in lumbar spine bone mineral density was less in their study during 6 month but change was more at 1 year duration although they continue treatment with Teriparatide for 1 year but we give it only for 6 months

In the zoledronic group significant positive mean difference in bone mineral density T score lumbar spine was observed at first follow up in 0.49 ±1.268sd (p =0.001s) and 2 follow up 1.0 ±1.43 sd (p=.004) but the effect was lesser as compared to teriparatide, similar results were obtained by Felicia cosman et al [3],black et al [7] in their study.

The baseline mean value for bone mineral density DXA T score of total hip in the Teriparatide group was -2.46 ± 0.58 sd and in the Zoledronic group was -2.52 ± 0.58 sd (p =0.770 not significant) indicating both groups were comparable at baseline .

In the Teriparatide group mean value for bone mineral density DXA T score hip was increased to -2.2±1.15 sd at 3 month, -2.18±1.31sd at 6 month and increased to -2.28 ±0.62 at 9 month, whears in the Zoledronic group mean value increased to -2.23±1.05 sd at 3 month, further increased to -2.38±1.03 sd at 6 month and finally increased to -2.01±0.84 at 9 month.

In the Teriparatide group bone mineral density of total hip was observed to increase from baseline by 5.4% at 3 months, 9.5% at 6 month 4.8 % at 9 month , while in the Zoledronic group it increased by 4.8 % at 3 months, 13% at 6 months and 15% at 9 months. At no point in time during the study period, BMD of hip reach the baseline value.

In the Zoledronic group increase in BMD was 10% more after 9 months as compared to the tereparatide group. Felicia Cosman get similar results in their study in which hip BMD was increased more by zoledronic acid as compared to teriparatide

Increment in bone mineral density T score of hip following both Zoledronic and teriparatide was apparent throughout the study period but the significant level was achieved at 9 months during the 3 follow up but the change in BMD of the hip was more significant in the Zoledronic group

By observing the results, we found that both the agents Zoledronic acid and Teriparatide are helpful in treating and preventing osteoporosis in post menopausal women During the study we found that when we stop Teriparatide bone mineral density decreases after 3 months, so it requires longer duration of therapy with Teriparatide to further maintain the bone mineral density and some other treatment options should be planned.

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In case of Zoledronic acid effect is maintained upto 1 year and after stopping ,the results are reversible after one year

Treatment with both regimes is safe and well tolerated. The overall percentage of adverse events was comparable in both groups A single dose of Zoledronic acid was well tolerated except a transient acute phase reaction, experiencing acute flu-like symptoms of myalgia, fever, and nasal congestion.11 out of 26 developed a self-limiting acute phase reaction which subsided with acetaminophen.

Teriparatide was also well tolerated except 4 patients out of 29 developed localized skin rashes at injection sites which was self-limiting ,no another serious side effect was noted

Discrepancies between studies may be due to

1. The short duration of teriparatide treatment
2. Difference between patient populations and race
3. Short duration of the study as different conclusion might be drawn after the second year of therapy particularly for total hip BMD change which was more during the second year of therapy in several clinical trials.

Conclusion

Zoledronic acid 5 mg intravenous and Teriparatide 20 µgm subcutaneous daily, both are effective in prevention and treatment of post menopausal osteoporosis

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