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EFFECT OF RISEDRONATE AND STRONTIUM THERAPY ON BONE MINERAL DENSITY IN POSTMENOPAUSAL OSTEOPOROSIS

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ABSTRACT
Clinical studies show that treatment with strontium ranelate which is comparatively a new oral agent leads to relatively larger increases in (Bone Mineral Density) BMD compared with alternative agents such as biphosphanates. The present study was designed to compare the effect of treatment with Risedronate and Strontium ranelate on clinical and radiological parameters, DEXA scans and various biochemical values. In this randomized controlled trial study, 190 patients were divided into two groups. The risedronate group (148 patients) received risedronate 35 mg weekly. Strontium group (42 patients) received strontium-ranelate 2 gm/day. The primary end point was the percentage of change at the end of one year over baseline in BMD at lumbar spine (L1 to L4) and femoral neck on both sides taken as mean. Secondary end points included clinical and radiological improvement with bone turn over markers. The mean difference in lumbar spine BMD at baseline and after one year of treatment with risedronate was 0.121 with a standard deviation change of 0.079. While in patients on strontium ranelate was 0.145 with a standard deviation change of 0.074. On applying the paired t-test to the pre and post-treatment BMD at hip and spine there was a significant improvement in both the treatment groups at spine ($t = -10.997$) ($p < 0.05$) and at hip ($t = -7.60$) ($p < 0.05$).There was a significant improvement in BMD at lumbar spine and total BMD at hip after one year treatment with risedronate and strontium ranelate. There was no significant difference between the two groups.
Key Words: Bone mineral density, dual energy X-ray absorbtiometry, strontium ranelate, risedronate.

INTRODUCTION

With increasing life expectancy there is exponential increase in osteoporotic fractures. It is projected that the number of hip fractures worldwide will exceed six million by 2050, [1] these facts make osteoporosis a critical health issue and entire world focus has shifted on to osteoporotic fractures. Bone quality and strength cannot be measured easily. Bone Mineral Density (BMD) is the parameter that can be determined best in-vivo. It has high precision and it correlates well with the biomechanically determined bone strength. Because Bone mineral density is a partial predictor of bone strength and a powerful predictor of fractures,[2,3] an operational definition of osteoporosis was developed by a study group of the W.H.O. that empirically defined osteoporosis as a BMD that is >2.5 S.D. below peak bone mass.[4]

A number of antiresorptive agents are reported to have anti fracture efficacy in the treatment of women with postmenopausal osteoporosis. Comparisons of different agents are of much clinical interest. The 2 most studied osteoporosis therapies are alendronate and risedronate. While there are differences in the magnitude of changes in BMD and biochemical markers of bone turnover observed with these two agents, the magnitude of the reduction in vertebral and nonvertebral fracture risk appears to be similar.[5] Clinical studies also show that treatment with strontium ranelate leads to relatively larger increases in bone mineral density (BMD) compared with alternative agents such as biphosphanates.[6]

The present study was designed to compare the effect of treatment with Risedronate and Strontium ranelate on clinical and radiological parameters, bone density (DEXA scans) and various biochemical values.

MATERIAL AND METHODS

The present study was conducted at Department of Orthopedics and the Division of Endocrinology, Department of Medicine, J. N. Medical College Hospital, AMU, Aligarh. The study was approved by the board of studies and the protocol was approved by the local institutional review committee (Date of meeting- 6th August 2007). Informed consent was obtained from all subjects involved in the study.

Inclusion criteria

Women who were post-menopausal for at least one year and had osteopenia or osteoporosis and in whom BMD was not possible but they had fragility fractures and radiographs showed gross decrease in bone density.

Exclusion criteria

Deranged renal function (serum creatinine > 1.5 mg %) or renal calculi, abnormal thyroid function (serum TSH between 0.5 – 5.0 mIU/L), significant liver disease, history of cancer, peptic ulcer or esophageal disease requiring prescription medication within the previous five years, regular therapy with a phosphate binding antacid, estrogen replacement therapy within the previous 9 -12 months, therapy with any other drug that affect skeleton like steroids, anti convulsants and anticoagulants.

One hundred and forty-six women between 40 to 80 years attending the endocrine OPD were studied. To be eligible for the study they had to have been post-postmenopausal for at least one year and in good health with no vertebral abnormalities in the L1-L4 region which interferes with measurement of BMD by Dual Energy X-ray Absorptiometry (DEXA) and had decreased bone mineral density (lumbar spine or right or left femoral neck or both T-score -1.0 or less). Forty-four patients aged between 42

to 80 years with fragility fractures presenting to the Orthopedics OPD and to the casualty division of the J. N. Medical College Hospital, Aligarh Muslim University were also included. A fragility fracture may be defined as one that occurred as a result of minimal trauma, such as a fall from a standing height or less, or occurred without identifiable trauma. Out of one hundred and forty-six post-menopausal females registered from endocrine OPD, one hundred and fourteen had achieved natural menopause and thirty-two had their uterus and ovaries removed surgically due to some pathology before attaining menopause and were included due to decreased bone density on DEXA scan. Among the forty-four Orthopedic patients, except one all had attained natural menopause. This patient had her uterus and ovaries removed surgically due to fibroid uterus before attaining menopause.

Treatment

All the one hundred and ninety patients were divided into two groups. One group received risedronate and the other group was given strontium ranelate. The risedronate group comprised one hundred and forty-eight patients who received risedronate 35 mg weekly. The strontium group comprised forty-two patients and they were given strontium-ranelate 2 gm/day. All patients were given elemental calcium 1000 mg/day and vitamin D 1000 IU/day. Twenty-four patients on risedronate and eighteen patients on strontium ranelate completed one year treatment and repeat BMD was done. Patients were questioned at each visit adverse events including minor complaints.

Study design

In this randomized controlled trial study a detailed history and physical examination was carried out for every subject who entered the study as per predesigned performa covering all known risk factors for primary osteoporosis and all known conditions leading to secondary osteoporosis. The subjects were asked to report to the endocrinology laboratory after an overnight fast of 10-12 hours. Blood samples were collected in EDTA vials for Haemogramme and ESR, in plain vials for estimation of serum calcium, serum phosphorus, serum 25-hydroxy vitamin D, serum TSH, serum alkaline phosphatase, serum PTH, lipid profile and serum creatinine and in sodium fluoride vials for serum sugar. X-rays of pelvis, spine, wrist and calcaneum were done for assessment of bone density using various indices. The various indices estimated were the Saville Index for spine, Singh's Index for hip and Jhamaria-Lal Index or Calcaneal Index for calcaneum. For patients presenting to orthopedic OPD or to the casualty section with fragility fractures these tests were done after admitting the patient along with other investigations required for the management of fractures like x-rays of the affected part, x-ray chest, electrocardiogram, blood urea, NCCT head etc. Bone Mineral Density was estimated in the endocrine laboratory. BMD was estimated at three sites i.e., lumbar spine (L1- L2 level), right hip and left hip. Mean BMD at hip and difference between the values at both hips was also calculated.

Methodology 1

Bone Mineral Density: BMD was measured using DEXA at baseline and after one year by GE Lunar Densitometer. The patient was made to lie on a flat platform and two X-ray beams passed from above. It used a second x-ray beam to correct for absorption of x-ray energy in non-calcium containing tissues. 2-Serum 25-hydroxy vitamin D: Using LIAISON 25 OH Vitamin D chemiluminescent immunoassay (310900). 3-Serum TSH: The RIA kit (TSH IRMA KIT) was obtained from Immunotech, Czech Republic and the assay procedure was followed as per the directives of the supplier.4-Serum PTH: Using LIAISON N-tact PTH Chemiluminescent Immunoassay (310910).5-Serum Alkaline Phosphatase: measured by spectrophotometry and normal range was between 40 and 129 U/L. To ensure proper test performance, the operating instructions of the manufacturer were strictly adhered to 6-Plasma Glucose: Glucose oxidase peroxidase method.7-Serum Creatinine: Jaffe Manners Method. 8-Serum Lipids: by enzokits, Ranbaxy diagnostics and cholesterol reagent set supplied by Pointe Scientific Inc. Michigan, USA. Serum Cholesterol, Serum Triglycerides (Fasting), HDL and LDL Cholesterol were estimated.

Table 1: Baseline Characteristics of patients according to treatment group

SN	Variable	Risedronate Group (N=148)		Strontium Group (N=42)		Total N=(190)	
		Mean	S. D.	Mean	S. D.	Mean	S. D.
1.	Age (yrs)	55.6	9.1	57.7	7.8	56	8.9
2.	BMI (kg/m2)	26.1	4.7	27.4	4.9	26.4	4.7
3.	Lumbar spine BMD (gm/cm2	0.849	0.130	0.849	0.150	0.849	0.134
4.	Lumbar spine t-score	-2.6	1.1	-2.7	1.2	-2.7	1.2
5.	Hip BMD (gm/cm2)	0.858	0.141	0.828	0.319	0.851	0.198
6.	Hip t-score	-1.4	1	-1.4	.8	-1.4	1
7.	S.Calcium(ionised) (mmol/L)	1.08	0.07	1.06	0.08	1.07	0.07
8.	S.25-OH vitamin D (ng/ml)	19.1	7.8	21.7	9.5	19.7	8.2
9.	S. TSH (mIU/L)	2.52	3.64	2.23	1.03	2.45	3.25
10.	Creatinine (mg%)	0.96	0.23	1.02	0.29	0.97	0.25
11.	Total cholesterol (mg %)	181	42	170	37	178	41
12.	Triglycerides (mg%	129	55	134	75	130	60
13.	HDL (mg %)	47	14	46	10	47	13
14.	LDL (mg %)	118	47	113	36	117	45
15.	VLDL (mg %)	33	22	28	15	32	21
16.	Milk Intake (ml/day)	171	126	139	134	164	128
17.	Sun exposure (mts./day)	33	26	31	26	33	26

Table 2: Change in BMD after 1 year of treatment

	Treatment group					
	Risedronate group		Strontium group		**Total**	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Pretreatment spine BMD (gm/cm2)	.7894	.11885	.8083	.10001	.7975	.11028
Pretreatment spine Tscore	-3.2833	1.10990	-3.1722	.69266	-3.2357	.94503
post treatment spine BMD (gm/cm2)	.9106	.09632	.9533	.08462	.9289	.09290
post treatment spine Tscore	-2.4958	.74336	-2.5389	.47791	-2.5143	.63652
change in BMD spine (gm/cm2)	**.1212**	**.07954**	**.1449**	**.07467**	**.1314**	**.07747**
% change spine	**16.4985**	**11.46999**	**18.8128**	**10.52794**	**17.4904**	**11.00468**
Pretreatment hip BMD (gm/cm2)	.8372	.15114	.8477	.12180	.8417	.13782
Pretreatment hip Tscore	-1.6958	.93923	-1.5389	.60014	-1.6286	.80646
post treatment hip BMD (gm/cm2)	.9178	.09846	.9433	.12470	.9287	.10977
post treatment hip Tscore	-1.2833	.77385	-1.3000	.50643	-1.2905	.66509
change in BMD hip (gm/cm2)	**.0848**	**.07739**	**.0956**	**.06346**	**.0894**	**.07113**
% change hip	**11.1920**	**11.49354**	**11.7848**	**8.49791**	**11.4461**	**10.20473**

Table 3: Significance of Change in BMD at spine and hip (Paired t-test)

		Mean	Std. Deviation	t	df	Sig. (2-tailed)
Pair 1	pretreatment spine BMD(gm/cm2) - post treatment spine BMD(gm/cm2)	-.1314	.07745	-10.997	41	**.000**
Pair 2	pretreatment hip BMD(gm/cm2) - post treatment hip BMD(gm/cm2)	-.0871	.07405	-7.620	41	**.000**
Pair 3	pretreatment spine Tscore - post treatment spine Tscore	-.7214	.60265	-7.758	41	**.000**
Pair 4	pretreatment hip Tscore - post treatment hip Tscore	-.3381	.27136	-8.075	41	**.000**

Table 4: Percentage of change in BMD at spine and hip (Unpaired t-test)

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
% change spine	10.300	41	.000	17.4904	14.0611	20.9197
% change hip	7.269	41	.000	11.4461	8.2660	14.6261

Table 5: Comparison between risedronate and strontium groups

	Treatment Group	N	Mean	Std. Deviation	Std. Error Mean
Pretreatment spine BMD (gm/cm2)	Risedronate group	24	.7894	.11885	.02426
	strontium group	18	.8083	.10001	.02357
Pretreatment spine Tscore	Risedronate group	24	-3.2833	1.10990	.22656
	strontium group	18	-3.1722	.69266	.16326
Post treatment spine BMD (gm/cm2)	Risedronate group	24	.9106	.09632	.01966
	strontium group	18	.9533	.08462	.01994
Post treatment spine Tscore	Risedronate group	24	-2.4958	.74336	.15174
	strontium group	18	-2.5389	.47791	.11264
Change in BMD spine (gm/cm2)	Risedronate group	24	.1212	.07954	.01624
	strontium group	18	.1449	.07467	.01760
% change spine	Risedronate group	24	16.4985	11.46999	2.34130
	strontium group	18	18.8128	10.52794	2.48146
Pretreatment hip BMD (gm/cm2)	Risedronate group	24	.8372	.15114	.03085
	strontium group	18	.8477	.12180	.02871
Pretreatment hip Tscore	Risedronate group	24	-1.6958	.93923	.19172
	strontium group	18	-1.5389	.60014	.14145
Post treatment hip BMD (gm/cm2)	Risedronate group	24	.9178	.09846	.02010
	strontium group	18	.9433	.12470	.02939
post treatment hip Tscore	Risedronate group	24	-1.2833	.77385	.15796
	strontium group	18	-1.3000	.50643	.11937
Change in BMD hip (gm/cm2)	Risedronate group	24	.0848	.07739	.01580
	strontium group	18	.0956	.06346	.01496
% change hip	Risedronate group	24	11.1920	11.49354	2.34611
	strontium group	18	11.7848	8.49791	2.00298

Evaluation

Results following treatment were assessed based on the following parameters: Clinical improvement- pain, deformity, level of activity, clinical union of fractures. Radiological improvement- radio-density of bones, alignment of trabeculae, healing of fractures, metacarpal index and Singh's index. Dexa improvement in bone density. The primary efficacy end point was the percentage of change at the end of one year over baseline in bone mineral density (BMD) at lumbar spine (L1 to L4) and femoral neck on both sides taken as mean.

Statistical analysis

It was performed using SPSS version 11.5 statistical package for windows (SPSS, Chicago, IL). Continuous variables were expressed as mean +/- S.D. (Gaussian distribution) or range, and qualitative data was expressed in percentages. Unpaired and paired t tests for independent and dependent samples were used in comparing continuous data between two groups. The association between continuous variables was tested by linear correlation using Pearson's coefficient. All tests were two tailed, and a P-value of </= 0.05 was considered

significant. All confidence intervals were calculated at 95% level.

RESULTS

The baseline clinical and biological characteristics of all the one hundred and ninety patients included in the study are given in Table 1. The data on baseline characteristics were analyzed. The mean age was 55.6+- 9.1 years in the risedronate group and 57.7+- 7.8 years in the strontium ranelate group. All the subjects were above 40 years of age. The mean Body Mass Index (BMI) was 26.1±4.7 and 27.4±4.7 respectively in risedronate and strontium groups. Mean BMD at lumbar spine in both the groups was 0.849 ± .13 and mean T-score was -2.7. Mean BMD at hip was 0.858± 0.141 and 0.828± 0.319 respectively, in risedronate and strontium ranelate groups. The mean T-score was -1.4 in both the groups. Similarly there was not much difference between the values of other parameters like serum ionized calcium, serum 25-hydroxy vitamin D, serum TSH, serum creatinine, and serum lipids including total cholesterol, triglycerides, HDL, LDL and VLDL. A large number had history of only occasional milk intake and many subjects living in urban areas had practically no sun exposure. But as shown in table 1, on calculation of mean, each patient in the risedronate group was taking 171 ml milk daily and had sun exposure for around 33 minutes per day. The values for strontium ranelate group were 139 ml and 31 minutes. History of back pain was present in eighty three patients and fourteen patients had history of fragility fractures. Sixteen patients had history of cigarette smoking and 2 were chronic alcoholics but no significant liver disease. One hundred and twenty-three patients were living a sedentary life style with no or little weight bearing and muscle building exercise. Serum phosphorus was in normal range in all patients. Serum PTH was done randomly in forty-one subjects and was found to be within normal range. Serum alkaline phosphatase done in all patients and levels were raised in 56 patients. Total serum protein level was low in twelve patients. Serum creatinine was slightly raised in six patients who was either due to dehydration or old age and improved on proper hydration and repeat testing. On radiographic assessment, bone density was decreased in majority of the subjects.

The primary end point for efficacy evaluation was change in BMD at baseline and after one year of treatment with risedronate and strontium ranelate in 148 and 42 patients, respectively. Forty-two patients completed one year of treatment before conclusion of the study in whom repeat BMD was done to assess the effect of treatment. Twenty-four of these were taking risedronate and eighteen were on strontium ranelate. The mean difference in lumbar spine BMD at baseline and after one year of treatment with risedronate in twenty four patients was 0.121 with a standard deviation change of 0.079 [Table 2].

Similarly the mean difference in the eighteen patients on strontium ranelate after one year of treatment was 0.145 with a standard deviation change of 0.074. On applying the paired t-test to the pre and post-treatment BMD at hip and spine showed there was a significant improvement in both the treatment groups at spine ($t= -10.997$) ($p< 0.05$) and at hip ($t= -7.60$) ($p< 0.05$) [Table 3].

The mean percentage of change in BMD at baseline after 1 year treatment was 17.49 % in risedronate group and 11.19 in the strontium group. On applying the unpaired t-test to the percentage change in BMD at both the sites, the change was again very significant ($t=10.20$) ($p=0.00$) [Table 4].

On comparing the changes in various parameters of BMD after 1 year of treatment among the risedronate and strontium ranelate, there was not much difference between the two groups [Table 5]. Following treatment, there was definite clinical improvement in all patients in terms of pain, disability and mobility, especially in patients with osteoporotic vertebral fractures. On radiographic evaluation there was no significant change in bone quality.

DISCUSSION

Long term study of the risedronate and strontium on change in BMD has not been reported from India. In the present study we found that in both the treatment groups there was a significant increase in bone mineral density at lumbar spine and at total hip mean after one year of treatment. There was an increase of 11.46% and 11.49% in the BMD at baseline at lumbar spine and at hip, respectively. In the risedronate group (N=148) receiving 35 mg of risedronate weekly. Steven T. et al (1999) have reported in a randomized control study an increase in BMD of 5.4% at lumbar spine and 1.6% at femoral neck after 3 years of 5 mg risedronate weekly.[5] Similarly significant improvement in BMD and fracture risk has been reported by various authors after risedronate and other bisphosphonates.[5,7-10] Overall, the most common adverse events reported were upper gastrointestinal complaints like dyspepsia, abdominal pain and gastritis. Most of these events were of mild to moderate severity and settled with symptomatic treatment and discontinuation of therapy was not required in any subject.

In the strontium group (N=42), the change in BMD was 18.81% at lumbar spine and 11.78% at hip which is in accordance with the observation of P. J. Marie et al (2001) who have concluded that both preventive and strontium treatments induce beneficial effects on bone mass[11] and Pierre J. Meunier et al (2002) who have reported an increase in bone mineral density at 3 years by 14.4% at lumbar spine and by 9.8% at total hip (mean).[12] Pierre et al (1993) have reported a fracture risk reduction of 49% at one year and 41% at 3 years on daily 2 gm strontium ranelate. Similar reports are there in some other studies.[13, 1, 14] Diarrhea was the most common adverse event reported in 5.3% of cases. However it disappeared after first 3 months of therapy. Gastritis, nausea, headache, dermatitis and eczema were the other side-effects reported. All these events settled down within the first few weeks of therapy.

In our study we found that vitamin D deficiency (< 20 ng/ml) is quite common in India (64.3%) as has been reported by various other studies. Arya et al (2004) reported an incidence of 66.3% using 15 ng/ml as the cut-off point.[15] Using 20 ng/ml they reported an incidence of more than 78 %. We also found a significant correlation between low 25-hydroxy vitamin D levels in serum and

baseline BMD at lumbar spine. Many studies have earlier reported similar results .[16-19]

CONCLUSION

Our study showed that there was a significant improvement in BMD at lumbar spine and total BMD at hip after one year treatment with risedronate and strontium ranelate. There was 11.5% change in lumbar spine and hip BMD in the risedronate group. There was 17.5% change at lumbar spine BMD and 11.5% change in total hip BMD in the strontium ranelate group. There was no significant difference between the two groups. Most of the patients (64.3%) had associated Vitamin D deficiency indicating the importance of putting all patients on adequate calcium and vitamin D supplementation before starting bisphosphonates or any other specific treatment for osteoporosis.

A long term multicentric study is needed to find out not only change in BMD but also the impact of treatment.

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