Prospective Randomised Study of the Effect of Alendronate (Fosamax), Calcitriol (Rocaltrol) and Calcium on the Bone Mineral Density of Patients with Osteoporotic Hip Fractures

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ABSTRACT

Osteoporosis has been stated as one of the major causes of pathological hip fractures in the elderly. Improving the bone mineral density of these osteoporotic patients may prevent further fractures from occurring. We conducted a prospective randomised study on the effect of alendronate (Fosamax, MSD), Calcitriol (Rocaltrol, Roche) and calcium on the Bone Mineral Density (BMD) of patients with osteoporotic hip fractures. Patients who had surgery done for their osteoporotic hip fractures between December 1996 and May 1999 were entered into the study. The patients were divided into 3 groups. The first group, was given 1500 mg of elemental calcium in divided doses, the second group, alendronate 10 mg om and 1500 mg of elemental calcium and the final group, calcitriol 0.25 mcg bid. Forty-seven patients in group 1, 36 in group 2 and 39 in group 3 had repeat dexa scans at 1 year.

At one year, the BMD was increased in group 2 (alendronate and calcium) and decreased in groups 1 (calcium) and 3 (calcitriol). In patients with osteoporotic hip fractures, alendronate and calcium combination was able to improve BMD at one year.

INTRODUCTION

Osteoporosis is a silent disease that is characterised by low bone mass and microarchitectural deterioration of bone[1]. The consequence is that of an increased risk of fractures, most commonly at the vertebra, wrist and the hip[2]. Osteoporosis is becoming an important issue in Singapore as the population is rapidly ageing. In 1990, only 6% of the population was above the age of 65. In 2030, this will rise to 17%[3]. The incidence of osteoporosis as defined by bone mineral density measurements, is unknown in Singapore. At the Singapore General Hospital, in 1998, we had conducted 391 surgical procedures on patients above 60 years with intertrochanteric or neck of femur fractures. A large number of these fractures are due to osteoporosis. An analysis of patients[4] who had sustained osteoporotic hip fractures in Singapore in 1990, demonstrated a mortality of 26% in the first year. Of the survivors, 9% were bedridden and 24% wheelchair bound. The agents used to treat osteoporosis are calcium[5-6] vitamin D[7] and its active metabolites – alphacalcidiol[8] and calcitriol[9], bisphosphonates – etidronate[10] and alendronate[11] and, calcitonin[12].

The objective of this prospective randomised study was to compare the effect of three of these therapeutic agents, calcium, alendronate (Fosamax) and calcitriol (Rocaltrol) on the bone mineral density of our osteoporotic hip fracture patients, after a one year period.

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MATERIALS AND METHODS

Patients of age greater than 45 years, who had intertrochanteric fracture or neck of femur fractures that were admitted to the Singapore General Hospital between December 1996 and May 1999 were first screened for osteoporosis. The criteria for admission into the study were that they must have normal serum calcium, phosphate, serum alkaline phosphatase and liver function tests. The bone mineral density at the femoral neck is below the normal peak bone mass of our normal values by 2.5 SD or greater. These patients would have had surgery done for their hip fracture, either a fixation of the intertrochanteric fracture or a hemiarthroplasty. The bone mineral density (BMD) was determined at the point of admission into the study and at one year after, using the same Lunar DPX densitometer (Lunar, Madison, WI) (our institution has one scanner). The contralateral unaffected hip (at the femoral neck) and the lumbar spine (where at least 3 vertebrae from L1 to L4 were screened and the average result taken) were the areas screened. Should the patients have had both hips fractured, then the BMD at the lumbar spine was the only measure taken. The point of entry into this study was when they had surgery for the hip fracture and met the above criteria during the admission for their hip fracture.

The selected patients were then randomised into 3 groups according to the last digit of their admission number. The first group of 91 patients, the control group, were given 1500 mg of elemental calcium in divided doses, in the form of calcium carbonate. The second group were given 10 mg of alendronate (Fosamax, MSD) and 1500 mg of elemental calcium, as calcium carbonate, after excluding a history of peptic ulcer disease. Eighty-four patients were recruited in

this group. The final group of 86 patients were given calcitriol (Rocaltrol, Roche) 0.25 microgram b.i.d. The patients in the second group were advised to take alendronate tablet on its own, first thing in the morning with half a glass of plain water and not to lie down nor consume any food or medicines for the next half hour. The patients in the calcitriol group were advised not to take supplementary calcium in any form as there were reports that hypercalcaemia[8,13] could result. Serum calcium was to be checked every 3 monthly in this final group to detect hypercalcaemia. These patients were followed up at 3 monthly intervals to record any adverse outcome due to the treatment they were receiving and to review their progress after their hip surgery.

The statistical method used was to detect the percentage change of the bone mineral density at the spine and hip, after one year. Significant BMD change was taken to be a change of 2.2% at the hip and 3% at the spine[14].

PATIENT PROFILE

The age range of these patients was from 48 years to 97 years with the mean age at 72.5 years and the median decade the 70 to 80 years. One hundred and fourteen patients had a single co-morbidity of hypertension, diabetes mellitus, hypercholesterolaemia, hypothyroidism or opium addiction. Eighty-six others had two or more co-morbidities. These were hypertension, ischaemic heart, diabetes mellitus, previous cerebral vascular accident and a previous acute myocardial infarction. Eleven patients had diabetes mellitus, hypertension and IHD, while 5 patients diabetes mellitus, hypertension and hypercholesterolaemia.

One hundred and twenty-four patients had sustained an intertrochanteric fracture while 126 patients had suffered a neck of femur fracture. One hundred and twenty-one patients had fixation done with a dynamic hip screw for their intertrochanteric fracture while 3 had fixation done with the small proximal femoral nail (Synthes, Madison). One hundred and sixteen patients in the neck of femur fracture group received a hemiarthroplasty – an uncemented Moore's prosthesis, a cemented Thomson's prosthesis or a cemented bipolar prosthesis. Ten patients had cancellous screw fixation done for their neck of femur fracture. The treatment of the neck of femur fracture patients was determined by the protocol set in our department.

Post-operatively and after discharge, the patients that came for review were ambulant either in a wheelchair or were walking with a walking aid or independently. Patients in the intertrochanteric fracture group and the 10 patients who had cancellous screw fixation done for their neck of femur fracture all had their fractures united by 3 months. Three patients in the alendronate arm were excluded as they developed gastric symptoms. No patient in the calcitriol group experienced symptoms of hypercalcaemia or had an elevated serum calcium. This group did not have their serum calcium measurements done strictly to protocol, but all had at least one serum calcium level done during this one year period. No patient in the calcium group experienced constipation. One patient in the calcium arm had sustained bilateral neck of femur fractures at different times and had a Thomson's hemiarthroplasty done on one side and a cancellous screw fixation on the other.

RESULTS

There were 49 males and 212 females giving a male-female ratio of 1: 4.3. The BMD range at the hip was 0.29 to 0.71 g/cm^2 and 0.36 – 1.26 g/cm^2 at the spine. At one year follow-up, 47 patients in the calcium or control group, 36 patients in the alendronate group and 39 patients in the calcitriol group were available for a second bone mineral density study. The rest were lost to follow-up or were excluded for various reasons of developing complications due to treatment or for not following the study protocol.

In group 1 (calcium group), 45 patients experienced a decrease in BMD at the 'hip and spine'. Two patients had an increase in BMD at the spine.

In group 2 (alendronate & calcium), 31 patients had significant increase in BMD at the hip and 34 a significant increase at the spine. Seven patients had a significant increase at the hip (2 patients) or spine (5 patients).

In group 3 (calcitriol), 32 patients experienced a significant decrease in BMD at the hip and 36 at the spine.

The results are summarized in Table 1.

Table 1. Change in BMD at 1 year for the 3 groups in g/cm^2 and percentage ranges.

	Group 1 (Calcium)		Group 2 (Alendronate & Calcium)		Group 3 (Calcitriol)	
	Hip	**Spine**	**Hip**	**Spine**	**Hip**	**Spine**
Range of BMD change in g/cm^2	↓0.01 to ↓0.12	↓0.11 to ↑0.02	↓0.02 to ↑0.07	↑0.01 to ↑0.13	0 to ↓0.04	↓0.02 to ↑0.04
Range of BMD change in percentage	↓1.7 to ↓20.7	↓21.2 to ↑2.2	↓2.7 to ↑18.4	↑0.8 to ↑14.9	0 to ↓8.9	↓2.4 to ↑6.0

DISCUSSION

At one year follow-up, our study shows that the patients in the alendronate group experienced a significant increase in the BMD at both the hip and spine and in 7 patients, an increase at either the hip or the spine. The increase in the BMD is similar to that of other reports but for a few who had exceptional increase in percentage terms. It would be possible to assume that this could be an error but for the use of a single machine for BMD measurements. These results contrast with a FOSIT[15] study which at one year showed increases in BMD at the lumbar spine, femoral neck, trochanter and total hip at the 4.9%, 2.4%, 3.6% and 3.0% respectively.

The patients in this study are a different cohort from those reported in the FOSIT[15] study. These patients have severe osteoporosis, with BMD of > 2.5SD below the norm and having a hip fracture and some have significant co-morbidities. These patients have such low BMD levels that a small increase or decrease in g/cm^2 terms is exaggerated greatly in percentage terms.

Dirschl et al[16], in their 6 year longitudinal prospective study of patients with hip fractures, found that BMD decreased significantly at a mean of 4.3% at the femoral neck in the first year. This was followed by a progressive increase in BMD for the next 5 years to levels preceding the fracture. They postulated that there is some undefined metabolic process that is triggered by the hip fracture, which caused their patients to lose BMD in the first year following the fracture. This undefined metabolic process may be at work, explaining the different response seen in our patients as compared to patients in the FOSIT group. This study has shown that alendronate is able to counter this process partially in some and totally in the majority.

The majority in calcium or control and calcitriol groups did show a significant decrease in the BMD at both the hip and spine with some exceptions. Both calcium and calcitriol have been reported to have a positive effect on BMD[6,9] and the minority in these groups did respond or experience no significant drop in the BMD at both or one of the sites measured. The treatment by the mechanisms of increase in calcium availability as the calcium group was given adequate amounts of calcium, and by the increased absorption of calcium in the gut due to the action of calcitriol respectively could have come into play[9]. This increase in BMD in the minority of patients in both these groups is indicative of the potential beneficial effects of calcium and calcitriol in this group of severely osteoporotic patients, who have significant co-morbidities.

All patients in the alendronate group experienced a significant increase in BMD in at least one site. This is due to its mechanism of action as an anti-resorptive agent acting on the osteoclast[17] which is not influenced by the presence of other co-morbidities. Patients in the alendronate group did have GI effects which is similar to that reported by others, while the other groups did not experience any adverse effects.

Limitations to this study include the significant number lost to follow-up and exclusions due to various reasons. Patients that were non-ambulant were self-excluded as they were not able to come for follow-ups. The calcitriol group too were not followed to protocol with regard to checking of serum calcium levels. No attempt was made to study the bone turnover in this study[15] and the BMD follow-up was limited to after one year rather than at shorter intervals as have been done in several studies[6,15]. This was done in the interest of cost saving and the difficulty in getting this group of mainly elderly patients to come for regular BMD studies as there is considerable logistics involved.

In conclusion, patients with severe osteoporosis with a hip fracture, are a unique group. They have a significant mortality and morbidity and may have an undefined metabolic process that causes significant loss in BMD in the first year, following the fracture. The treatment of choice for their osteoporosis is alendronate. This study has shown that at one year, the BMD is increased significantly in the group treated with alendronate. The benefit of alendronate treatment is however partial in some and total in the majority. Further investigation is needed to ascertain if there are other processes at work that cause the decrease in BMD in the first year following a hip fracture.

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