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Original Research Article

The Efficacy of a Structured Exercise Program versus Zoledronic Acid in Persons with Primary Osteoporosis: A Prospective, Randomized Controlled Trial

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ABSTRACT

Background: Osteoporosis is an age-related decline in bone health wherein treatment with bisphosphonates, such as zoledronic acid, remains a popular choice. Recently, exercise has emerged as a non-pharmacological alternative; however, the extent of its efficacy remains unclear.
Research question: Is a structured exercise program as efficacious as zoledronic acid in improving bone mineral density, reducing pain and improving quality of life in persons with primary osteoporosis?
Methods: Diagnosed cases of primary osteoporosis from consecutive patients visiting OPD of PM&R were recruited for a prospective, randomized controlled trial in a tertiary hospital. Participants were randomly allocated to receive one year of exercise, or, a single infusion of zoledronic acid. Primary outcome of the study was bone mineral density (BMD). The principal investigator, outcome assessor and statistical analyzer were masked to the allocations; intervention administrators were masked to the outcome measures. Data was analyzed using intention-to-treat with multiple imputations.
Results: Two hundred patients of osteoporosis were recruited between April 2018 and May 2019. Statistically significant($p<0.05$) differences were found for BMD between the groups at the 12 months follow-up in favor of zoledronic acid except for the wrist site. Symptoms of mild whole body pain and impaired quality of life were reported at baseline. On comparing the two groups, statistical significance was found in favor of zoledronic acid at both the 6 months and the 12 months follow-up for both the parameters.
Conclusion: Exercise is not as efficacious as a Zoledronic acid infusion in persons with primary osteoporosis.
Trial registration: CTRI/2018/03/012837

Keywords: Osteoporosis, Bone Mineral Density, Exercise, Zoledronic acid, Randomized controlled trial

INTRODUCTION

Primary osteoporosis is an age-related systemic condition, whose management still lacks clear consensus. The definition of Osteoporosis (OP) is "Bone Mineral Density (BMD) of more than 2.5 standard deviations (SDs) below the young normal mean. [1] A third of the postmenopausal women tend to develop osteoporosis, amounting to an estimated 75 million people in the USA, Europe, and Japan. [2] Over the past century, there has

been an increased scientific interest in osteoporosis research given the rapid increase in older generations. In fact, the latest projections show that osteoporosis will soon be a leading cause of disability for women over the age of 50 years. [3]

The course of treatment has been a contentious subject with bisphosphonates remaining the mainstay of treatments, whether pharmacological or non-pharmacological, due to their prominent anti-osteoclastic activity. Apart from this, bisphosphonates have also been reported to have an analgesic effect on whole body pain symptoms. [4] A typical regime consists of a yearly infusion, for a period of three to five years, [5] subsequently followed by a 'drug holiday'. For this reason, clinicians frequently look into non-pharmacological substitutes such as exercise programs to either push off the age of onset of osteoporotic symptoms, or, to serve as an adjunct to the existing pharmacological treatments.

The goals of exercise programs commonly prescribed in persons with osteoporosis include the correction of faulty postures and fall prevention techniques. The rationale of recommending exercises comes from the fact that significant pain and kinesiophobia [6] hampers the motivation and ability to move, progressively causing disuse-based loss of bone density. Thus, it would stand to reason that a gradual loading of mechanical stress would help build up the bone density. [7,8] Though, theoretically logical, there exists a certain lack of confidence [9] in recommending exercises in people with weakened bones. The exact mechanism of exercise therapy is challenging as analysis of bony architecture at the tissue level is limited by technology. Further, most of the treatment modalities have not been compared with each other using clinically relevant outcome measures. [10-12]

It was against this backdrop, that such a study was conceptualized. The aim of the present study was to compare the efficacy of a structured exercise program in comparison to a single infusion of zoledronic acid, which is a relatively popular treatment. The primary outcomes were bone mineral density by dual-energy x-ray absorptiometry at the spine, hips, and wrist site. The secondary outcomes were pain intensity, quality of life, and any harms arising out of the study. We hypothesized that a year-long exercise program could provide a symmetrical active comparator to a single infusion of zoledronic acid in persons with primary osteoporosis.

METHODS

Study design and participants

The present study was a prospective, parallel-design, active-controlled, randomized clinical trial done in the Department of Physical Medicine and Rehabilitation in a tertiary care institute. Consecutive patients attending Physical Medicine and Rehabilitation OPD and diagnosed with primary osteoporosis aged 45 to 65 years of either gender were included.

Patients having received any medications for osteoporosis (other than calcium and vitamin D_3) within the last 1 year, having impaired kidney function, uncontrolled cardiac conditions such as arrhythmia, any neurological, muscular or orthopedic condition, that hinders participation in the exercise program, and with insufficient understanding to fill the quality of life questionnaire or follow the structured exercise program at home were excluded from the study. Written informed consent was taken from participants and a code was assigned to each participant to maintain confidentiality. The study protocol was ethically approved by the Institute Ethics Committee and registered prospectively.

Randomization and Blinding

Participants were randomly allocated to each arm in a 1:1 ratio according to a computer generated random number sequence in a block of two to ensure an equal number of participants in each group. These numbers were generated prior to inclusion and were done by a person who

had no involvement in the rest of the study. Participants were allocated to intervention arms by opening a sealed envelope corresponding to the computer-generated random numbers. Baseline assessments and follow-ups were done by a person blinded to allocation. The investigator performing the statistical analysis was unaware of group allocation and tables and charts were prepared according to the plan prepared at the initial phase of the study. Records were maintained according to the participants' serial number and all the identifiable participant data was concealed.

Interventions

Patients, after filling informed written consent forms and screened for the inclusion and exclusion criteria were subjected to baseline investigations of Calcium and Vitamin D levels. In case any of the two were deficient, supplementation was done according to standard protocol prior to inclusion. Maintenance dose of calcium and vitamin D_3 was given throughout the period of the study. Participants were randomly allocated to either receive zoledronic acid infusion or where patients received a structured exercise program.

In the Zoledronic Acid (ZA) group, a single intravenous infusion of zoledronic acid 5mg with 100 ml of Normal saline over 30 minutes was administered on an OPD basis under the supervision of a physiatrist with six years of experience in the field. Subjects were prescribed Tablet Acetaminophen 500mg on an SOS basis for three days in case of flu-like symptoms. They were asked to contact the administering Physiatrist over the telephone in case of the occurrence of any adverse reactions.

The Structured Exercise Program was instructed and monitored by a senior Physiatrist of 30 years of experience. Subjects recruited to the Structured Exercise Program were taught exercises as per the International Osteoporosis Foundation's Recommendations for Postmenopausal Women and included the following sequences: (i) *Warm up/Endurance sequence:* First three months- Walking and running for 20 minutes to start with and gradually increased according to tolerance to get patients prepared for higher impact exercise in the future. The next three months comprised of 10 minutes long low to high impact aerobic exercise with a gradually increasing amount to improve aerobic endurance. (ii) *Jumping sequence:* It was started after six months of training. It was initiated with rope skipping exercises and later more extensive exercises such as closed leg jumps were incorporated. (iii) *Strength-training sequence.* This was modified to ensure feasibility without departing from the recommendations. The patient was asked to demonstrate the exercises taught every 15 days and rectifications were made in case the technique was wrong. Patients were asked to keep a log book throughout and enter details about the exercises done. They were considered as dropouts if they failed to do exercise on more than 10% of days.

Outcomes

Patients were assessed at baseline, 6 months and at 1 year. BMD by DXA scanning was the primary outcome measure. Pain and Quality of Life (QOL) were secondary outcome measures. BMD was measured by DXA scanning and reports were interpreted by another Physiatrist with six years of experience, unaware of group allocation. Pain was evaluated with Numeric Pain Rating Scale (NPRS) and QOL by using ECOS – 16 Questionnaire. ECOS 16 has been validated and used in patients of Osteoporosis. [13] Assessment Pain and QOL were done by a Resident Physiatrist, who was blinded to group allocation. Pain and QOL were evaluated at baseline and each follow-up. DXA scan was done at baseline and at the one-year follow-up.

Statistical analysis

The total sample size was taken as 200 patients (100 patients per group) based on an unpublished pilot study conducted in the same department. Intention to treat analysis with multiple imputations was done

to include data of dropouts. Continuous variables are expressed as Mean ± SD, Median value (25th, 75th quartile), and 95% confidence intervals, as applicable. The normality of data was tested by the Kolmogorov-Smirnov test. If the normality was rejected, non-parametric test were used. Quantitative variables were compared using the Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups and Paired t-test/ Wilcoxon test within the groups across follow-ups. Qualitative variables were compared using Chi-Square test /Fisher's exact test. A p-value of less than 0.05 was considered statistically significant. The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) for Windows version 21.0 (Armonk, NY: IBM Corp).

RESULTS

Between April 2018 and May 2019, consecutive patients were screened for the eligibility criteria. The most common reason of ineligibility was having conditions that prevented full participation in exercise and for declining to participate was the inability to visit the clinic at the pre-scheduled time-points. Two hundred subjects were enrolled for the study having a mean bone mineral density of -2.72 ± 0.27 at spine (range: -3.40 to 1.80), -2.80 ± 0.27 (range: -3.40 to 2.40) at the right hip, -2.80 ± 0.21 (range: -3.40 to 2.20) at left hip, and -2.69 ± 0.36 (range: -3.40 to 1.80) at the radius. All the recruited patients were right-handed females with an average age of 55.56 ± 6.43 years (range: 45 to 65 years) in early post-menopausal stages (self-reported). The pain symptoms were mild (average: 2.89 ± 0.91, range: 1 to 5 arbitrary units) and quality of life was 2.42 ± 0.46 (range: 1.00 to 4.43 scores). Baseline characteristics were balanced between the therapy arms at randomization. Refer to Table 1 for patients' characteristics at randomization.

Table 1.Patient characteristics at randomisation.

	Structured exercise program (n=100)	**Zoledronic acid (n=100)**	**p-value (between the groups)**
Age (in years)	55·50 (49·00, 61·00)	57·00 (49·00, 62·00)	0·50
BMD as T-scores (Spine)	-2·80 (-2·90, -2·60)	-2·70 (-2·90, -2·50)	0·27
BMD as T-scores (Hip, right)	-2·80 (-2·90, -2·60)	-2·80 (-2·90, -2·70)	0·32
BMD as T-scores (Hip, left)	-2·80 (-2·90, -2·60)	-2·80 (-2·90, -2·70)	0·50
BMD as T-scores (Radius, right)	-2·75 (-2·90, -2·40)	-2·80 (-2·90, -2·60)	0·12
Pain intensity (as NPRS scores)	3·00 (2·00, 3·00)	3·00 (2·00, 3·50)	0·84
Quality of life (as ECOS-16 scores)	2·46 (1·87, 3·00)	2·31 (1·81, 2·75)	0·14

Data have been depicted as median values (25th quartile, 75th quartile). BMD: bone mineral density using dual-energy x-ray absorptiometry; NPRS: numerical pain rating scale; ECOS-16: assessment of health-related quality of life.

One hundred and eighty-five subjects (92.5%) completed the therapy allocated to them. Compliance to exercises was noted using diary entries at each visit, with the included participants having performed exercises on 93% of the prescribed days (data not shown); eight subjects were excluded at the 6 months time-point due to inadequate adherence to the exercise program. Six subjects (four in the zoledronic acid group; two in the exercise group) left the intervention due to unspecified reasons as they could not be contacted (see Figure 1. Consort flow-diagram).

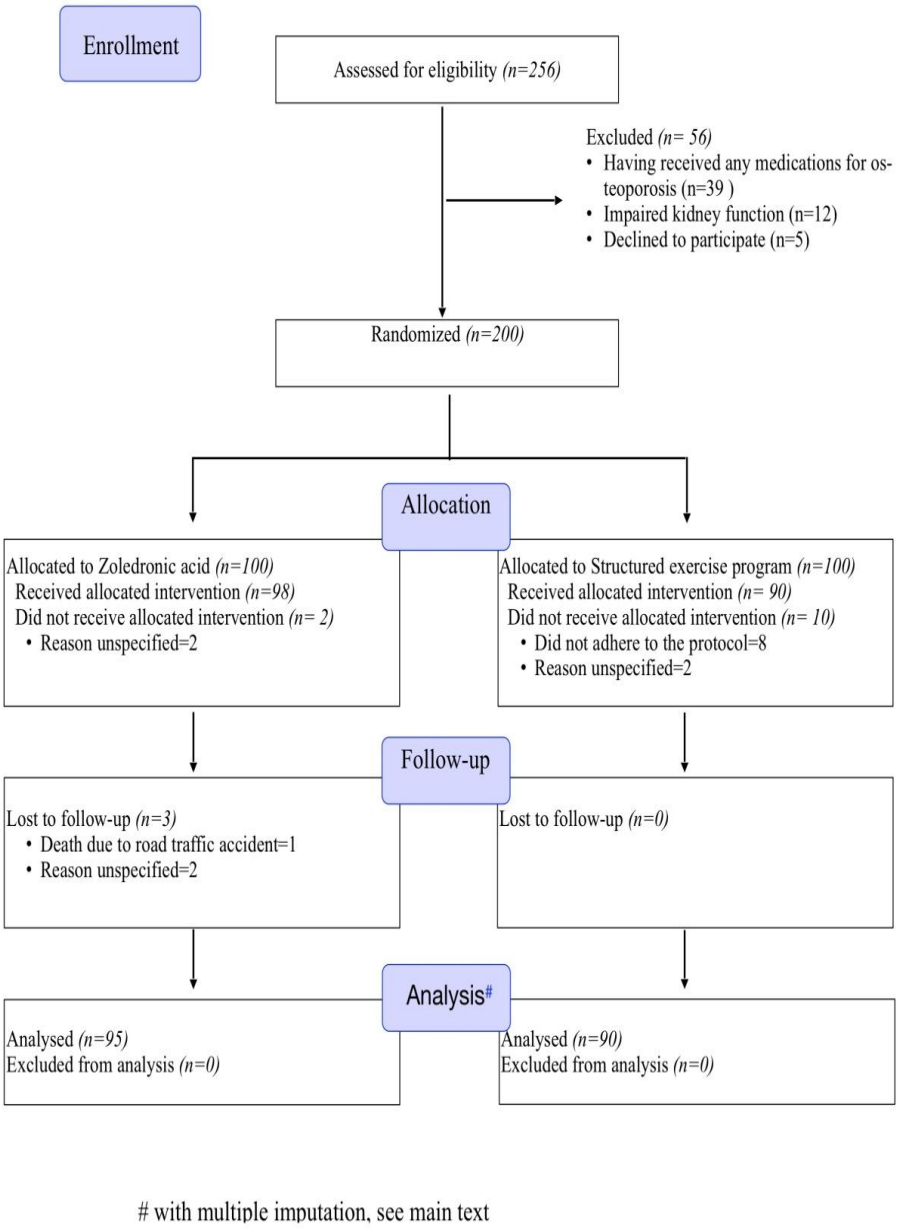

Figure 1. Consort flow-diagram

Table 2. **Efficacy of a structured exercise program *vs.* zoledronic acid on bone mineral density.**

		Structured exercise program (n=100)	Zoledronic acid (n=100)	p-value (between the groups)
BMD as T-scores (Spine)	Baseline	-2·80 (-2·90, -2·60)	-2·70 (-2·90, -2·50)	0·27
	1 year	-2·70 (-2·90, -2·49)	-2·50 (-2·70, -2·35)	<0·01*
	p-value (within the group)	0·01*	<0·01*	
BMD as T-scores (Hip, right)	Baseline	-2·80 (-2·90, -2·60)	-2·80 (-2·90, -2·70)	0·32
	1 year	-2·70 (-2·90, -2·50)	-2·60 (-2·71, -2·50)	0·02*
	p-value (within the group)	<0·01*	<0·01*	
BMD as T-scores (Hip, left)	Baseline	-2·80 (-2·90, -2·60)	-2·80 (-2·90, -2·70)	0·50
	1 year	-2·70 (-2·90, -2·51)	-2·6 (-2·78, -2·50)	0·03*
	p-value (within the group)	<0·01*	<0·01*	
BMD as T-scores (Radius, right)	Baseline	-2·75 (-2·90, -2·40)	-2·80 (-2·90, -2·60)	0·12
	1 year	-2·60 (-2·80, -2·20)	-2·60 (-2·80, -2·40)	0·29*
	p-value (within the group)	<0·01*	<0·01*	

Data have been depicted as median values (25th quartile, 75th quartile). Asterisk (*) shows the significance of p-value less than 0·05. BMD: bone mineral density using dual-energy x-ray absorptiometry.

Univariate analysis showed that exercise or zoledronic acid therapies could improve bone mineral density at the spine, right hip, left hip, and wrist. One year of the exercise was not as effective as a single infusion of zoledronic acid barring wrist, where the two were statistically comparable. Table 2 shows efficacy of a structured exercise program *vs.* zoledronic acid on bone mineral density.

Symptoms of mild whole body pain were reported at the baseline. Reduction in pain intensity was found to be significant in both the groups. On comparing the two groups, statistical significance was found in favor of zoledronic acid. Refer to Table 3 for efficacy of a structured exercise program group *vs.* zoledronic acid on the pain intensity.

***Table 3.*Efficacy of a structured exercise program *vs.* zoledronic acid on pain intensity.**

	Structured exercise program (n=100)	Zoledronic acid (n=100)	p-value (between the groups)
Baseline	3·00 (2.00, 3.00)	3·00 (2·00, 3·50)	0·83
6 months	2·00 (1·00, 3·00)	2·00 (1·00, 2·00)	0·01*
1 year	1·00 (1·00, 2·50)	1·00 (1·00, 2·00)	0·03*
p-value (within the group)	<0·01*	<0·01*	

Pain intensity has been measured using 11-point NPRS. Data have been depicted as median (25th quartile, 75th quartile). Asterisk (*) shows the significance of p-value less than 0·05. NPRS: numerical pain rating scale.

Another outcome of the study was the assessment of health-related quality of life in osteoporosis. Improvement was seen in both the groups. Statistical significance was found in favor of zoledronic acid on the comparison of the two groups. Refer to Table 4. Efficacy of a structured exercise program group *vs.* zoledronic acid on quality of life.

***Table 4.*Efficacy of a structured exercise program *vs.* zoledronic acid on quality of life.**

	Structured exercise program (n=100)	Zoledronic acid (n=100)	P-value (between the groups)
Baseline	2·46 (1·87, 3·00)	2·31 (1·81, 2·75)	0·14
6 months	2·28 (1·81, 2·75)	1·97 (1·50, 2·37)	0·01*
1 year	1.81 (1.50, 2.40)	1.75 (1.25, 2.09)	0.01*
P value (within the group)	<0·01*	<0·01*	

Quality of life has been assessed using ECOS-16 scores. Data have been depicted as median values (25th quartile, 75th quartile). Asterisk (*) shows the significance of p-value less than 0.05. ECOS-16: assessment of health-related quality of life.

Minor side effects such as muscle soreness and cramps were reported by 72 subjects in the exercise group; mild, self-limiting, flu-like symptoms were experienced by 8 subjects in the zoledronic acid group. None of these symptoms persisted for more than 48 hours. Additionally, no incidence suggestive of an overt fracture was reported by any of the patients.

DISCUSSION

Primary osteoporosis is an age-related systemic condition whose management still lacks clear consensus. Despite skepticism, existing literature shows promising results for exercises in people with osteoporosis. The objective of the present study was to compare the efficacy of a structured exercise program in comparison to a single infusion of zoledronic acid, which is arguably the most used anti-resorptive agent. The results of this study were an improvement in bone mineral density, reduction of pain symptoms and quality of life, regardless of the intervention. The exercise was not comparable to zoledronic acid with regard to most of the outcome measures, except for BMD at the wrist site. The interventions were well-accepted, with minor side effects being reported in each group. No incidence of fracture or any adverse effects were noted.

Though the documentation of the effect of exercise in post-menopausal

population is gaining stride, it still remains unclear whether it is as efficacious as the currently available pharmacological interventions. To date, several comparative studies have considered exercise and several anti-resorptives, [14-16] but only preliminary animal evidence exists for zoledronic acid. [17] Our results are not in line with the latter evidence [17] as the exercise was found to not be as efficacious as zoledronic acid in increasing the BMD (at spine and hip), reducing pain, and increasing quality of life. The inconsistency may be attributed to the lack of clear understanding of time or the intensity of exercise therapy. To this date, the current understanding of both these aspects of exercise therapy remains unclear and needs to be clarified. Few reports suggest that the effect of exercise is certainly effective in one year, but the gains are likely to be incremental in the second year. [14] Another viewpoint comes from the fact that the previous studies comparing pharmacological agents with exercises have used a combinatorial approach, which is known to have a synergistic effect. [18] Having said that, it may be pointed out that a combination of exercise and zoledronic acid did not show any additive or additional effect in osteoporotic model. [17] Nevertheless, testing a combinatorial effect of zoledronic acid and exercise may be worthy of investigation.

An important observation was that the comparable effect of either therapy at the wrist site. The result is difficult to fully explain, but one possible explanation could come from the fact that women [19] often have weaker wrists and upper body strength. An emerging perspective is that weaker bones often have a larger capacity to make adaptive gains. From this purview, it could be argued that either intervention may be able to produce a significant, yet, saturated improvement at the wrist. This, however, is a speculative viewpoint and needs to be formally tested.

There are some sources of errors that need to be mentioned. Some studies have shown that vitamin D supplements are known to improve skeletal health and therefore, may mitigate pain symptoms, even if in part. [20] However, this could not have had altered the outcome of the study as the basal serum levels of vitamin D of the participants were taken into consideration before being included in the study and were monitored throughout the study. In another aspect, the study did not control for the placebo aspects of zoledronic acid infusion, that is, the procedure of administrating a pharmaceutical agent could have favorably modulated the anticipation of symptom improvement. This may have resulted in an overestimation of the effect size of zoledronic acid. Also, our study was confined to a cohort of the south-east Asian population. Consequently, future studies may include more outcomes such as fracture risk and the above mentioned factors into consideration.

Notwithstanding the limitations, some potential sources of error have been mitigated by the use of appropriate study design, use of active comparator, blinding (principal investigator, outcome assessors, intervention administrators, and statistical analyzer), and uniformity of DEXA screening. No incidence of fracture or any adverse effect of the therapy was noted in either group in the followed-up patients. Both appear to prevent fractures equally, but further studies with fracture prevention as the primary outcome are needed.

CONCLUSION

The structured exercise program as well as zoledronic acid increase bone mineral density, reduce pain, and improve quality of life in persons with primary osteoporosis. However, exercise is not as efficacious as zoledronic acid, except for its effect on bone mineral density at the wrist.

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