Original Article

Clinical efficacy of amino bisphosphonate on periodontal disease status in postmenopausal women: Randomized double-blind placebo-controlled trial

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Abstract

Objectives: Osteoporosis is a common skeletal disorder affecting postmenopausal women. Data suggest that postmenopausal women are at increased risk of periodontal diseases. Amino bisphosphonates are potent inhibitors of bone resorption and effectively used in the treatment of osteoporosis. Preliminary data indicate that there is a potential role for bisphosphonates in the management of periodontitis. Hence, this randomized placebo-controlled trial was designed to investigate the clinical efficacy of amino bisphosphonate on periodontal disease status among postmenopausal women. **Materials and Methods:** Thirty patients were randomly allocated to two treatment groups: Group A, which received scaling and root debridement and 70 mg weekly single oral dose of alendronate drug, and Group B, which received scaling and root debridement and placebo drug for 6 months. Clinical periodontal measurements were carried out for all patients at the baseline and 6 months later. Mandibular bone mineral density (BMD) was measured using a dual energy X-ray absorptiometer at the beginning of the study and the end of 6 months. **Results:** A weekly single oral dose of 70 mg alendronate was well-tolerated. The intragroup comparison showed significant improvement in periodontal parameters in both groups. The intergroup comparison showed a significant increase in BMD after 6 months in Group A when compared with Group B ($P = 0.0179$). **Conclusion:** Single oral dose of 70 mg alendronate per week is well-tolerable, gastro-intestinally safe, and improves the clinical outcome of nonsurgical periodontal therapy.

Keywords: Bisphosphonates, bone mineral density, osteoporosis, periodontitis

Introduction

Periodontitis is a chronic infection-driven inflammatory disease of polymicrobial etiology, characterized by loss of connective tissue attachment and alveolar bone that support the tooth.[1]

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Osteoporosis is a skeletal disorder characterized by low bone mineral density (BMD) and deterioration of microarchitecture of bone, thereby, causing an increase in bone fragility and fracture.[2]

Periodontal diseases and osteoporosis are both bone resorptive diseases and are major public health problems. Both the diseases lead to a significant amount of morbidity and financial burden on the affected patients, but the good news is that both are preventable and can be diagnosed and treated at an early stage in a cost-effective manner.

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The evaluation of the relationship between osteoporosis and periodontitis is a complicated one. It can be understood by the fact that both diseases are multifactorial in etiology. Various systemic factors influence the progression of both diseases, namely, age, race, diet, gender, hormone therapy, smoking, genetic factors, exercise, and body weight. Furthermore, local factors, such as bacterial plaque and calculus, may also mask the effect of osteoporosis on the periodontal status.[3]

Recent literature suggests a positive association between osteoporosis and periodontal disease among postmenopausal females.[4] Loss of alveolar bone is a prominent feature of periodontal disease. Low BMD in postmenopausal women could act as an aggravating factor for bone destruction in periodontal disease.

Recently, there has been a lot of research on the host–microbial interaction in the pathogenesis of the periodontal disease, and this has presented the opportunity for exploring new treatment strategies. One of the developed treatment modality uses host-modulating agents. These host-modulating agents are used as an adjunct to tip the balance between periodontal health and disease progression toward a healing response.[5] Williams *et al.* have shown that by modulating the host response, periodontal disease progression can be prevented.[6]

Recently, bisphosphonates, which are bone-sparing agents, have been found to inhibit matrix metalloproteinases (MMPs) through a mechanism that involves chelation of cations. They are analogs of pyrophosphate that have a high affinity for calcium phosphate crystals and that inhibit osteoclast activity. MMPs are known to have a high affinity for bone and a high affinity to inhibit osteoclastic bone resorption. Preliminary data indicate that there is a potential role for bisphosphonates in the management of periodontitis in osteoporotic patients.[7,8]

For the diagnosis of osteoporosis, dual energy X-ray absorptiometry (DEXA) is a valid, noninvasive technique, which is considered as the gold standard method to evaluate BMD.[9]

To the best of our knowledge, there is a scarcity of published literature investigating the effect of bisphosphonate on periodontal disease status and measuring mandibular BMD using the DEXA scan in postmenopausal women. Hence, based on the available data, this study was designed to investigate the clinical efficacy of amino bisphosphonate on periodontal disease status among postmenopausal women, to investigate the safety of amino bisphosphonate, and to note any adverse event occurrence.

Materials and Methods

Study population

This study was a single-center, 6-month follow up, randomized, double-blind, placebo-controlled study conducted at the Department of Periodontics, Rajasthan University of Health Sciences College of Dental Sciences (RUHS-CDS), Jaipur, Rajasthan, India. The study protocol was reviewed and approved by the ethical committee of the RUHS, Jaipur, India. The RUHS, Jaipur, India, funded this study.

A total of 97 patients were screened in the outpatient section of the Department of Periodontics, RUHS CDS, Jaipur. Finally, 30 female patients (aged between 51 65 years) were selected for the study based on inclusion criteria [Figure 1].

Selection criteria

This study included systemically healthy female patients in the age group of 51 to 65 years, who had reached menopause and were diagnosed with chronic periodontitis (American Academy of Periodontology, 1999 criteria)[10]. Patients who had at least 20 natural teeth and no history of any kind of periodontal therapy in the last 6 months were included in the study. This study excluded patients on corticosteroids, hormone replacement therapy, and/or immunosuppressive treatment and those who had a history of bisphosphonate-use within 1 year before the start of the study. Patients who were on nonsteroidal anti-inflammatory drugs or any other drug known to affect bone/calcium metabolism and who were allergic to amino bisphosphonates were excluded from the study. In addition, patients diagnosed with esophagitis, reflux disease, peptic ulcers, ulcerative colitis, or any other conditions, which made it inadvisable for the patient to participate, were excluded from the study. All the study patients were informed of the nature, objectives, and possible risks of the study, and they signed the informed consent forms. Patients were followed up every 2 weeks for 6 months. Telephonic reminders were given for medication compliance, and the compliance was assessed at each visit by counting the capsules remaining with the patients.

Randomization and clinical procedure

On the basis of power calculation (power of the study 80% and $P \leq 0.05\%$), 30 patients were randomly allocated (computer-based random allocation) to two treatment groups. Patients were age-matched into two groups of 15 each. Group A received scaling and root debridement and a single dose of 70 mg amino bisphosphonate in capsule form weekly for 6 months, and Group B received scaling and root planning and placebo drug in an identical-appearing capsule. At the baseline, patients in both the groups received scaling and root debridement for removal of supra and subgingival plaque and calculus (local factors), which was done by a blinded investigator (a dental surgeon). Similar oral hygiene instructions were given to patients of both groups. Patients were unaware of the treatment group they were included in, and a masked investigator gave the capsules to all the patients along with the instructions.

Patients were asked to fix one day in a week (e.g., Sunday) for taking the capsule orally with plain water on an empty stomach, to not lie down or sleep for 2 h after taking the capsule, and to report any adverse side effect of medicine, if noticed, so that appropriate medical treatment can be provided to them.

Allocation concealment was done by keeping the drugs, that is, amino bisphosphonate and placebo in identical-appearing capsules.

Mandibular BMD measurement by DEXA scan[11]

DEXA is a considered gold standard investigation for the diagnosis of osteoporosis. DEXA measurement of BMD of the jaws was first described in 1993.[12] Following the method as described by Horner *et al.*, it was performed using a Lunar DPX-L densitometer (Lunar Corporation, Madison, Wisconsin, USA).[13] Forearm software was used as no DEXA software specifically designed for the mandible was available. For mandibular BMD measurement, patients were asked to position themselves in a semiprone position, with the right side raised, the neck slightly extended, and the head in a true lateral position to superimpose the contralateral sides of the mandible. DEXA scanning was done starting from 1 cm above the temporomandibular joints and continuing through the ramus to the body and ending in the symphysis region of the mandible. To derive data for mandibular BMD, manual analysis was performed using rectangular customized regions of interest (ROIs) placed over three areas: the ramus, body, and symphysis region. The shape and size of the ROIs were altered and adjusted to conform to the shape of the bone images of each patient. Data from the initial manual analysis were used for determining the relations between BMDs in the mandibular sites.

Statistical analysis

Data obtained were compiled in a Microsoft Office Excel sheet and were subjected to statistical analysis using the Statistical Package for Social Science (SPSS v 21.0, IBM, Armonk, New York, United States). Mean and standard deviation were calculated for the data. A probability value of $P < 0.05$ was considered to be statistically significant, keeping α at 5% and β at 20%, thereby , considering power of the study to be 80%. An intragroup comparison was done using a paired *t*-test, and an intergroup comparison of data was done using a *t*-test.

Results [Table 1]

A total of 97 patients were screened. Out of these 97 patients, 30 fulfilled the inclusion criteria. There were 15 participants in each group. The study was completed by 29 patients. One patient in Group A did not turn up at the stipulated time (i.e., 6 months of alendronate treatment) for the DEXA scan. She was excluded from the result analysis.

On intragroup comparison, in Group A, all the clinical periodontal parameters [Table 2] and BMD values [Table 3] showed significant improvement after 6 months. Group A showed a statistically significant increase in BMD values (1.16 ± 0.31 to 1.19 ± 0.31), that is, toward normal status ($P = 0.0261$).

Within Group B, except for the BMD values, all clinical periodontal parameters [Table 4] showed significant improvement after 6 months. Group B showed significant decrease in BMD values ($0.95 \pm 0.26 - 0.93 \pm 0.26$) [Table 5], that is, toward osteoporotic status ($P = 0.0028$).

On intergroup comparison at baseline, there was no statistically significant difference between the clinical periodontal parameters. All the clinical periodontal parameters at baseline showed significant improvement in both the groups after 6 months.

Intergroup comparison [Figure 2] showed a significant increase in BMD after 6 months in Group A when compared with Group B ($P = 0.0179$).

As far as the safety of amino bisphosphonates was concerned, the overall and upper gastrointestinal safety and tolerability profile of alendronate after 6 months of treatment were highly favorable, that is, oral 70 mg weekly single dose of alendronate was well-tolerated in this 6-months study, and there was no untoward incidence like an allergic reaction or gastric regurgitation reported with the use of the drug.

Discussion

This study evaluated the clinical efficacy of amino bisphosphonate on periodontal disease status in postmenopausal women.

Postmenopausal women are at increased risk of bone loss, which may affect their oral and periodontal health. The role of estrogen deficiency is critical and well-documented in the pathogenesis of osteoporosis in postmenopausal women.[14] Geurs *et al.* had proposed potential mechanism to explain the relationship between osteoporosis and periodontitis. The potential mechanism which causes periodontal disease progression in postmenopausal osteoporotic women maybe because of less crestal alveolar bone per unit volume, which gets more easily absorbed. There is an increase in active osteoclast numbers and reduced osteoclast apoptosis because of estrogen deficiency in menopause. The relationship between the two chronic diseases can also be explained by the action of proinflammatory

Table 1: Results at baseline and comparison after 6 months

Parameter	Baseline (mean±SD)			After 6 months (mean±SD)		
	Group A	Group B	*P* (inference)	Group A	Group B	*P*
SBI[a]	2.52±0.75	2.79±0.75	0.1708 (NS[b])	1.69±0.42	1.93±0.43	0.0419 (S[c])
Probing depth	4.73±0.81	4.33±0.51	0.1269 (NS)	3.33±0.41	3.12±0.46	0.1788 (NS)
Clinical attachment	2.94±0.73	2.39±0.61	0.0171 (S)	2.18±0.49	2.15±0.46	0.5212 (NS)
BMD[d] values	1.16±0.31	0.95±0.26	0.0543	1.19±0.31	0.93±0.26	0.0179

[a]SBI=Sulcus bleeding index. [b]NS = Not Significant. [c]S = Significant. [d]BMD=Bone mineral density

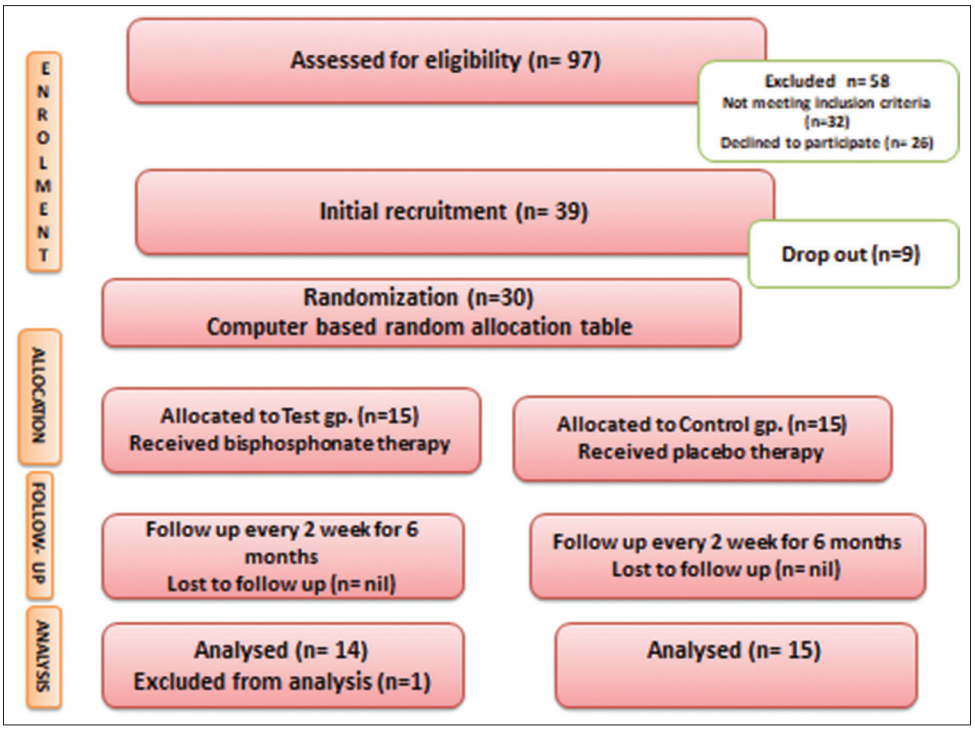

Figure 1: Consolidated Standard for Reporting Trials flow diagram

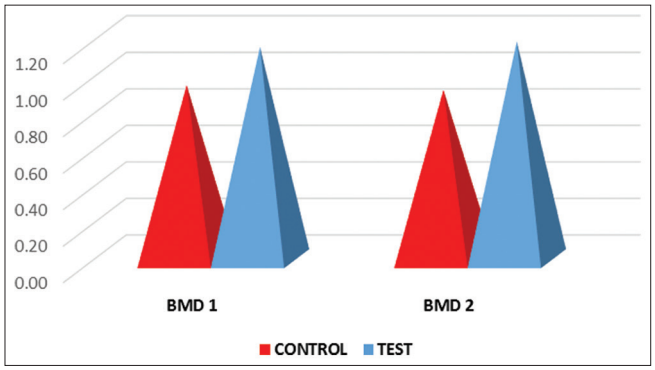

Figure 2: Graph showing the intergroup comparison of bone mineral density values of Group A and B at baseline and after 6 months

cytokines and prostaglandins. As the chemical mediators of inflammation develop in both the diseases, there is a possibility of a two-way relationship between these two diseases. Cytokines like interleukin-1 and interleukin-6, tumor necrosis factor, and prostaglandins have a bone resorption effect.[15]

Randomized clinical trials of alendronate demonstrated an increase in BMD in postmenopausal women with osteoporosis.[16] Literature also documents that the systemic and local administration of ALN Alendronate reduced the alveolar bone loss in periodontal flap surgical procedures[17,18] Recent literature data suggest that alendronate treatment improves the clinical outcome of nonsurgical periodontal therapy.

This randomized, double-blind assessment of the effect of bisphosphonate on periodontal disease status in systemically healthy postmenopausal women found that the clinical periodontal parameters improved in both Group A and B [Tables 2 and 4]. This improvement may be attributed in part to the scaling and root debridement and oral hygiene instructions given to the patients of both the groups at baseline. These results

Table 2: Intragroup comparison of the periodontal parameters of Group A at baseline and after 6 months

Parameter	Group A		
	Baseline	After 6 months	*P* (inference)
SBI[a]	2.52±0.75	1.69±0.42	0.0001 (HS[b])
Probing depth	4.73±0.81	3.33±0.41	0.0001 (HS)
Clinical attachment	2.94±0.73	2.18±0.49	0.0006 (HS)

[a]SBI=Sulcus bleeding index. [b]HS = Highly Significant

Table 3: Intragroup comparison of the mean bone mineral density of Group A

BMD[a] 1 (at baseline)		BMD 2 (after 6 months)		*P*	Inference
Mean	SD	Mean	SD		
1.16	0.31	1.19	0.31	0.0261	S[b]

[a]BMD=Bone mineral density. [b]S = Significant

Table 4: Intragroup comparison of periodontal parameters of Group B at baseline and after 6 months

Parameter	Group B		
	Baseline	After 6 months	*P* (inference)
SBI[a]	2.79±0.75	1.93±0.43	0.0002 (HS[b])
Probing depth	4.33±0.51	3.12±0.46	0.0002 (HS)
Clinical attachment	2.39±0.61	2.15±0.46	0.0013 (VS[c])

[a]SBI=Sulcus bleeding index. [b]HS = Highly Significant. [c]VS = Very Significant

are in accordance with the results obtained in several previous studies.[19,20]

There was a significant improvement in the mandibular BMD in the bisphosphonate group in most of the patients. Group A showed statistically significant increase in BMD values (1.16 ± 0.31 – 1.19 ± 0.31), that is, toward normal status (P = 0.0261) [Table 3]. This can be attributed to the inherent mechanism of action of bisphosphonates. The improvement in other periodontal variables in the bisphosphonate group may be explained by the other pharmacological actions of bisphosphonate, which may include anti-inflammatory action.

As expected, Group B showed a significant decrease in BMD values (0.95 ± 0.26 – 0.93 ± 0.26), that is, toward osteoporotic status (P = 0.0028), which can be attributed to the pathogenesis of osteoporosis in postmenopausal women [Table 5]. The findings of this study correlate well with previous studies.[19,20]

Studies have shown that alendronate can reduce bone loss in animal models of experimentally induced and naturally developing periodontitis.[21] Human studies that assessed the effect of bisphosphonate therapy on periodontitis reported clinical improvement with bisphosphonate therapy. Six months of treatment with alendronate 10 mg/day improved the alveolar bone crest height and decreased gingival bleeding in a paired-case control trial in 40 patients with type 2 diabetes and established periodontitis.[22] In another 6-month study, alendronate 10 mg/day improved clinical periodontal measurements (Probing Depth (PD), Clinical Attachment Level (CAL), and gingival index) and significantly improved bone density as measured by DEXA at the maxilla and mandible in 24 patients.[23]

In this study, we selected mandibular bone as a peripheral site to assess BMD, as various studies have shown that mandibular BMD assessed by DEXA correlates significantly with BMD measurements of other important skeletal sites.[24,25] Horner *et al.*, in their study, showed that higher correlation coefficients and greater sensitivity and specificity for the body of the mandible suggest that this site should be used for potential clinical application of dental radiographs in detecting osteoporosis.[13]

In our study, we selected alendronate over other bisphosphonates as an agent of choice because of its efficacy and well-tolerability, as data from scientific literature demonstrate that alendronate reduces the incidence of fractures by about 50%.[26] The 70 mg weekly dose of alendronate is approved by the Food and Drug Administration for the treatment of osteoporosis in postmenopausal women and has shown to produce modestly greater increases in BMD and reduction in indices of bone turnover than other approved dose of the drug.[27]

Alendronate in oral 70 mg weekly dose was well-tolerated in this 6-months study. Dosing convenience plays an important role in the effective medical management of a chronic disease.[28] In this study, a once-weekly dose (70 mg) of bisphosphonate drug was preferred over 10 mg per day dose to improve the compliance of the patients for the study. Less frequent dosing (once a week) with any medication may enhance compliance, thereby, maximizing the effectiveness of therapy. In addition, the potential for esophageal irritation, observed with daily oral bisphosphonates, may be substantially reduced with once-weekly dosing.[28] Hence, in this study dosing regimen of once-weekly 70 mg alendronate provided patients with a more convenient, therapeutic equivalent dose alternative to 10 mg daily dosing regimen.

In this study, the DEXA scan was done for the estimation of BMD values. DEXA is currently considered the gold standard method for bone densitometry analysis. It has a low radiation exposure (<0.1 microGy) and is an accurate and reliable method to estimate BMD. DEXA requires a short scan time and has a consensus that BMD results can be interpreted using the World Health Organization (WHO) T-score [Table 6].[11]

The data from this study stress upon an important area in medical and dental communities—bisphosphonates may be a promising candidate for treating periodontal disease in postmenopausal women. It is also very important for primary care physicians to understand the relationship between the two chronic diseases, osteoporosis and periodontitis, which are major public health problems, as patients seeking advice and treatment for postmenopausal-associated problems, osteoporosis, and chronic periodontitis are a part of their daily practice.[29] Therefore, they can help in reducing the economic and social burden on patients by improving prevention, early diagnosis, and treatment of these diseases.[30]

Limitations

The limitations of this study are a small sample size (n = 30), short duration of the study (6 months), and mandibular BMD not being correlated with whole-body BMD because of cost factors.

Table 5: Intragroup comparison of the bone mineral density of Group B

BMD 1[a] (at baseline)		BMD 2 (after 6 months)		*P*	Inference
Mean	SD	Mean	SD		
0.95	0.26	0.93	0.26	0.0028	VS[b]

[a]BMD=Bone mineral density. [b]VS = Very Significant

Table 6: The World Health organization criteria for diagnosing osteoporosis using Bone Density measurements

Terminology	T-score definition
Normal	T ≥ −1.0
Osteopenia	−2.5 < T < −1.0
Osteoporosis	T ≤ −2.5
Established osteoporosis	T ≤ −2.5 (in the presence of one or more fragility fractures)

Conclusion

Notwithstanding the importance of future research, it can be concluded that a single oral dose of 70 mg alendronate per week is safe and effective in improving the clinical outcome of nonsurgical periodontal therapy. Further randomized clinical controlled trials with large sample size are required to obtain data regarding the long-term safety and clinical efficacy of amino bisphosphonates to support the findings of this study.

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Conflicts of interest

There are no conflicts of interest.

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