

The Effect of Alendronate on Symptoms of Knee Osteoarthritis: A Randomized Controlled Trial

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Abstract

Background: Knee osteoarthritis is a common degenerative joint disorder and a major cause of pain and disability. Recent studies have suggested that bisphosphonates such as alendronate may have a role in the treatment of osteoarthritis. The purpose of the present study was to investigate the potential effect of alendronate on the symptoms of knee osteoarthritis.

Methods: Thirty nine patients with mild to moderate knee osteoarthritis were enrolled in a randomized, double-blind, placebo-controlled trial with parallel-group design. The patients received either placebo or alendronate pills (70mg, weekly) in a blinded fashion for six months. Symptoms of osteoarthritis were scored by Western Ontario and McMaster Universities (WOMAC) osteoarthritis index at enrollment and at weeks 4, 12, and 24.

Results: In both groups there was a significant improvement in total WOMAC score and WOMAC subscales scores of pain, stiffness, and function at 4, 12, and 24 weeks of treatment. Maximum improvement occurred at week 4. There was no statistically significant difference between the two groups regarding their total WOMAC score and its subscales at the end of weeks 4, 12, or 24 ($P=0.94$).

Conclusion: Alendronate does not reduce symptoms of mild to moderate knee osteoarthritis.

Trial Registration Number: IRCT138803271479N2

Iran J Med Sci 2010; 35(1): 9-15.

Keywords • Bisphosphonate • degenerative joint disease • knee • arthritis

Introduction

Osteoarthritis is the most common chronic joint disorder in humans. It causes pain and deformity and ultimately leads to chronic disability. OA is an age-related disorder. Because the prevalence of aging populations is increasing worldwide, the number of patients with osteoarthritis of knee will be increased.^{1,2} The disease is characterized by destruction of articular cartilage and subchondral bone. The knee joint is one of the most common joints that is affected by osteoarthritis.

The aims of management of patients with knee osteoarthritis are to control pain and reduce disability. There are two basic groups of medications to manage osteoarthritis: symptom modifying and disease modifying agents. There are, at present, no specific pharmacologic treatments that can prevent the

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Received: 24 May 2009

Revised: 13 August 2009

Accepted: 15 November 2009

progression of joint damage caused by the disease.

OA has been considered as a disease of the cartilage, however, certain evidence suggests that subchondral bone is also involved in its pathogenesis.³⁻⁶ The changes in the subchondral bone are not only mechanical, but also biological. The increased inflammatory cytokines of joint liquid and cartilage ratio is caused by changes in the secretion of these cytokines by osteoblasts. This process ultimately causes the acceleration of knee osteoarthritis. The use of bisphosphonates may help to lower the speed of this process. Several studies have shown that antiresorptive agents including estrogens, selective estrogen receptor modulators, calcitonin, and bisphosphonates may have effects to modify osteoarthritis.⁷⁻¹¹

At this time, bisphosphonates are the main drugs to treat osteoporosis. However it seems that these drugs may also have a role in the treatment of osteoarthritis. Bisphosphonates can alter bone remodeling through a direct inhibitory effect on the osteoclasts. Such effects could retard subchondral bone remodeling, which is important in osteophyte formation and subchondral sclerosis. In addition, bisphosphonates may have slight immunomodulating effects via inhibition of pro-inflammatory cytokines.¹²

We aimed to investigate possible changes in the symptoms of knee osteoarthritis during the regular use of alendronate (a bisphosphonate) within 24 weeks.

Patients and Methods

Study Design and Patients Selection

This double-blind, randomized, parallel study was conducted on patients with knee osteoarthritis according to American College of Rheumatology (ACR) criteria.¹³ Eligible patients were those who met the ACR criteria of primary knee osteoarthritis, radiologically ascertained grade I or II of knee osteoarthritis on the Kellgren-Lawrence scale,¹⁴ had a Western Ontario and McMaster Universities (WOMAC) pain subscale index of at least 2 at baseline (the 5-point Likert version of the WOMAC) and presence of daily knee pain for at least 6 months preceding the study. Patients were not eligible if they had: (1) secondary osteoarthritis, (2) arthroscopy or surgery of target knee within previous six months, (3) intra-articular treatment of target knee within previous six months, (4) other chronic inflammatory processes, (5) previous gastrointestinal problems (such as gastroesophageal reflux or esophageal stricture), (6) previous allergic reactions to

bisphosphonates, and (7) any risk factors for osteoporosis.

Ethics Committee of Mashhad University of Medical Sciences approved the study protocol. A written informed consent was obtained from each patient before enrollment.

Patients were randomly assigned into a 1:1 fashion to receive 70mg alendronate orally (Alenate®; Dr. Abidi Company, Tehran, Iran) or placebo per week for 24 weeks. The Placebo pills that contained no medication were produced by Faculty of Pharmacy, Mashhad University of Medical Sciences. Randomization was conducted by using Random Permuted Blocks procedure.

Treatment Assignment

The patients were trained to answer the WOMAC Function Scale so that their primary score could be established. They were permitted to continue their usual treatment with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). However, they were urged not to use analgesics and NSAIDs 48 hours prior to physician visit in order to prevent scrambled test results. All adverse events that were reported by the patients were recorded.

Symptoms Outcome Measures

Symptoms were scored by WOMAC index at enrollment and at weeks 4, 12, and 24. We used the 5-point Linkert version of the index in which patients answered each question using a 0-4 scale, with a higher score representing greater symptom severity (0=none, 1=slight, 2=moderate, 3=severe, 4=extreme). The total index score for the signal knee corresponded to the weighted composite of the 24 question scores. Scores were also determined for the subscales of pain (five questions), stiffness (two questions), and physical function (17 questions).

Statistical Analysis

Data were analyzed by SAS software (SAS Institute, USA). One-way analysis of variance (ANOVA) for repeated measurements was used for intergroup comparisons followed by post hoc Bonferroni tests. Values obtained from the alendronate group were compared with the placebo group using Student *t* test. A $P < 0.05$ was considered statistically significant.

Results

Fifty-one patients were introduced to the study from the rheumatology clinics. Twelve patients were not eligible. Of the remaining 39 patients enrolled into the trial, 34 completed the study.

Five patients discontinued the treatment because of the adverse events (figure 1). Approximately 85% of patients were women with an average age of 47 years. The baseline characteristics of the patients can be found in table 1. There was no significant difference in baseline characteristics between the two groups.

Table 1: Baseline characteristics of the study participants

Variable	Placebo group	Alendronate group	P value
Number	19	20	-
Age (Y)	47.3	47.8	0.94
Female sex, number (%)	17 (89)	16 (80)	0.40
WOMAC total score	16.2	15	0.64
WOMAC pain score	6.2	5.9	0.73
WOMAC function score	1.7	1.6	0.79
WOMAC stiffness score	8.3	7.5	0.75

Improvement, based on total WOMAC Function Scale and its subscales, was observed at the end of the 4th week (P=0.005). Both groups had an equal degree of improvement, with no significant difference between the two groups (P=0.94). On average, about

35% of the severity of patients' symptoms was decreased based on the last WOMAC Function Scale test. Moreover, we found that there was no major difference between the total WOMAC Function Scale and its subscales between the study arms (P=0.94).

As shown in figures 2-5, maximum improvement occurred at the 4th week. During the remaining time, the treatment slowed down and the two groups had no major difference. In other words, there was no significant difference between alendronate and placebo effect on WOMAC Function Scale score among patients with mild to moderate knee osteoarthritis.

Consuming Analgesics and NSAIDs

During the trial, consumption of analgesics and NSAIDs to control the symptoms, reduced from an average of two pills to 1.5 pills daily in both groups. About 82% of patients used several NSAIDs to control pain. There was not a statistically significant difference in the use of these drugs between the two groups (P=0.85).

Side Effects

There was an equal level of side effect occurrence between the two groups, with no significant difference (P=0.18). One patient within the alendronate group temporarily

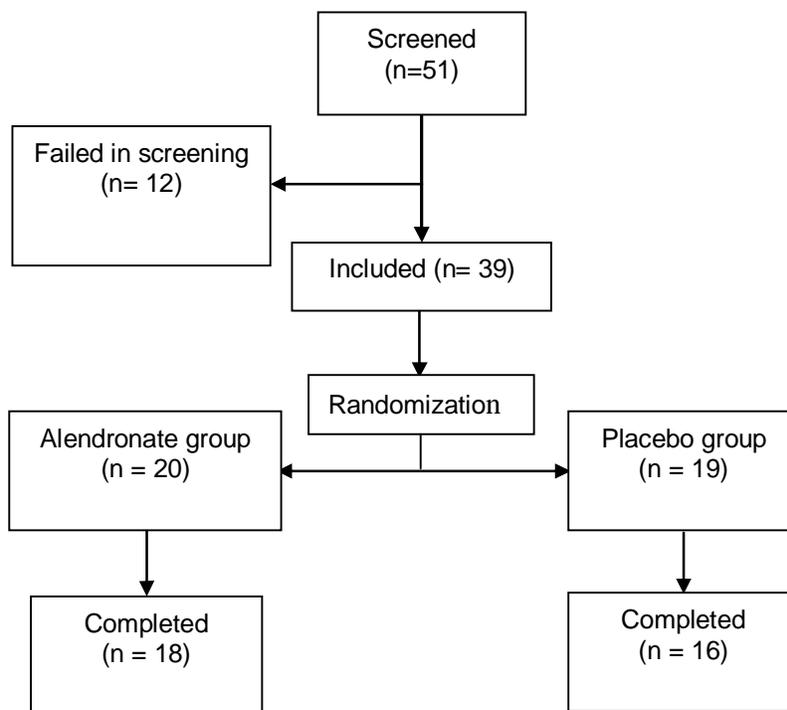


Figure 1: Flowchart showing the process of assigning patients in the trial arms.

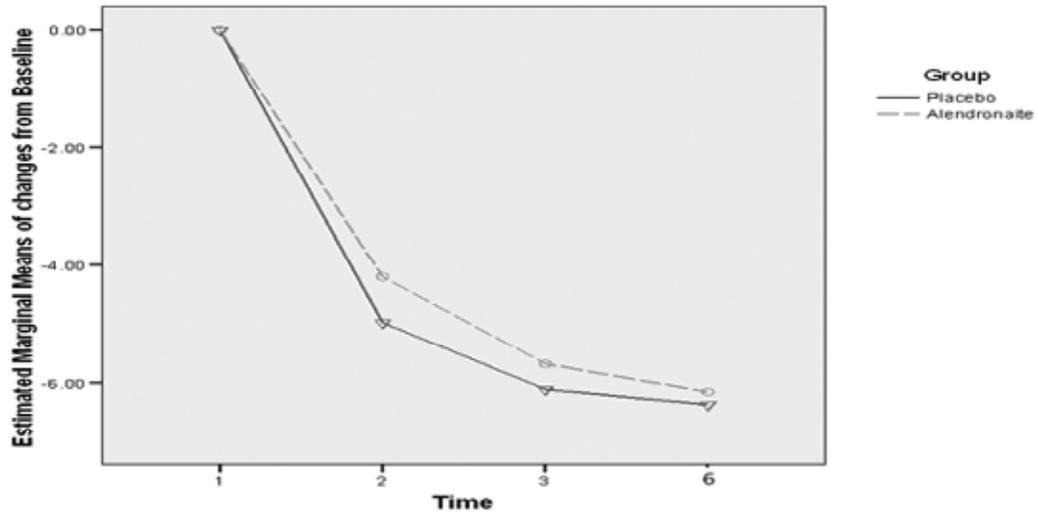


Figure 2: The effect of alendronate on total WOMAC score during 24 weeks of treatment in patients with knee osteoarthritis.

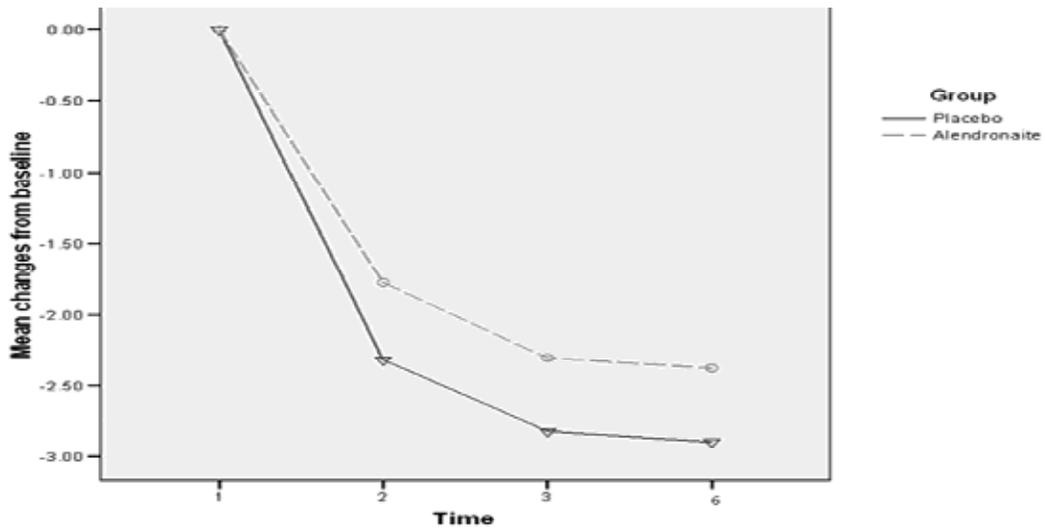


Figure 3: The effect of alendronate on WOMAC pain score during 24 weeks of treatment in patients with knee osteoarthritis.

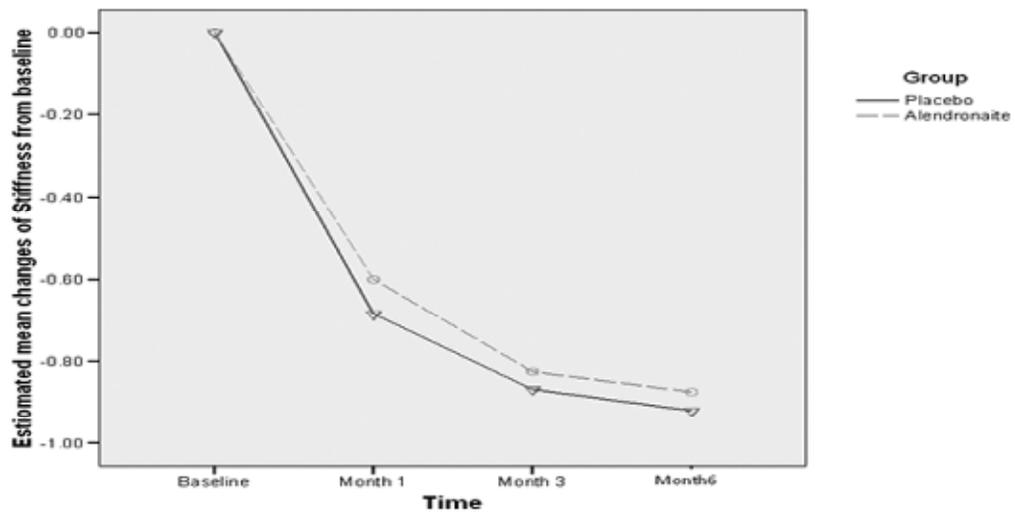


Figure 4: The effect of alendronate on WOMAC stiffness score during 24 weeks of treatment in patients with knee osteoarthritis.

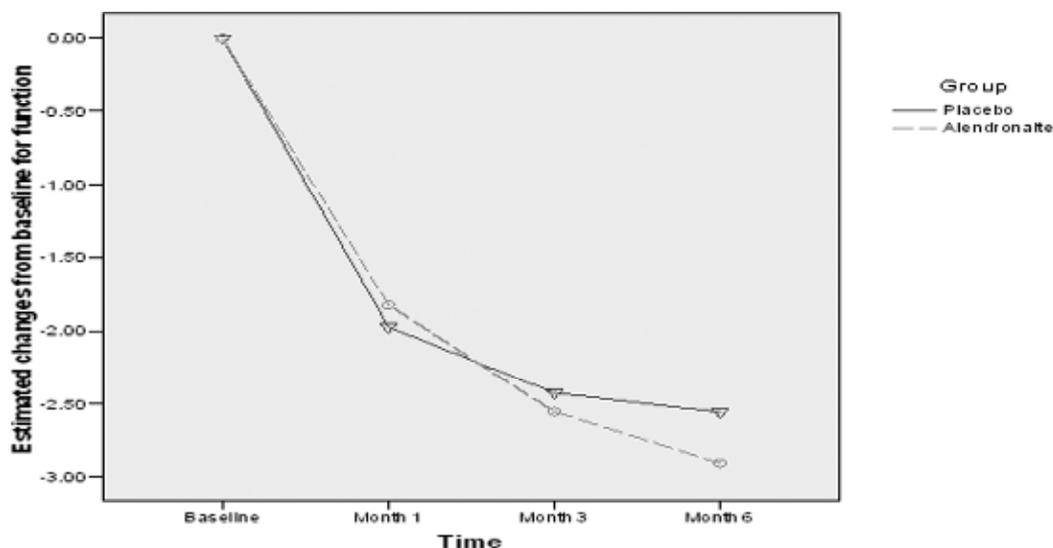


Figure 5: The effect of alendronate on WOMAC function score during 24 weeks of treatment in patients with knee osteoarthritis.

developed severe leg pain after the first treatment session; however the pain subsided over the next few months. As a consequence of gastrointestinal related side effects, a total of five patients (two from the alendronate group and three from the placebo group) were not able to complete the study (table 2).

Table 2: Side effects reported by patients receiving alendronate or placebo

Side effect	Placebo group	Alendronate group	P value
Dyspepsia, number (%)	2 (10)	3 (15%)	
Heart burn, number (%)	2 (10)	2 (10)	
Bone pain, number (%)	-	1 (5)	
Total	4 (20)	6 (30)	0.18

Discussion

The present study was designed to evaluate the effect of alendronate on mild to moderate knee osteoarthritis symptoms. Our patients were younger than patients in similar studies. The average age of the patients in our study was 47, compared with 63 for Bingham,¹¹ 63 for BRISK,¹⁰ and 74 for Carbon,¹⁵ and Colleagues' studies. The age difference was caused by three factors: (1) women included in our study had to be under the age of menopause according to Ethics Committee recommendations of our medical center, (2) elderly patients with severe knee osteoarthritis pain were excluded from the present study, and (3) knee osteoarthritis in Iran may involve younger people compared with some other countries.

The proportion of women/men (33 out of 39) in our study was the same as previous studies (approximately 80% female patients).

There was a 35% decrease in patients' complaints compared with total primary WOMAC Function Scale and its subscales in both groups. We selected alendronate because it was readily available in Iran. However in recent years, many studies have used risedronate, the other bisphosphonate. For example, BRISK trial used risedronate (5-15mg daily) and Bingham study used the same amount of risedronate daily or 35 to 75mg weekly.^{10,11} Nonetheless, alendronate was used in other studies.¹⁶ Lehman and colleagues, showed that alendronate (20mg/day) induced a 50% reduction in C-terminal cross linking telopeptide of type II collagen (CTX-II) in urine.¹⁶ In the study of Carbon and co-workers,¹⁵ alendronate decreased symptoms based on the WOMAC Function Scale. MRI scans of patients' knees reported a visible decrease in bone damage in that trial.¹⁵

As stated earlier, signs of recovery were observed in both groups, although there was no significant difference. In the study by Carbon and co-workers,¹⁵ WOMAC Function Scale was completed after the treatment, along with a comparison between patients using alendronate and the patients who did not use it. In BRISK trial, patients using risedronate (15mg daily) felt less severe symptoms than those who did not use it during the study (P=0.05).¹⁰ Nevertheless, the difference was not statistically significant.

In a study by Clifton and colleagues,

patients received risedronate (daily or weekly) compared with patients who received placebo for two years.¹¹ There was no significant difference in symptoms between the two groups according to WOMAC Function Scale. However, there was a 20% reduction in the symptoms based on primary WOMAC Function Scale. In all of the trials the difference between urinary CTX-II levels of patients received bisphosphonates and those who did not receive them, was significant.

In the present study, similar to the BRISK and Bingham studies, patients showed an accelerated recovery time in the first 4 weeks.^{10,11} Although there was not a significant difference between the two groups, our results were similar to the study of Clifton and co-workers.¹¹

An important factor in interpretation of our data is the use of analgesics and NSAIDs by the patients. This factor could be a reason for the patients' rapid recovery and reduced symptoms in placebo group. Furthermore, use of analgesics and NSAIDs may be responsible for accelerated recovery time in the first 4 weeks. Our trial's results were further obscured by the WOMAC Function Scale's limitation to precisely classify the mild to moderate osteoarthritis symptoms. The average of our WOMAC Function Scale was 16, which was significantly less than BRISK trial (50) and study of Clifton and co-workers (45).^{10,17} In other words, when the patients' pain is mild, it may be relieved without any intervention and it is hard to justify a drug's effect. It will be easier to investigate a drug's effect on severe osteoarthritis with continuous pain to get more objective results. The present study can be used as a model for future clinical trials of osteoarthritis treatment with alendronate.

Conclusion

Alendronate does not reduce symptoms of patients with mild to moderate knee osteoarthritis.

Acknowledgment

This study was supported by a research grant from the Vice Chancellor for Research, Mashhad University of Medical Science.

Conflict of Interest: None declared

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