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Evaluation of the effect of zoledronic acid on back pain in patients with osteoporosis in the Tertiary Care Teaching Hospital of Chhattisgarh

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Abstract

Background: Osteoporosis is a chronic, progressive, systemic condition of the skeletal tissue that is characterized by reduced bone density, microarchitecture deterioration, and fragile bones, making osteoporotic fractures or fragility fractures more likely to occur. **Aim and Objective:** To examine the effect of zoledronic acid on back pain in patients with osteoporosis in a tertiary care teaching hospital in Chhattisgarh. **Material and Method:** This prospective study was conducted on 60 patients above 50–80 years of age who presented with a chronic low back ache to the Outpatient Department of Orthopaedics, SSIMS, Bhilai, Chhattisgarh. **Result:** All the patients found excellent clinical improvement following zoledronic acid infusion in early and long-termlly, it was found that zoledronic acid's effectiveness was excellent, with significant improvement in bone mineral density (BMD), T-score, and Z-score. follow-ups. Additionally, it was found that zoledronic acid's effectiveness was excellent, with significant improvement in bone mineral density (BMD), T-score, and Z-score. **Conclusion:** Zoledronic acid has a definite clinical effect in the treatment of senile osteoporosis. It can effectively alleviate pain and related clinical symptoms, and the incidence of adverse reactions is low. It is worthy of clinical application.

Keyword: osteoporosis, zoledronic acid, back pain

Introduction

Osteoporosis is a systemic disease whereby complex, composite, and complicated molecular pathways interact to reduce bone mass and strength by triggering micro-architectural degradation of bone [1]. Decreased bone mineral density (BMD) is a

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major consequence that is associated with feeble, frail, and fractured bones [2]. Osteoporosis and its worst outcomes, such as fractures and chronic pain, are common in both genders; however, women are more vulnerable, accounting for 70–80 percent of all traumas, including hip, spine, and wrist fractures [3]. This prevalence increases further in postmenopausal women because of reduced estrogen levels, resulting in accelerated bone mass loss [4].

Several reports have revealed many factors that are associated with osteoporosis and may increase its risk [1]. These factors are female gender, advancing age after menopause, low body mass index (BMI), family history, poor diet, sedentary lifestyle, smoking, alcohol consumption, and affiliated comorbidities [4]. The magnitude and impact of these risk factors, individually or in concert, vary due to different geographies [5]. For instance, the chances of osteoporosis and its associated fractures are more prevalent in Scandinavian populations than in people of Africa and South America, due to the lesser exposure of vitamin D in Scandinavia than in countries with more annual sun and sunshine [6]. According to statistics given by the World Health Organization (WHO), 30 percent of postmenopausal women suffer from osteoporosis [4]. It has been reported that 61 million people in India have osteoporosis, and, out of these, 80 percent are women [7]. The peak incidence of osteoporosis in India occurs 10–20 years earlier than in Western countries, which impinges harshly on health and economic resources [8, 9]. This condition often remains asymptomatic and undiagnosed until it presents with fractures involving the hip, spine, proximal humerus, pelvis, and wrist resulting from low-velocity trauma, frequently leading to hospitalization [10]. Seldom does it also present with severe backache or loss of height.

Zoledronic acid is a new generation of bisphosphonates for the treatment of osteoporosis and has been widely used in the treatment of hypercalcemia caused by tumors such as prostate cancer and multiple myeloma. In recent years, it has become a hot research topic. At present, there are related reports on the study of the application of zoledronic acid in postmenopausal women and the bone metastasis of malignant tumors [11–12], but reports on its role in osteoporosis are rare. In order to study the therapeutic value of zoledronic acid (Aclasta) in the treatment of osteoporosis, the clinical effect of zoledronic acid in the treatment of osteoporosis was observed in this study.

Materials and Methods

This prospective study was conducted on 60 patients above 50–80 years of age who presented with a chronic low backache to the Outpatient Department of Orthopaedics, SSIMS, Bhilai, Chhattisgarh. All patients volunteered to participate in the study and signed the informed consent form after the approval of the ethics committee.

Inclusion Criteria

- Patients of either sex aged above 50 years.
- Patients experiencing focal back pain, which was insidious in onset for more than six weeks of duration,.
- Pain not relieved by NSAIDs, opiods, and physiotherapy

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Exclusion Criteria

- Patients with primary and/or secondary tumors of the spine.
- Patients on bisphosphonate therapy.
- Patients with traumatic fractures of the spine and

They were selected for this study after giving informed consent. Demographic data, history, clinical examination, and details of investigations were recorded in the study proforma. In addition, the baseline visual analog score and Modified Oswestry low back pain and disability assessment scores were recorded.

The assessment tools used are radiographs, dual-energy X-ray absorptiometry (DEXA scan), routine blood investigations, electrocardiograms for the selected patients, and lumbosacral spine anteroposterior and lateral view radiographs. In addition, the patients with osteoporotic features in radiographs were advised for DEXA 10 of spine anteroposterior assessment. In our study, bone density was assessed using a GE Healthcare Prodigy Encore-based DEXA scan. Those patients who were found to be osteoporotic as per WHO definition criteria were taken into this study. After explaining the study and possible adverse events of a 5 mg infusion of zoledronic acid, consent was obtained. Blood investigations and ECGs were done to find contraindications to zoledronic acid infusion. The patients without contraindications were advised to take sufficient fluids orally for adequate hydration. Later, a 5 mg zoledronic acid infusion was given for a minimum duration of 15 minutes. The patients were monitored for any allergic reactions and other immediate adverse events for one day and recorded. Prophylactic antipyretic medication paracetamol was given to all patients. Upon discharge, patients received advice on back strengthening exercises, and oral vitamin D and calcium supplements were given to all patients for a whole year. The analgesics were avoided to assess the exact effect of zoledronic acid. They were followed up and assessed for pain and functional ability improvement using a visual analog scale (VAS) and modified Oswestry low back pain disability index (MODI) (at 12 weeks, 24 weeks, and one-year follow-up). In the final follow-up after a year, every patient underwent a bone density assessment by DEXA. Assessment protocols for the initial visit, follow-up, and final visits are mentioned.

Initial or baseline assessment:

- Screening the patients clinically for factors suggestive of osteoporosis.
- A VAS chart and modified Oswestry back pain and disability questionnaire were given, and baseline scores were recorded.
- Radiographs of the lumbar spine were taken to assess for osteoporosis.
- Patients suspected of having osteoporosis were evaluated with a DEXA scan of the spine.
- Patients who turned out to be osteoporotic on DEXA with a T-score of -2.5 and below were evaluated with routine blood investigations and an ECG to rule out contraindications for infusion.
- Patients who did not have contraindications were admitted, and a 5 mg zoledronic acid infusion was administered over a minimum duration of 15 minutes under monitoring and observed for one day for adverse events and allergic reactions.
- Calcium 500 mg and vitamin D3 600000 IU supplement were advised.

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Assessment at the initial visit

VAS: Visual analog scale; DEXA: Dual energy X-ray absorptiometry.

Assessment at weeks 12 and 24

- Clinical examination of patients.
- Assessment of improvement in pain and function by recording VAS and MODI.
- Advised to continue calcium and vitamin D3 supplements.

Assessment at second and third visits

VAS: Visual analog scale; MODI: Modified Oswestry low back pain disability index.

Assessment at 1 year:

- Clinical examination of patients.
- Assessment of final improvement in pain and function by recording VAS and MODI.
- Assessment of the final improvement in bone density using the DEXA scan.
- Study completed.

Assessment at the final visit.

VAS: Visual analog scale; MODI: Modified Oswestry low back pain disability index; DEXA: Dual energy X-ray absorptiometry.

Observation and Results

The study includes 60 patients with a female predominance, 35 female patients, and 25 male patients. The average age of the patients in the study is 67.29 years, ranging from 50 years to 80 years. The gender-specific age distribution tells us that the risk of osteoporosis in females is at an early age compared to males, as shown in Table 1.

Table No. 1: Gender-specific age distribution.

Age in years	Male	Female	Total
50-60	5	15	20
60-70	9	12	21
70-80	9	13	22
>80	1	1	2

Table No. 2: Duration of Symptoms

Duration of symptoms (years)	Number

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<1	6
1-2	20
2-3	19
>3	21

Patients in our study exhibited a variable duration of symptoms ranging from 6 months up to 10 years, as depicted in Table 2.

Table 3: Patient distribution according to bone mineral density in the first visit and final follow-up.

BMD in gm/cm2	Number . of patients in the first visit	Number . of patients at 1-year follow-up
0.500-0.600	1	0
0.601-0.700	3	0
0.701-0.800	20	7
0.801-0.900	32	13
0.901-1.000	2	30
1.001-1.100	0	15

In the study we conducted, out of 65 patients, 19 had type II diabetes, 7 had essential hypertension, and 5 had both. The remaining 34 patients had no comorbidities. The average baseline BMD done at the first visit was 0.772 gm/cm2 and ranged from 0.530 to 0.92 gm/cm2. The average final BMD done at the 1-year follow-up visit was 0.953 gm/cm2, which ranged from 0.701 to 1.092 gm/cm2. The values are shown in Table 3.

Table No. 4: Incidence of adverse events.

Adverse Events	Number of patients
Number . of adverse events	12
Headache	37
Fever	39
Post-transfusion palpitation	12
Allergic Reactions	0
Arrhythmias	0

In our study, a few adverse reactions developed only during the first week after the infusion of zoledronic acid. 12 patients had no adverse effects. Headache was the most frequently observed adverse effect, seen in 37 patients the next day after infusion. 39 patients had a fever in the evening or the next day after infusion. 12 patients complained of palpitation immediately after transfusion for about ½ to 1 hour. No patients had allergic reactions or arrhythmias. The same is shown in Table 4.

Table No. 5: Average VAS and MODI scores.

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Duration	Change in VAS	MODI score
On presentation	6.15	46.98
12 weeks	4.11	30.22
24 weeks	9.72	31.1
1 year	2.46	18.21

The average and trend of the VAS score and MODI score assessed at each follow-up are shown in Table 5.

Table No. 6: Statistical calculations by paired student t-test.

Pairs	Paired difference	P- Value
Baseline BMD-BMD at 1 year	0.15±0.081	<0.0001
T-Score at 1 year	1.44±0.21	<0.0001
Z-Score at 1 year	1.42±0.18	<0.0001
Baseline VAS-Baseline VAS at 1 st FU	1.82±0.59	<0.0001
Baseline VAS-Baseline VAS at 2nd FU	2.35±0.98	<0.0001
Baseline VAS-Baseline VAS at 3rd FU	3.51±1.12	<0.0001
Baseline OPI-Baseline OPI at 1 st FU	16.12±3.37	<0.0001
Baseline OPI-Baseline OPI at 2nd FU	18.11±4.22	<0.0001
Baseline OPI-Baseline OPI at 3rd FU	28.11±5.62	<0.0001

[Note: BMD: bone mineral density; VAS: visual analog score; OPI: oswestry pain index; FU: follow-up; DF: degree of freedom.]

The statistical assessment of the collected data was done using IBM SPSS Statistics, version 23.0. The calculated values are shown in Table 6.

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Discussion

The current study consists of 60 patients of either sex, 35 males and 25 females, with lower back pain lasting more than six weeks and vertebral osteoporosis with a few non-traumatic compression fractures of the spine. Seven of the 60 patients in total were lost to follow-up. Therefore, 53 patients who finished their one-year follow-up and had a repeat BMD evaluation at that point were taken into account for statistical computation and evaluation. Using VAS scoring with a p-value of less than 0.001, the study's findings demonstrate that zoledronic acid has an excellent pain-reduction impact at both the early (3, 6 months) and long-term (1 year) follow-ups.

The study also showed excellent results in functional improvement when reviewed using the MODI questionnaire scoring with a p-value of <0.001 in early (3, 6 months) and long-term (1 year) follow-ups. When assessed by statistically calculating the mean, the standard error means, SD, 95% CI of differences, and T-value by paired student t-test considering the degree of freedom as 60 (n-2). The p-value was found to be less than 0.0001, which meant the study result was statistically significant with excellent results. Headache, fever, and post-transfusion palpitations were the most common adverse effects found in the study. There were no cases of arrhythmias, allergic reactions, or jaw osteonecrosis. Taking into account all of these findings, the patients' early and long-term follow-ups revealed outstanding clinical improvement as a result of zoledronic acid infusion. There were no new acute or atraumatic spinal compression fractures in any of the research participants. This suggests that, in addition to its analgesic effects, zoledronic acid infusion-induced pain reduction may also be due to the strengthening of the spine's trabeculae and the prevention of future compression fractures.

A similar study was done by M et al. Zoledronic acid, an antiresorptive drug with better compliance, is very effective in controlling low back pain, improving bone mineral density, and preventing the occurrence of atraumatic fragility fractures. With all the above factors, zoledronic acid is a preferable bisphosphonate for the treatment and prevention of osteoporosis compared to other modalities of treatment. [13] A study by Koivisto K et al. on the efficacy of zoledronic acid for chronic back pain showed that improvement in the intensity of chronic lower back ache (LBA) was more significant with zoledronic acid compared to placebo. They have also recommended it as an interesting treatment alternative for LBA with osteoporosis, which is challenging to treat with a conservative approach [14]. Orwoll E et al. found that in the study comparing IV zoledronate and oral alendronate, compliance with zoledronic acid was significantly better than with alendronate. The study also demonstrates that zoledronate is effective in treating osteoporosis in males [15]

Chun-Feng Huang et al. found that at baseline, there was no difference in sex, ASM, ASMI, or bone mineral density between the zoledronic acid treatment group and the control group. The treatment group’s skeletal muscle mass increased by 841 g in ASM and 0.35 kg/m in ASMI after three years, while it decreased in the control group. That study, for the first time, demonstrated that zoledronic acid is beneficial not only

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to the bone but also to muscle. [16] *Li Kong et al. found that* zoledronic acid is helpful to alleviate clinical symptoms, reduce the degree of bone pain, promote the increase of bone mass, and has high safety in the treatment of senile osteoporosis, which is worth promotion. [17]

Cauley J. et al., in their research study on zoledronic acid, stated that treatment with zoledronic acid significantly reduced hospital admission duration and limited activity. Additionally, the study concluded that a three-year treatment with zoledronic acid significantly reduced disability and fractures compared with a placebo in women with osteoporosis [16]. James R. Berenson et al. At study end, for all patients (N = 54), L-spineT-scores improved by a median of +0.27 (range, -0.38 to +3.91), corresponding to a median increase in bone mineral density of +15.0% (range, -18.0% to +1,140.0%; $P < 0.0001$). Hip T-scores improved by a median of +0.10 (range, -2.40 to +2.03), corresponding to a median increase of +6.0% (range, -350.0% to +165.0%). During the study, no new fractures, osteonecrosis of the jaw, or significant renal adverse events were reported.

Zoledronic acid administered i.v. at a dosage of 4 mg every 6 months for three doses total was well-tolerated and substantially improved bone mineral density for patients with MGUS and bone loss. Zoledronic acid may be effective for the prevention of new fractures in this high-risk population. [19] Ramalingaiah A et al., in their study, stated that once a year, the zoledronic acid infusion has excellent compliance with minimal incidence of adverse effects. It has also been shown to improve pain during the first six months after infusion and modestly improve BMD. On comparing the results of our study, it has demonstrated excellent results in pain control and BMD improvement [20].

Our study found that fever is the most common adverse reaction to zoledronic acid. In this study, there were 39 cases of fever symptoms, accounting for 21%, and the highest body temperature was 39 oC, which was similar to the foreign reports. [21-22] The fever disappeared after taking antipyretic analgesics.

Strength and limitation

There are a few limitations to the study. In the present study, only 50–80-year-old subjects participated in the research. Hence, in the feature, we would like to include an increase in the number of participants to reach a concrete conclusion. Other lifestyle factors influencing osteoporosis, like involvement in physical activity, drinking and smoking habits, and dietary factors, were not considered. The study takes lower back aches as the chief complaint, which arises due to a spectrum of diseases. Also, the study was not a randomized controlled study. Furthermore, it did not compare the efficacy of oral vs. IV infusions of bisphosphonates.

Conclusions

Chronic low back aches in elderly patients without any identifiable causes will usually be due to vertebral osteoporosis. In addition to affecting an individual's quality of life, vertebral osteoporosis can lead to substantial healthcare costs. Most of the population

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in this age group is often unaware of the consequences of age-related osteoporosis. Early diagnosis, appropriate treatment, and regular follow-up, when practiced among treating doctors, have proven to be essential factors in preventing fragility fractures and reducing lower back pain. Zoledronic acid, an antiresorptive drug with potent action and better patient compliance, is very effective in controlling low back pain, improving BMD, and preventing the occurrence of atraumatic compression fractures. With all the above factors, zoledronic acid can be considered a preferable bisphosphonate for the treatment and prevention of osteoporosis, with no known history of anaphylaxis or cardiac or renal impairment.

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