ORIGINAL ARTICLE

Clinical Safety and Efficacy of Zoledronic Acid in the Treatment of Osteoporosis: A Retrospective Study

Nasreen Boby[1], Md. Al-Amin Sarkar[2], Afroza Akter[3], Chhamita Sultana Chhanda[4], A.K.M. Nurujjaman Khan[5], AKM Akhtaruzzaman[6]

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Abstract

Background: Zoledronic acid and denosumab now a days represent the most potent antiresorptive agents for the prevention and treatment of osteoporosis. Although same effects on bone resorption, these agents have distinct mechanisms of action. The aim of this study was to evaluate and compare the clinical safety and efficacy of zoledronic acid and denosumab in the treatment of osteoporosis.

Methods: This retrospective study included 385 patients with osteoporosis treated at Dhaka Specialized Pain Management & Research Center Ltd., Bangladesh between January 2023 and December 2024. Patients were divided into two groups. In one group, 294 patients received intravenous zoledronic acid and in another group 91 patients received subcutaneous denosumab. All patients were routinely followed up for up to 12 months. These patients were also monitored for drug-related adverse effects and pain relief after drug administration.

Results: In this study, the mean age of the patients was 57.1±11.8 and most of the patients were female (76.1%). The mean BMI was 23.5±3.1 kg/m^2. The baseline BMD in spine T-score found -2.51±1.31. The baseline VAS scores were 7.9 ± 1.1 and 7.1 ± 1.3, in zoledronic acid and denosumab group, respectively. After 1 year, the reduction in pain was statistically significant in both groups ($p < 0.001$), but pain relief was more pronounced in the zoledronic acid group. Both groups experienced mild and self-limiting adverse effects. Flu-like symptoms like fever (95%), myalgia (60%), and headache (5%) were more common in the zoledronic acid group.

Conclusion: Zoledronic acid is a safe and effective treatment agent for osteoporosis and may offer better pain control compared to denosumab.

Keywords: Zoledronic acid, Denosumab, Osteoporosis, Safety, Efficacy, VAS

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1. *Anaesthesiologist, Department of Anaesthesia, Pain, Palliative and Intensive Care Medicine, Dhaka Medical College and Hospital, Dhaka*
2. *Junior Consultant, Department of Prosthodontics, Dhaka Dental College Hospital, Dhaka.*
3. *Assistant Professor, Department of Anaesthesia, Pain, Palliative and Intensive Care Medicine, Dhaka Medical College and Hospital, Dhaka*
4. *Assistant Professor and Clinical Fellow, Pain Medicine, Department of Anaesthesia, Analgesia and Intensive Care Medicine, Bangladesh Medical University, Dhaka.*
5. *Junior Consultant, Department of Anaesthesiology, Kushtia Medical College Hospital, Kushtia.*
6. *Professor, Department of Anaesthesia, Analgesia and Intensive Care Medicine, Bangladesh Medical University, Dhaka.*

Correspondence:
Nasreen Boby
Email: dr.nasreen.boby@gmail.com
ORCID: 0009-0001-9642-0178

Introduction

Osteoporosis is a systemic disease of skeleton characterized by decreased bone mineral density (BMD) and deterioration of bone microarchitecture[1]. Osteoporosis that means 'porous bone' increases bone fragility and susceptibility to fracture[2]. It is a silent and progressive disease that often goes undiagnosed until a fracture occurs. More than 200 million people worldwide suffer from osteoporosis[3]. Increased life span will add to the burden of osteoporosis. In Bangladesh, according to WHO life expectancy is nearly 73.1 years and is expected to increase to 75 years by 2050. The lifetime risk of osteoporotic fractures is 30% - 40%

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in developed countries, which is comparable to coronary heart disease[4] significantly impacting quality of life, mobility, and independence, especially in older adults and postmenopausal women. In addition to the personal burden, osteoporotic fractures place a substantial economic strain on healthcare systems worldwide[5].

The maintenance of skeletal integrity depends on the dynamic balance between bone resorption by osteoclasts and bone formation by osteoblasts. Several pathophysiological mechanisms contribute to this imbalance between osteoblast and osteoclast. Estrogen deficiency, which occurs rapidly after menopause, is one of the most significant factors. Estrogen normally promotes osteoclast apoptosis and supports osteoblast survival. Its deficiency leads to an increase in of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-17 and tumor necrosis factor-alpha (TNF-α), in the first ten years after menopause[6]. This resulting in enhanced osteoclast activity and bone breakdown[7,8].

Another critical contributor to secondary osteoporosis is long-term glucocorticoid therapy. Glucocorticoids reduce calcium absorption, increase renal calcium excretion. It also directly suppresses osteoblast differentiation and function. They induce apoptosis in osteoblasts and osteocytes while prolonging osteoclast survival, leading to net bone loss and structural deterioration[9]. This form of osteoporosis called glucocorticoid-induced osteoporosis (GIOP). It develops rapidly, with significant BMD loss occurring within the first 3–6 months of therapy.

In response to the high burden of GIOP, the American College of Rheumatology (ACR) released updated 2022 guidelines for its prevention and treatment. The guidelines recommend assessing fracture risk in adults aged ≥40 years who are expected to receive ≥2.5 mg/day of prednisone (or equivalent) for ≥3 months. Treatment is advised for those at moderate to high risk of fracture, based on clinical risk factors or FRAX® scores. While oral bisphosphonates are typically first-line, the ACR endorses intravenous zoledronic acid and subcutaneous denosumab as effective alternatives, particularly in patients with gastrointestinal intolerance, poor adherence, renal impairment, or high risk of rapid bone loss[10].

Zoledronic acid is a nitrogen-containing bisphosphonate that inhibits farnesyl pyrophosphate synthase in the mevalonate pathway. Thereby reduce osteoclast function and promoting their apoptosis[11]. It binds avidly to hydroxyapatite in bone, resulting in a long duration of action and the convenience of once-yearly intravenous administration. The HORIZON-Pivotal Fracture Trial demonstrated that once-yearly infusion of zoledronic acid during a 3-year period significantly reduces risk of vertebral fracture by 70%, hip fractures by 41%, and non-vertebral fractures by 25% in postmenopausal women[12,13].

In contrast, denosumab is a fully human monoclonal antibody that inhibits bone resorption by binding to the receptor activator of nuclear factor- kappa B ligand (RANKL). Thereby decreasing the differentiation of osteoclasts[14]. Denosumab has shown sustained efficacy in increasing bone mineral density and decreasing fracture risk. The FREEDOM trial showed that denosumab administered twice yearly for 36 months reduces vertebral fractures by 68%, hip fractures by 40%, and non-vertebral fractures by 20% in women with osteoporosis[15,16]. However, denosumab's discontinuation is associated with a rapid rebound in bone turnover and increased vertebral fracture risk, necessitating careful transition planning[15,17].

Both zoledronic acid and denosumab are effective antiresorptive agents with strong evidence supporting fracture prevention. However, their differing mechanisms of action, pharmacokinetics, dosing intervals, adverse effect profiles, and post-discontinuation outcomes make direct comparison clinically meaningful. This is especially relevant for populations such as postmenopausal women and glucocorticoid users. Because long-term safety, adherence, and risk mitigation are essential.

This study aims to evaluate the clinical safety and efficacy of zoledronic acid in the treatment of osteoporosis, with a comparative analysis against denosumab. This study focusing on adverse effects of drugs and improvement of pain thereby improving quality of life in various populations, including those affected by GIOP.

Methods

This was a retrospective study conducted at a private pain management center of Bangladesh between January 2023 and December 2024. A total of 385 patients diagnosed with osteoporosis were enrolled after proper counseling and obtaining written informed consent.

Patients were included if they had a diagnosis of osteoporosis, defined by a bone mineral density (BMD) T-score ≤–2.5. Exclusion criteria included patients with contraindications to either medication, such as hypersensitivity to the drug, hypocalcemia, or renal impairment (defined as creatinine clearance <35 mL/min).

All patients were monitored under the supervision of a pain physician. Standard noninvasive monitoring was applied during the procedure, including pulse oximetry and automated blood pressure measurements.

Out of 385 patients, 294 patients received intravenous zoledronic acid and 91 patients received subcutaneous denosumab. In the zoledronic acid group, an intravenous cannula was inserted into the non-dominant hand under full aseptic precautions. Each patient received 5 mg of zoledronic acid diluted in 100 mL of normal saline, administered slowly over 20 minutes. Complications such as extravasation and hypersensitivity reactions were closely monitored throughout the infusion. In the denosumab group, patients received 60 mg/1 mL of denosumab via subcutaneous injection in the abdomen or anterior thigh at baseline (day 0) and again at a 6-month interval.

All patients were prescribed daily oral calcium and vitamin D supplementation as adjunct therapy. They were also counseled about potential adverse effects, including flu-like symptoms commonly associated with zoledronic acid. Patients were followed up on day 3, after 1month, 6months and then routinely up to 12 months. The primary outcomes included: clinical safety, assessed by recording the incidence of drug-related adverse events, and pain severity, measured by the Visual Analog Scale (VAS).

Statistical analysis:

Statistical analyses were carried out using the Statistical Package for Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Frequencies and percentages indicated the quantitative observations. An unpaired Student's t-test was used to compare continuous variables. Chi-square test was used to compare categorical data. A p-value of <0.05 was considered statistically significant.

Results

Total 385 patients with osteoporosis were analyzed. Five (5) patients were excluded due to discontinuation of treatment. Drug related adverse effects are less in Denosumab than Zoledronic acid. Relief of pain assessed by VAS score was better in Zoledronic acid than Denosumab.

Table-I: Demographic and clinical baseline characteristics

Variable	Value
Age(years)	57.1 ± 11.8
Gender	
Female	293(76.1%)
Male	87(22.59%)
BMI	23.5± 3.1
Spine T-score	-2.51± 1.31
History steroid use1	71 (18.44%)
History of previous fracture	24 (6.23%)

Data expressed as mean+/- SD and number (%).

In our study according to age distribution mean age of the patients found 57.1± 11.8. There was significant difference found in gender distribution and most of the patients with osteoporosis were female (76.1%). The mean BMI was23.5±3.1 kg/m2. BMI remained essentially unchanged throughout the study in both groups. After analysis baseline BMD in spine T-score found -2.51±1.31. History of previous pathological both vertebral and non-vertebral fracture found among 24 patients. History of previous intake of steroid either oral or intravenous form found 18.44% patients. (table I)

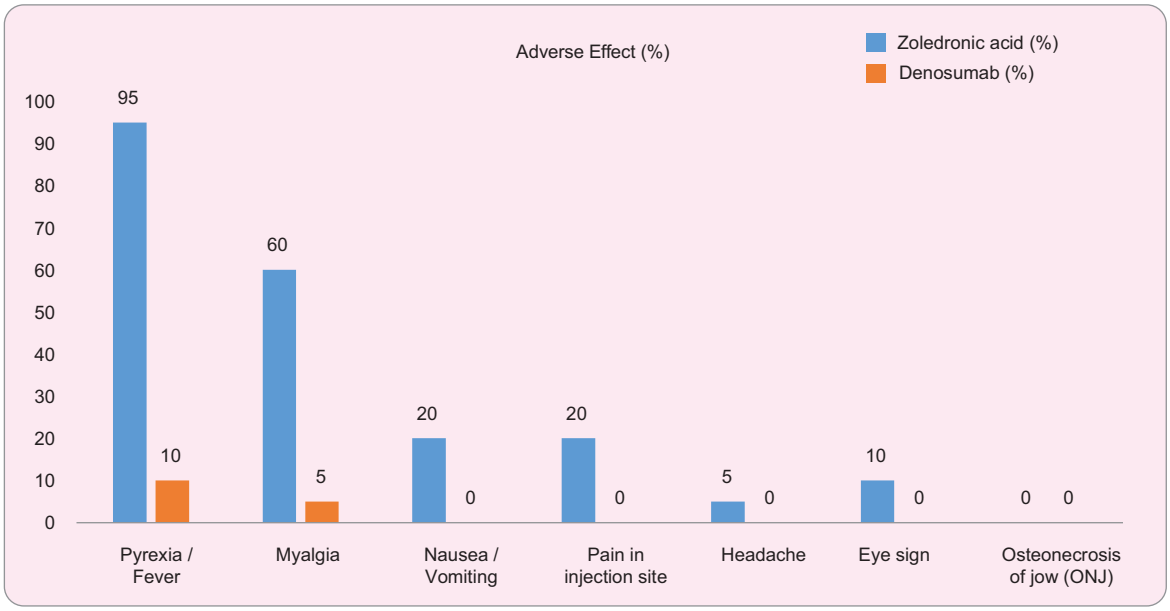

Figure 1: Comparison of adverse effects of Zoledronic acid and Denosumab

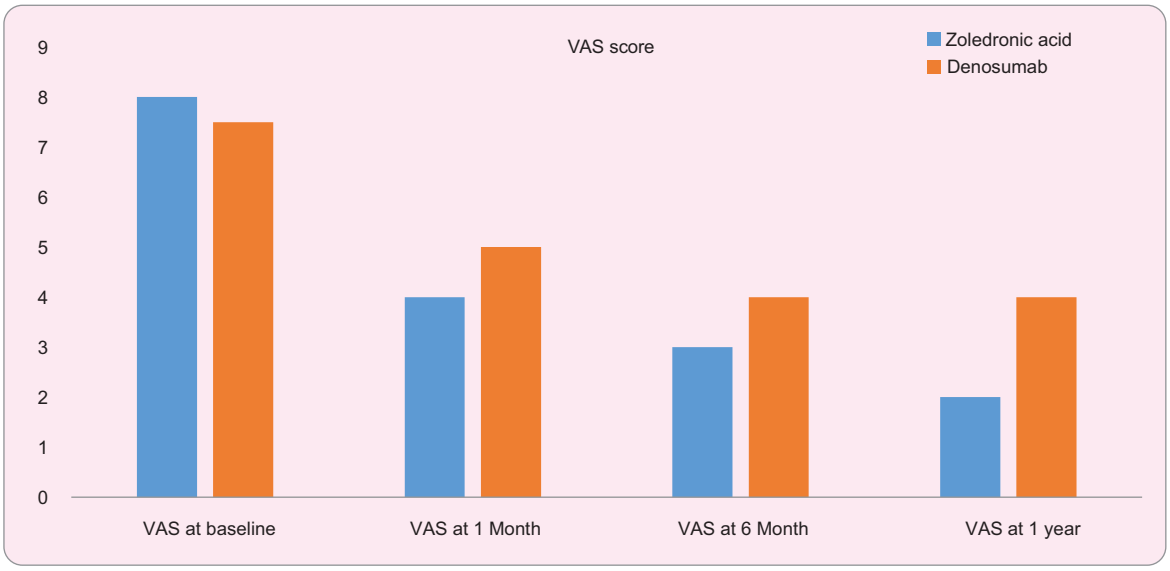

Figure 2: Assessment of pain by VAS score

Both groups experienced mild and self-limiting adverse effects. Flu-like symptoms like fever (95%), myalgia (60%), and headache (5%) were more common in the zoledronic acid group. While no patient reported pain in injection site and eye sign like conjunctivitis, uveitis in denosumab group. No severe adverse event such as osteonecrosis of the jaw were reported in either group during the follow-up period. (Figure 1)

Pain severity was measured using the Visual Analog Scale (VAS) at baseline, and follow-up intervals at 1month, 6month, and 1 year (Figure 2). At baseline, both groups had similar mean VAS scores that was zoledronic acid: 7.9 ± 1.1 and denosumab: 7.1 ± 1.3. At 1 year, the mean VAS scores were with Zoledronic acid: 1.9 ± 0.7 and with denosumab: 3.9 ± 0.9. The reduction in pain was statistically significant in both groups ($p<0.001$), but pain relief was more pronounced in the zoledronic acid group. The between-group difference at 1year was also statistically significant ($p=0.04$).

Discussion

This retrospective study compared the clinical safety and efficacy of zoledronic acid and denosumab in treating osteoporosis over 24 months. Our findings demonstrate that both agents' adverse effects were mild and manageable with improve patient outcomes. Zoledronic acid showing superior efficacy in pain relief and thereby improving quality of life.

The safety profiles of both drugs align with existing evidence, emphasizing their tolerability in routine clinical use. In our study, zoledronic acid was associated with a higher incidence of transient, flu-like symptoms (95%), consistent with the well-documented acute phase reaction following intravenous bisphosphonate administration[18]. These symptoms, thought to be related to cytokine release, generally occur within 24 to 48 hours post-infusion and resolve without intervention.

Denosumab demonstrated a favorable immediate safety profile, with fewer adverse events such as fever (10%) and musculoskeletal pain (5%). This aligns with prior large-scale trials indicating denosumab's generally mild side effect profile[16]. However, clinicians should remain vigilant about potential serious adverse effects reported in the literature, including infections, hypocalcemia, and osteonecrosis of the jaw (ONJ), especially with long-term use[14].

Importantly, no serious adverse events such as osteonecrosis of the jaw or atypical femoral fractures occurred in either group during the study. These rare but significant complications often emerge after prolonged treatment, highlighting the need for continued surveillance and risk stratification, particularly in patients with additional risk factors like dental procedures or corticosteroid use[12].

Both agents led to substantial reductions in VAS pain scores over 12 months, reflecting their effectiveness in mitigating skeletal pain associated with microfractures and bone turnover. Zoledronic acid resulted in greater pain relief (VAS 1.9 vs 3.9; p=0.04) at12 months. This may be due to its ability to induce osteoclast apoptosis and sustained suppression of bone resorption through inhibition of farnesyl pyrophosphate synthase[11].

Denosumab also effectively reduced pain, though its mechanism via RANKL inhibition might produce a more reversible effect on osteoclasts, which could influence pain outcomes over longer terms[17]. Furthermore, denosumab discontinuation is associated with rapid bone turnover rebound and increased fracture risk, which may adversely affect long-term pain control[14].

Our findings support current ACR 2022 guidelines recommending both zoledronic acid and denosumab as effective options for patients with glucocorticoid-induced or postmenopausal osteoporosis[10]. Zoledronic acid's once-yearly administration may improve adherence and provide consistent skeletal protection, which is especially valuable in settings with limited healthcare access.

Denosumab remains a useful alternative for patients intolerant to bisphosphonates or with renal impairment, as it is not cleared renally. Clinicians should individualize therapy by balancing efficacy, safety, patient preference, and logistical considerations.

The retrospective study limits causal inference, and potential confounding factors may exist despite comparable baseline characteristics. Absence of formal quality of life and BMD assessments limits comprehensive evaluation. Larger randomized controlled trials with extended follow-up and detailed functional outcomes are needed.

Conclusion

Both zoledronic acid and denosumab are effective treatments for osteoporosis, significantly reducing pain over a 12-months period. In this study, zoledronic acid demonstrated greater pain relief with a favorable safety profile. Given its once-yearly dosing and long-lasting effects, zoledronic acid may offer practical advantages, especially in settings where adherence or follow-up is a concern. Denosumab remains a strong alternative, particularly for patients who cannot tolerate bisphosphonates. Treatment choice should be individualized, and further studies are needed to confirm long-term outcomes.

Declaration

Ethics approval: Not applicable

Author contributions

Conception and development of the idea: AKMA, NB

Writing: NB, MAS

Data analysis: NB, MMK, CSC

Data collection: NB, AA, AKMNK

Review and Editing: NB, MMK, AKMA

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