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Additional Dose of Zolendronic Acid for Inadequate Response in Avascular Necrosis

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Abstract

Background: Bisphosphonates have demonstrated efficacy in management of Avascular necrosis of femoral head (AVNFH) and in delaying or obviating the need for surgical interventions. However, the delayed onset of pain relief following bisphosphonate therapy can reduce patient compliance, prompting some to opt for surgical alternatives. This study evaluates the clinico-radiological outcomes of an additional dose of zoledronic acid (ZA) in AVNFH. **Methods:** This retrospective observational study was conducted between January 2020 and December 2022. Patients diagnosed with AVNFH received a bisphosphonate regimen consisting of 5 mg intravenous zoledronic acid (ZA) annually, alongside 35 mg of oral alendronate twice weekly for three years. Patients who experienced less than 50% improvement in the Visual Analogue Scale (VAS) score at 6 weeks were administered an additional dose of ZA. The study assessed clinical outcomes through VAS and Harris Hip Scores (HHS), clinical failure rates, radiological progression and collapse rates. **Results:** Among 362 hips included in the study, 338 hips (93.4%) achieved a satisfactory clinical outcome, avoiding THR at a mean follow-up of 28 months (12-51 months). The clinical failure rates were as follows: 5% in Stage I (1/20 hips), 9.1% in Stage II (28/306 hips), and 13.9% in Stage III (5/36 hips). Radiological progression rates were 65% for Stage I, 31.7% for Stage II, and 13.9% for Stage III. An additional dose of zoledronic acid at 6 weeks significantly improved the VAS score from 7.9 to 2.7, and the HHS from 50.9 to 75.5 at 3 months. **Conclusion:** Our study demonstrates that combination bisphosphonate therapy is effective in managing AVNFH by reducing disease progression, collapse rates, and the need for THR. The addition of an extra dose of ZA at 6 weeks leads to significant improvements in both pain and function, likely due to the dose-dependent effect of bisphosphonates in AVNFH treatment.

Keywords

Avascular Necrosis, Bisphosphonate, Zolendronic Acid

1. Introduction

Avascular necrosis of the femoral head (AVNFH) is a progressive and disabling condition caused by the death of bone tissue due to impaired blood supply. This disease commonly affects younger patients, often requiring multiple revision surgeries and potentially leading to the need for total hip arthroplasty (THA). While various medical therapies have been explored to delay the need for THA, their outcomes have been inconsistent [1].

In 2001, Agarwala *et al.* first established the beneficial role of alendronate in the treatment of osteonecrosis of the femoral head [2]. Their subsequent research, including a 10-year follow-up in 2011, demonstrated that 87% of hips did not require arthroplasty following a 3-year bisphosphonate regimen [3]. More recently, combination therapy involving intravenous zoledronic acid (ZA) and oral alendronate has been shown to be effective in improving clinical outcomes and delaying disease progression [4] [5]. ZA is thought to achieve higher blood concentrations more rapidly than oral bisphosphonates, providing quicker pain relief and reducing bone marrow edema [4] [5].

However, some patients continue to experience inadequate pain relief after a single dose of zoledronic acid. The variable response to this treatment could be due to factors such as the size of the necrotic area, the Kerboul angle, bone marrow edema, and individual patient responses. We hypothesize that an additional dose of zoledronic acid at 6 weeks may enhance treatment efficacy by further reducing bone marrow edema and improving clinical outcomes.

2. Materials & Methods

2.1. Study Design and Approval

This retrospective observational study was conducted at a tertiary care hospital in Mumbai, India, involving patients diagnosed with AVNFH between January 2020 and December 2022. All patients received a bisphosphonate regimen consisting of 5 mg intravenous zoledronic acid annually, along with 35 mg oral alendronate twice weekly. Additionally, all patients received daily 1000 mg calcium and 1000 IU vitamin D supplementation. Follow-ups were scheduled at 6 weeks, 3 months, 6 months, and yearly thereafter.

Patients who exhibited less than 50% improvement in their VAS score at 6 weeks were administered an additional dose of zoledronic acid. Inclusion criteria comprised patients with Ficat-Arlet stages I, II, or III AVN and less than 50% improvement in VAS at 6 weeks. Exclusion criteria included patients with stage IV AVN, contraindications to zoledronic acid (e.g., renal dysfunction, hypocalcemia), and those with follow-up shorter than one year.

2.2. Outcome Measures

Primary outcomes included clinical measures (VAS and HHS scores) and radiological assessments (progression and collapse rates). Clinical failure was defined as the need for surgical intervention, such as THR. Radiological progression was

assessed by comparing initial and follow-up plain radiographs (anteroposterior and lateral views) and MRIs, with progression categorized as a one- to two-grade shift in Ficat-Arlet staging. Radiologic collapse was noted to occur when progression from Ficat-Arlet stage I or II to stage III was observed.

2.3. Statistical Analysis

Statistical analysis was conducted using STATA-IC Version 13.1. Data were summarized using descriptive statistics, with means, standard deviations (SD), medians, and interquartile ranges (IQR) for continuous variables, and frequencies and percentages for categorical variables. A two-way repeated measures ANOVA was used to assess changes in VAS and HHS scores over time. An independent t-test was used to compare mean age differences between male and female patients.

3. Results

A total of 231 patients (389 hips) were initially screened for the study, with 211 patients (362 hips) meeting the inclusion criteria. 20 patients (27 hips) were excluded from the study of which 15 patients (19 hips) were stage 4 AVNFH and 5 patients (8 hips) had intolerance to bisphosphonate therapy. The mean age of the patients was 39.3 years, with a higher prevalence of AVNFH in males (mean age: 39.9 years) compared to females (mean age: 37.1 years).

3.1. Clinical Outcomes

Among the 362 hips studied, 338 hips (93.4%) avoided THR at a mean follow-up of 28 months (12 - 51 months), indicating the efficacy of the bisphosphonate regimen. The need for THR was 5% in Stage I, 9.1% in Stage II, and 13.8% in Stage III at the final follow-up. Clinical outcomes showed significant improvement in VAS and HHS scores following bisphosphonate therapy (Figure 1, Figure 2).

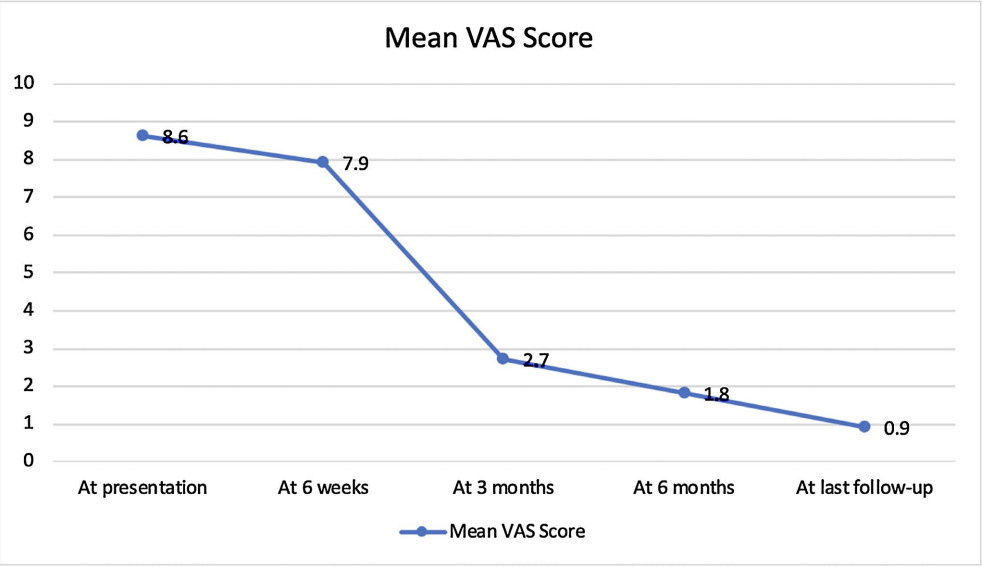

Figure 1. Line graph showing improvement in mean VAS at various follow-up.

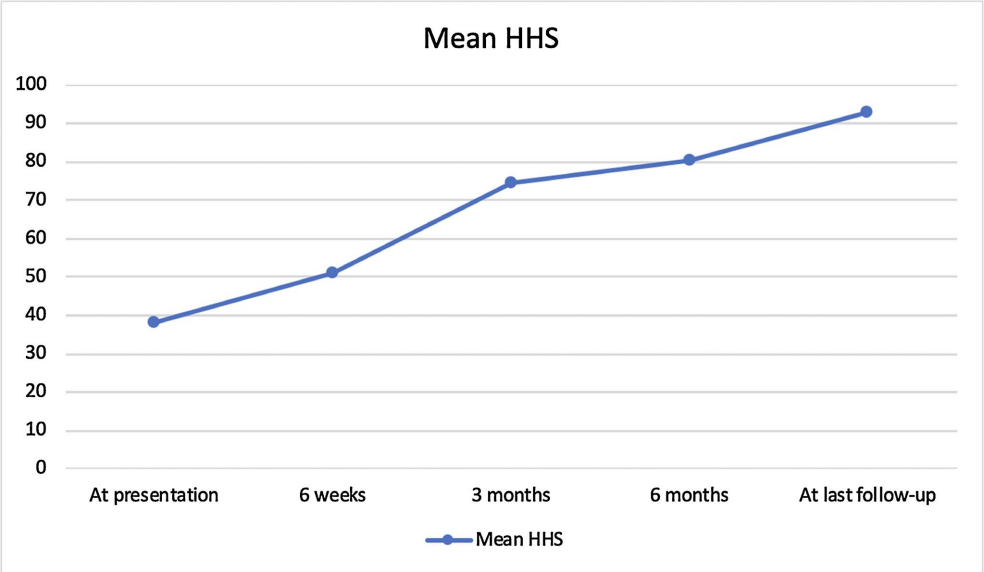

Figure 2. Line graph showing improvement in mean HHS at various follow-up.

At 6 weeks, there was modest improvement in VAS and HHS scores. However, in patients who had less than 50% improvement in VAS at 6 weeks, the additional dose of ZA resulted in substantial improvements, with the mean VAS score decreasing from 7.9 to 2.7, and the HHS increasing from 50.9 to 75.5 at 3 months.

3.2. Radiological Outcomes

At 1 year, the radiological progression rates were 65% for Stage I, 31.7% for Stage II, and 13.9% for Stage III (Table 1, Table 2). The collapse rate was highest in

Table 1. Table showing the clinical failure rate, radiological progression rate and the collapse rate at the final follow-up

Stage at presentation	Clinical Failure rate	Radiological Progression rate	Radiological collapse rate
I	5% (1/20 hips)	65% (13/20 hips)	15% (3/20 hips)
II	9.1% (28/306 hips)	31.7% (97/306 hips)	29.1% (89/306 hips)
III	13.8% (5/36 hips)	13.9% (5/36 hips)	-----

Table 2. Table showing the stage-wise radiological progression rate and the collapse rate at the final follow-up visit

Stage at presentation	Radiological Progression rate	Radiological Collapse rate
I (20 hips)	I to II- 9 (45%) I to III- 3 (15%) I to IV- 1 (5%)	I to III- 3 (15%)
II (306 hips)	II to III- 89 (29.1%) II to IV- 8 (2.6%)	II to III- 89 (29.1%)
III (36 hips)	III to IV- 5(13.9%)	-

Stage I (15%) and Stage II (29.1%), with fewer cases progressing to Stage IV in the follow-up period. These findings suggest that the combination therapy, including the additional dose of zoledronic acid, effectively retarded radiological progression.

4. Discussion

Agarwala *et al.* have demonstrated the effectiveness of combination bisphosphonate therapy for the treatment of Avascular Necrosis of the Femoral Head (AVNFH) [4]. In their study, involving 874 hips, patients were divided into two groups: one group received alendronate alone, while the other received a combination of intravenous zolendronic acid (ZA) and oral alendronate. The study showed that at 6 weeks post-therapy, the mean Visual Analog Scale (VAS) score improved from 7.93 ± 0.85 to 7.00 ± 0.82 in the alendronate-only group and from 7.10 ± 0.69 to 3.66 ± 1.47 in the combination therapy group. The authors concluded that both alendronate alone and combination bisphosphonate therapy could retard disease progression, reduce the collapse rate, and decrease the need for joint replacement surgery. However, intravenous zolendronic acid, due to its faster absorption, achieves higher blood levels quickly and reduces bone marrow edema, providing earlier pain relief compared to oral therapies [4].

In the present study, while we observed some improvement in the VAS score at 6 weeks after combination bisphosphonate therapy, the response was not significant enough. Consequently, patients who had less than 50% improvement in pain were given an additional dose of zolendronic acid at the 6-week follow-up. This additional dose led to significant clinical improvements, suggesting that early intervention with a second dose may further enhance treatment outcomes.

The positive results in our study can be attributed to the dose-dependent mechanism of action of bisphosphonates in AVN [6]. Previous animal studies have indicated that bisphosphonates prevent the resorption of necrotic bone, and this effect is enhanced with higher doses [7]. One study demonstrated that doses 4 to 50 times higher than those used for osteoporosis were required to prevent necrotic bone resorption in AVN [8]. This underscores the need for higher doses of zolendronic acid in AVN, as the distribution of bisphosphonates is less effective in necrotic bone compared to healthy bone tissue.

In our study, the additional dose of zolendronic acid at 6 weeks significantly improved the VAS score from 7.9 to 2.7 and the Harris Hip Score (HHS) from 50.9 to 75.5 at the 3-month follow-up. The improvement in pain and function led to better patient compliance with medical management and delayed or avoided the need for surgical intervention, such as total hip replacement (THR). At a mean follow-up of 28 months (range 12 - 51 months), 338 out of 362 hips (93.4%) showed satisfactory clinical outcomes and did not require THR. We attribute the early improvement in pain (VAS) and function (HHS) to the dose-dependent effects of bisphosphonates.

While additional doses of zolendronic acid show promising results, potential adverse effects to the administration of more dosages of zolendronic acid must be

considered. Zolendronic acid has been proven to be safe when used monthly for the management of skeletal metastases in patients with lung cancer and other solid tumors [9]. In a study by Lee-Rosen *et al.*, the outcomes of zolendronic acid versus placebo, administered every three weeks for nine months, showed no major side effects [10]. In various medical conditions, zolendronic acid has been found to reduce bone turnover and increase bone mineral density without significant systemic side effects, due to its high affinity for bone surfaces and selective action [11]. Recent meta-analysis and controlled experiments have shown that bisphosphonates have promising results in the management of ON, but need randomised controlled trials with large cohort of patients [12] [13].

5. Limitations

Despite promising results, this study has certain limitations. The retrospective design and the lack of a control group make it difficult to isolate the specific effect of the additional dose of Zolendronic acid. Future randomized controlled trials would provide more definitive evidence regarding the efficacy of this approach. Additionally, longer follow-up periods would be beneficial to assess the long-term outcomes and to determine whether this therapy can effectively delay or prevent the need for total hip replacement. However, this is the largest series to date with the longest follow-up period for the medical management of AVN.

6. Conclusion

This study provides supporting evidence for the use of an additional dose of Zolendronic acid in the treatment of AVN of the hip, building on the previous research on bisphosphonates. The treatment appears effective in preserving hip function, reducing pain, and potentially decreasing the need for total hip replacement. These findings are particularly relevant for managing AVN even more in younger patients who may benefit from non-surgical treatment options. This represents the largest series with the longest follow-up, addressing the management of this debilitating disease and its role in preventing total hip replacement (THR) in young patients.

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Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Author 1 has contributed towards conceptualization, design, data collection, analysis, decision to publish, and preparation of the manuscript.

Author 2 has contributed towards conceptualization, design, data collection, analysis, decision to publish, and preparation of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by Institutional ethics committee with approval number 1712-24-SA dated 14/06/2024.

Declaration of AI and AI Assisted Technologies in the Writing Process

We declare that AI and AI assisted technology was not used in the writing process.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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