Effect of Zoledronic Acid and Alendronate on Bone Edema and Pain in Spontaneous Osteonecrosis of the Knee: A New Paradigm in the Medical Management*

Efeito do ácido zoledrônico e do alendronato no edema ósseo e dor na osteonecrose espontânea do joelho: Um novo paradigma no manejo médico

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Rev Bras Ortop 2020;55(5):543–550.

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Abstract

Objective The aim of the present study was to determine the effect of combined zoledronic acid and alendronate therapy on bone edema and knee pain in cases of spontaneous osteonecrosis of the knee. We report our experience with this treatment.

Methods A retrospective case series of 11 patients with spontaneous osteonecrosis of the knee confirmed by magnetic resonance image (MRI). The patients were treated with a single dose of 5 mg of intravenous zoledronic acid combined with 35 mg twice a week of oral alendronate, for 16 weeks. The visual analogue scale scores were noted before the beginning of the therapy, at 8 weeks, and at 16 weeks of follow-up. The size of the bone marrow edema adjacent to the lesion was measured on T2-weighted MRI coronal images at the beginning of the therapy and at 16 weeks.

Results The average visual analogue scale score at 0 weeks was of 7.72, and of 0.81 at 16 weeks of therapy; the difference was statistically significant ($p = 0.03$). The mean bone marrow involvement at 0 weeks was of 80%, which reduced to 11.81% at 16 weeks of therapy. This change was statistically significant ($p = 0.03$).

Conclusion Our data shows that the combination therapy causes early pain relief and reduction of the bone edema, and it is safe, effective and well-tolerated for a painful disease entity like spontaneous osteonecrosis of the knee.

Keywords

- necrosis
- bisphosphonates
- osteoarthritis
- knee joint

Resumo

Objetivo Determinar o efeito do tratamento combinado de ácido zoledrônico e alendronato no edema ósseo e na dor no joelho em casos de osteonecrose espontânea do joelho. A experiência dos autores com este tratamento é relatada.

Métodos Série de casos retrospectiva, incluindo 11 pacientes com osteonecrose espontânea do joelho confirmada por ressonância magnética. Os pacientes foram

* *Study conducted at the Hinduja Hospital and Medical Research Centre, Mumbai, India. Published Originally by Elsevier Editora Ltda.*

received
July 30, 2017
accepted
December 7, 2017

DOI https://doi.org/10.1016/j.rboe.2017.12.008.
ISSN 0102-3616.

tratados com uma dose intravenosa única de 5 mg de ácido zoledrônico combinada com 35 mg de alendronato oral, 2 vezes por semana, por 16 semanas. Os escores da escala visual analógica foram aferidos antes do começo do tratamento, em 8 semanas e em 16 semanas de acompanhamento. O tamanho do edema da medula óssea adjacente à lesão foi medido em imagens de ressonância magnética coronal ponderadas em T2 no início do tratamento e em 16 semanas.

Resultados A média dos escores da escala visual analógica em 0 semanas foi de 7,72, e de 0,81 em 16 semanas de tratamento, uma diferença estatisticamente significativa ($p = 0,03$). O envolvimento médio da medula óssea em 0 semanas foi de 80%, e reduziu para 11,81% em 16 semanas de tratamento, uma diferença estatisticamente significativa ($p = 0,03$).

Conclusão Os dados mostram que a terapia combinada proporciona alívio da dor inicial e redução do edema ósseo, sendo segura, eficaz e bem tolerada em uma enfermidade dolorosa como a osteonecrose espontânea do joelho.

Palavras-chave
- necrose
- bisfosfonatos
- osteoartrite
- articulação do joelho

Introduction

Spontaneous osteonecrosis of the knee (SPONK) was first described by Ahlbäck et al.[1] in 1968. Osteonecrosis, which was originally described as a single entity, has been reclassified as three separate conditions: 1) SPONK, which usually affects a single condyle in older patients; 2) secondary osteonecrosis, which is when the condition has a known factor, such as sickle cell anemia, corticosteroid treatment etc., in which younger patients are more commonly affected, and the radiographic appearance is different, with lesions involving multiple foci; and 3) postarthroscopy osteonecrosis of the knee, which affects only one condyle. The onset is increasing knee pain with positive magnetic resonance imaging (MRI) findings.[2,3] Yamamoto and Bullough[4] concluded their findings based on the histological specimens of 14 patients in the postoperative period. In their study, they state that the subchondral insufficiency fracture that resulted from the underlying osteoporosis is the etiology of SPONK. The patients with SPONK are usually 55 years old or older, have no risk factors, and have unilateral monoarticular pain.[5] Women are more commonly affected.[6] The two major etiologic theories are trauma and vascular diseases.[7,8] The investigations including anteroposterior, lateral and oblique radiographs of the knee joint though MRI are necessary to make the diagnosis. In the early course of the disease, the radiographs are often negative, and, in a few cases, may remain negative for the total duration of the clinical symptoms.[9] The susceptibility of the medial femoral condyle to SPONK has been purported to be the result of varying blood supply between the medial and lateral condyles. A cadaveric study by Reddy and Fredericks[11] demonstrated that the medial femoral condyle has limited intraosseous blood supply with definite and apparent watershed areas, whereas the lateral femoral condyle has both a rich extra- and intraosseous vascular supply.[10,11] Spontaneous osteonecrosis of the knee in the proximal medial tibial plateau has also been described in the literature by Satku et al.,[12] and it is progressive in most cases, leading to degenerative joint disease. Lotke et al.[13] described that the symptoms of untreated patients who have roentgenographic evidence of SPONK can last up to seven years after the diagnosis of this painful condition has been made. The treatment of SPONK has traditionally been either non-surgical or surgical managements. The non-surgical management of SPONK includes protected weight bearing, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates and prostaglandins. The surgical management includes core decompression by drilling, bone grafting, osteochondral grafting, arthroscopy, tibial osteotomy, and unicompartmental or total knee arthroplasty.[10] The current treatment for SPONK seems unsatisfactory. The pathology of SPONK is similar to that of avascular necrosis (AVN) of the femoral head. Agarwala et al.[14] reported 16 patients in their pilot study with avascular necrosis of the hip with the use of alendronate. This study was then further followed up for eight years in 395 AVN hips.[15] They found significant improvement in pain as early as 12 weeks, and improved functional capacity with reduced requirement of analgesics, with this therapy. To our knowledge, there are only four papers that mention the outcomes of the use of bisphosphonates specifically in the case of SPONK lesions.[3,16–18]

Materials and Methods

The data of 11 patients with SPONK lesions involving only the femur were analyzed between March 2015 and July 2016. The present study was duly approved by the institutional review board. All of the patients included had an MRI-proven diagnosis of SPONK. The exclusion criteria were: known secondary cause of osteonecrosis; renal disorder; history of trauma; bone disorders that interfere with the MRI findings; allergy to bisphosphonates (in which cases zoledronic acid [ZA] or alendronate could not be administered); and follow-up < 16 weeks. A single intravenous dose of 5 mg of ZA was administered, and 70-mg alendronate tablets weekly divided into two doses taken on empty stomach was started immediately. This was supplemented with calcium, vitamin D and anti-inflammatory medications. This therapy enabled the possibility of discontinuing

the oral alendronate therapy in case of any unwanted side effects. In the initial three months of the treatment, all patients were advised to use a walker for partial weight bearing, and, later on, weight bearing was increased gradually as dictated by pain. The visual analogue scale (VAS) score was noted before the beginning of the therapy, at 8 weeks, and then at 16 weeks of follow-up (on a scale of 0 to 10, with 0 indicating no pain and 10 indicating the worst possible pain). The MRI scan and the radiographs of the affected knee joint were repeated at 16 weeks of therapy. The size of the bone marrow edema (BME) was measured on T2-weighted MRI coronal images by calculating the maximum width of the lesion affecting the articular surface in the coronal view as a percentage of the affected femoral condyle. This was measured at the beginning of the therapy and at 16 weeks of follow-up. The MRI scans were not performed before these 16 weeks. The BME was assessed by areas of decreased signal intensity of the subchondral bone on proton-density (PD) weighted MRI and increased signal intensity on T2-weighted images. The MRI results were interpreted by an experienced radiologist who was not part of the study.

Statistical Analysis

The data was recorded using Excel (Microsoft, Redmond, WA, US) spreadsheets. Baseline demographic characteristics were recorded. Based on normality, a comparison between the pretherapy and posttherapy VAS scores and bone edema was performed using the Wilcoxon signed-rank test. Values of $p \leq 0.05$ were considered significant.

Results

The data of 11 patients (6 women and 5 men) with MRI-confirmed femoral SPONK were analyzed between March 2015 and July 2016. The mean age of the patients was 52 years

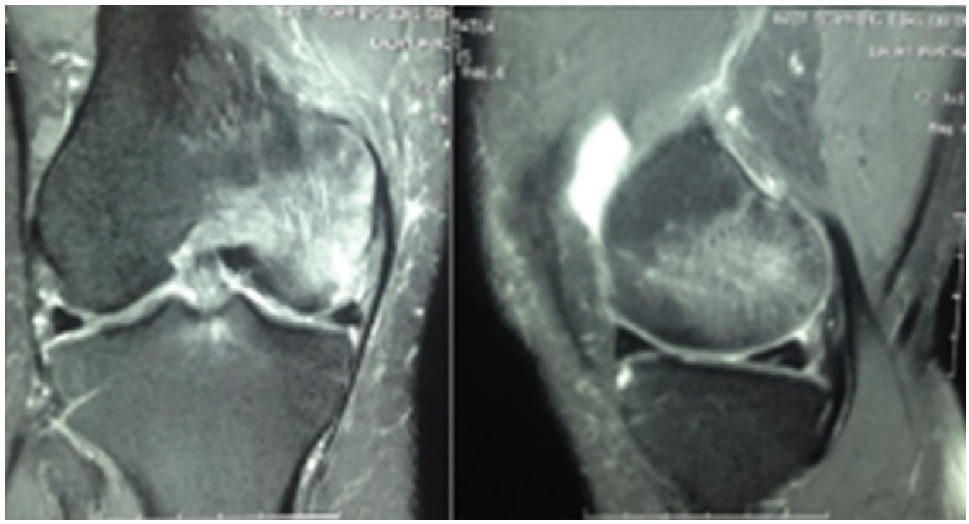

Fig. 1 Pretreatment MRI T2W coronal and sagittal sections of the knee joint showing bone edema involving more than half of the medial femoral condyle.

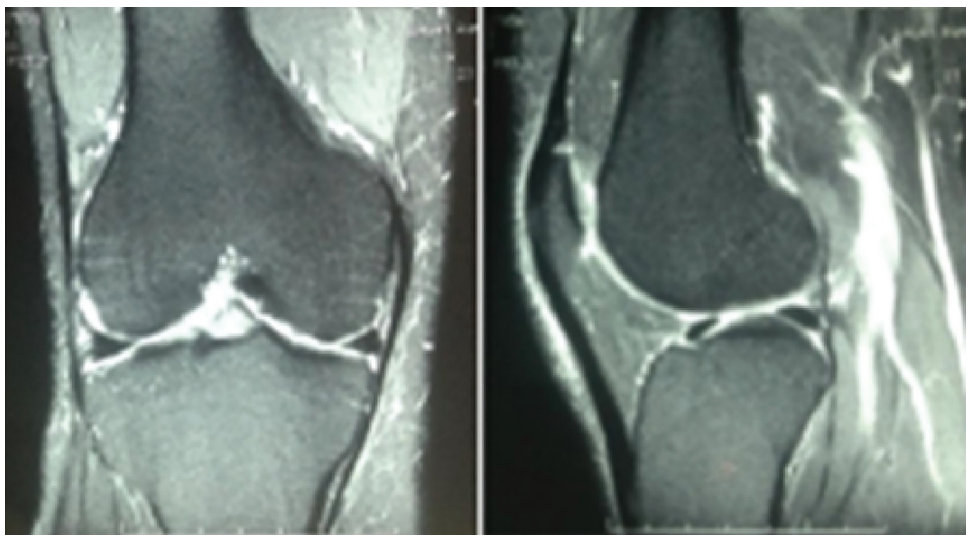

Fig. 2 Posttreatment MRI T2W coronal and sagittal sections of the knee joint showing near complete resorption of the bone edema after 16 weeks of the combination therapy.

(range 35–62 years). All patients had unilateral joint involvement (6 right-sided), with 10 cases of involvement of the medial femoral condyle, and 1 case of lateral femoral condyle SPONK. Cases of SPONK of the tibial condyle were not included in the study. The average VAS score at the beginning of the therapy was of 7.72, and of 0.81 at 16 weeks of therapy, the statistical difference being significant ($p = 0.03$). Overall, the pain considerably reduced 3 weeks after the beginning of the therapy, as it was described by the patients, but the VAS score was not calculated at this point in time.

The dosage and the frequency of analgesic requirement of all patients reduced over a period, and the maximum duration of analgesic intake recorded was of 8 weeks, after which no analgesics were required. The average VAS score at 8 weeks was of 1.64, the difference at this time also being statistically significant ($p \leq 0.05$). No patient required to stop oral alendronate till 16 weeks due to any major side effects. The average bone marrow involvement at 0 weeks was of 80%, which was significantly reduced to an average of 11.81% at 16 weeks ($p = 0.03$) (►**Figs. 1–7**). Three patients had subchondral cysts with small volumes, all of which were less than 14 mm long and 4 mm wide, and all of them had high signal intensity on T2-weighted images (which were criteria for a good prognosis according to Leucovet et al.).[19] A total of five patients had concurrent osteoarthritis (OA), and three had meniscal root tears, but none of them had articular contour alterations. No definite conclusion could be made for the possible risk factors of SPONK due to the small sample size.

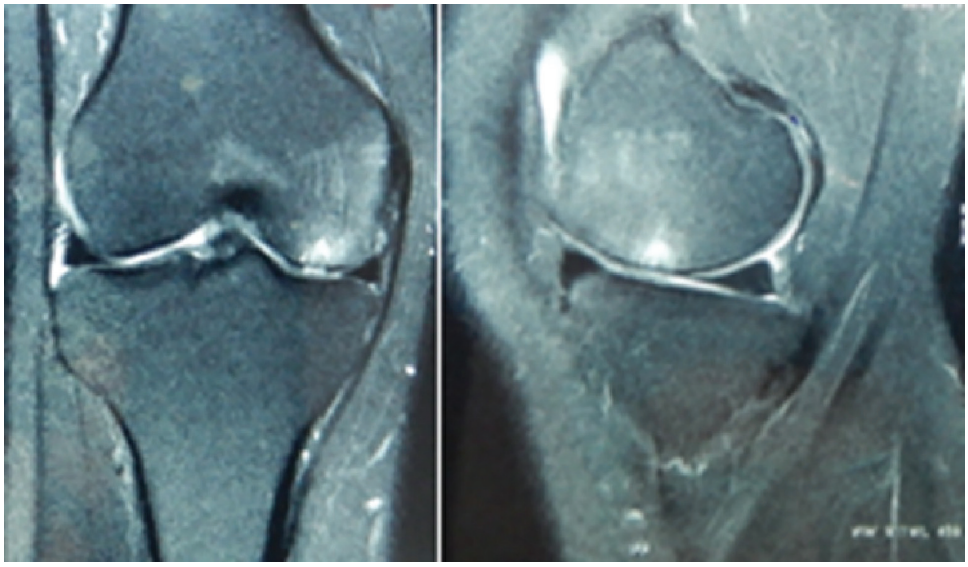

Fig. 3 Pretreatment MRI T2W coronal and sagittal sections of the knee joint showing bone edema involving 70% of the medial femoral condyle along with a subchondral cyst, thinning of the articular cartilage, and contour alterations of the cartilage.

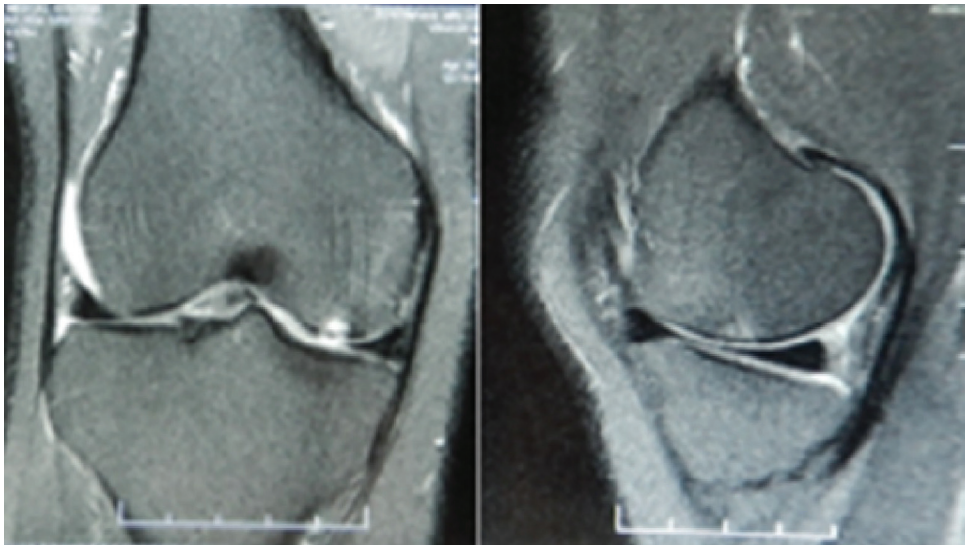

Fig. 4 Posttreatment MRI T2W coronal and sagittal sections of the knee joint showing complete resorption of the bone edema after 16 weeks of the combination therapy.

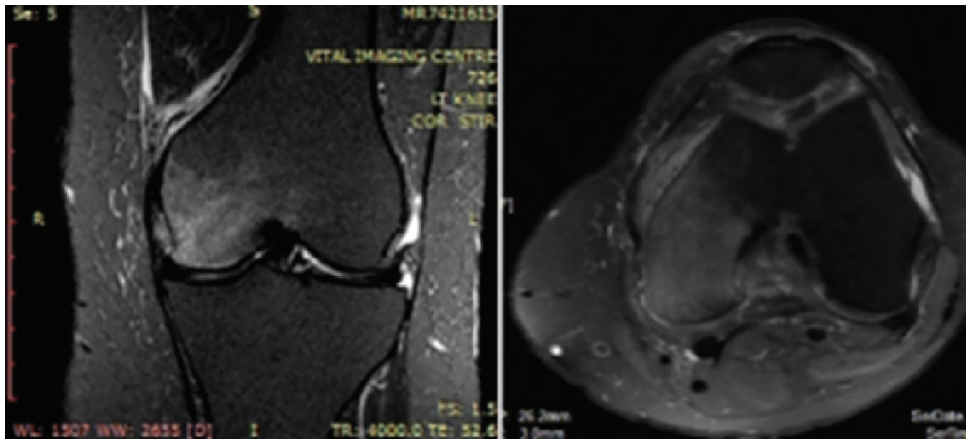

Fig. 5 Pretreatment MRI T2W coronal and axial sections of the knee joint showing bone edema involving about 90% of the medial femoral condyle.

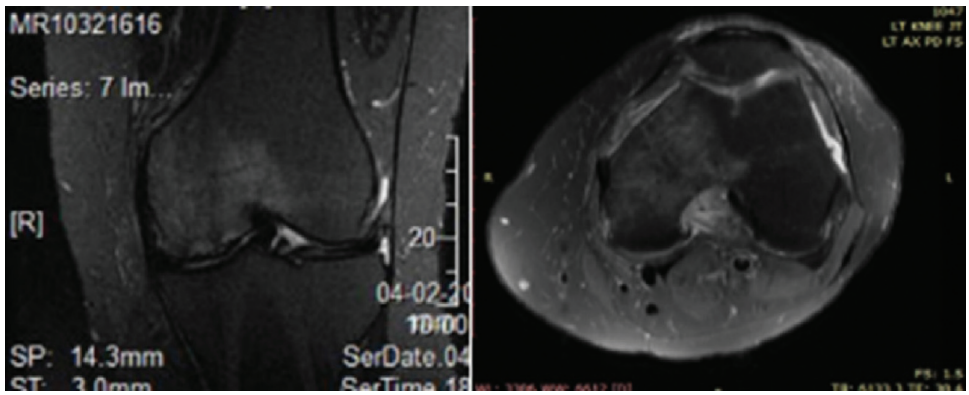

Fig. 6 Posttreatment MRI T2W coronal and axial sections of the knee joint showing considerable resorption of the bone edema after 16 weeks of the combination therapy.

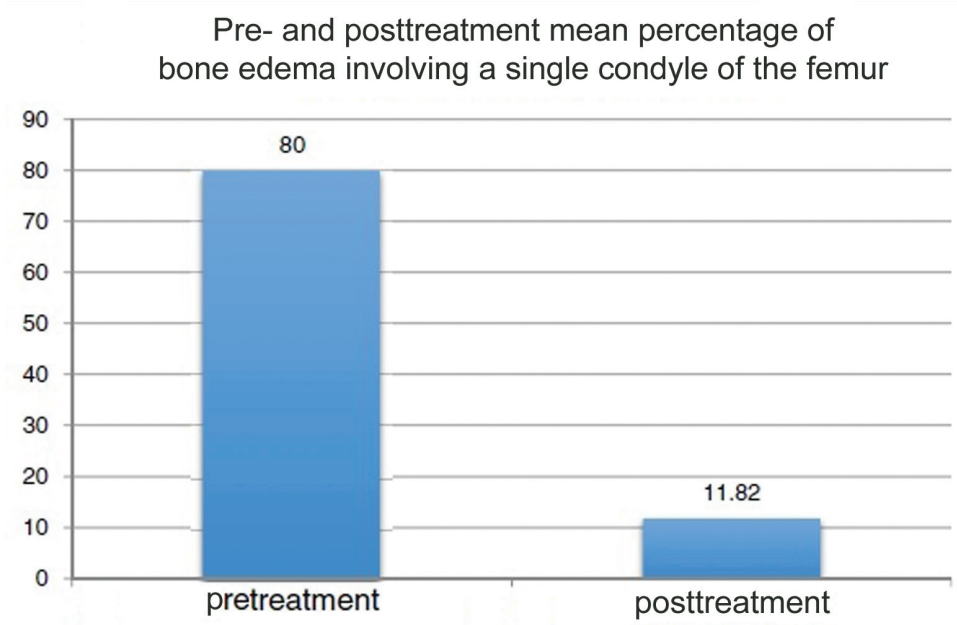

Fig. 7 Bar diagram showing the percentage of pretreatment and posttreatment of bone edema involving a single condyle of the femur.

Discussion

In the present study, we found that combining ZA with alendronate leads to a faster and significant reduction of the BME. There was a significant reduction in the VAS score after 8 weeks and 16 weeks of the beginning of the therapy. All patients started bearing their full weight after 16 weeks of therapy, which was pain-free, and they described the treatment as very effective symptomatically. The range of motion of the knee joint was pain-free at 16 weeks for all patients. Lecouvet et al.[19] studied MRI features to differentiate and prognosticate irreversible osteonecrosis and transient lesions of the femoral condyle having BME. According to this study, thick subchondral areas of low signal intensity on T2-weighted images, thin low signal intensity lines located deep in the trabecular bone, and subtle focal deformities of the epiphyseal contour are the most important features associated with an early stage of irreversible osteonecrosis. Most of the patients in our study had "good prognosis" according to the criteria described in the literature by Lecouvet et al.[19] Currently, there is no standard pharmacological therapy available for SPONK.

Laslett et al.[20] performed a study to compare the effect of a single infusion of ZA with placebo in patients with clinical knee OA. They found a reduction in the total bone marrow lesion that was significantly greater in the ZA group than in the placebo group after six months of therapy.[20] This evidence formed the basis of our strategy to incorporate ZA as part of our combination therapy.

The oral bioavailability of alendronate taken on an empty stomach is of only 0.7%, and food markedly inhibits oral absorption. The pharmacokinetics of alendronate is exclusively studied based on its urinary excretion, as extremely low plasma concentrations are achieved after the oral intake.[21] The slow onset of action of alendronate starts only after one month of drug intake.[22] Intravenous ZA administration has 100% bioavailability, and the onset of action is faster than that of alendronate.[23] Saag et al.[24] reported that the lowest levels of urinary N-terminal telopeptides (NTX) after administering 5 mg of ZA was achieved after 1 week of the beginning of the therapy, while with 70 mg of alendronate per week it takes 12 weeks. These data shows that combining ZA with alendronate ensures an early onset of action and sustained maintenance. We also believe that treating an acute painful condition like SPONK requires an aggressive initial treatment using a faster acting modality followed by the sustained delivery of bisphosphonates, unlike what is performed regarding a condition like osteoporosis, which requires long-acting low-dose bisphosphonates.

High doses of ZA are administered in conditions like metastasis-reported complications. A study by Berenson,[25] of phase-three clinical trials in more than 3,000 patients receiving intravenous 4 mg of ZA every 3 to 4 weeks for metastasis in conditions like multiple myeloma, breast cancer, prostate cancer or other solid tumors demonstrated it to be clinically safe and effective.[25] Hence, usually about 12 to 16 mg of ZA are administered in a short period of 9 to 16 weeks. This study shows that high doses of bisphosphonates are justified in cases of acute painful bone pathology. Although the analogy drawn is indirect, the authors have based the study rationale on sound understanding of the condition, on clinical experience in managing SPONK, and on the pharmacokinetics and pharmacodynamics of bisphosphonates.

Jureus et al.[16] performed a prospective study with 17 patients with SPONK treated with 70 mg of alendronate per week orally administered for a minimum of 6 months (mean of 11 months); the patients were followed up clinically and radiographically at 1 year of therapy. A total of 59% of the patients had complete radiographic recovery, against 25% of untreated cases in the same hospital. These results are similar to those of our study. Meier et al.[17] performed a randomized controlled trial with a placebo regarding the effectiveness of ibandronate on SPONK. A total of 30 patients were randomized to receive either intravenous ibandronate or placebo for 12 weeks, and they were followed up for 48 weeks to analyze the pain score, and the mobility and radiological outcomes. They reported that bisphosphonates had no additional benefit over anti-inflammatory medications at 12 weeks or 48 weeks both functionally and radiographically. Our study differs from that, as we used a combination of bisphosphonates. Raynauld et al.[26] analyzed the impact of risedronate on bone marrow and on cystic lesions of the knee by MRI over 24 months. The trial had 4 treatment groups: placebo; 5 mg daily of risedronate; 15 mg daily of risedronate; and 50 mg weekly of risedronate administered over 24 months. The study described no advantage of the bisphosphonates over the placebo treatment on the cysts and bone marrow lesions on the MRI.

Kraenzlin et al.[3] evaluated 28 patients with knee osteonecrosis treated with a combination of pamidronate with alendronate therapy (initially 120 mg of intravenous pamidronate divided into 3 to 4 perfusions over 2 weeks, followed by 70 mg of oral alendronate weekly for 4 to 6 months). There was an 80% reduction in the VAS score at 6 months posttreatment.[3,10] These study results are similar to ours – we found an 89% reduction in the VAS score (7.72–0.81) –, but the difference in our study was that our results were evaluated at 16 weeks (4 months) of therapy, which shows that the resolution of symptoms is much faster. Pamidronate combined with alendronate was well tolerated by the patients. Acute reactions due to intravenous pamidronate were observed in four patients, and there were no other side effects due to oral alendronate. All patients completed the intended course of therapy without interruption.

The mechanism of SPONK seems similar to that of avascular necrosis of the femoral head. Nishii et al.[27] performed a study to monitor the progression of collapse of the femoral head in patients with osteonecrosis treated with oral alendronate therapy. Their study showed a lower rate of collapse of the femoral head, and they reported lower hip pain in the necrosis group when compared to the control group.[27]

Nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and ZA) selectively inhibit farnesyl pyrophosphate synthase (FPPS) within the osteoclasts.[28] Bisphosphonates decrease resorption

parameters such as the extent of the actively-resorbing area and the depth of the erosion measured from the bone surface.[29] These effects arrest progressive bone resorption and collapse of the bone. The administration of ZA is convenient as it requires a single intravenous dose per year, and, hence, compliance is not a problem.

Limitations of the Study

This was a retrospective study with a small sample size and no control group. The correlation between SPONK and the progression of OA could not be established as this was a short-term study. Additionally, the risk factors of SPONK could not be established due to the small sample size.

Strengths of the Study

Limitations notwithstanding, these preliminary promising results of the present study, from both the objective and subjective assessments, provided consistent results, and showed that ZA combined with alendronate has a compounding effect and provides symptomatic and radiologic improvement in four months, which is faster when compared to other modalities reported in the literature. To the best of our knowledge, this is the first study evaluating the combination ZA and alendronate therapy for SPONK.

Conclusion

This proof-of-concept study confirms that a single injection of ZA combined with alendronate for SPONK provides faster recovery both clinically and radiographically when compared to ZA and/or ibandronate alone, which is described in the literature. Further studies, preferably blinded, randomized controlled trials, and with larger sample sizes are required to reestablish the effectiveness of ZA combined with alendronate over other bisphosphonates used alone for SPONK.

Key Messages

1. Combined therapy with bisphosphonates can be safely administered for a painful disease entity like SPONK.
2. The n atural history of SPONK can be greatly reduced with our treatment.
3. Symptomatic improvement is confirmed with radiological findings, which can obviate the need for surgery.

Conflicts of Interest
The authors have none to declare.

Acknowledgements
The authors would like to thank Dr. V.R. Joshi and Dr. Pratishtha Banga for their support with the writing.

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