

RESULTS OF ALENDRONATE TREATMENT IN PATIENTS DIAGNOSED WITH ASEPTIC OSTEONECROSIS OF THE FEMORAL HEAD

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Abstract

Aseptic osteonecrosis of the femoral head is a disabling condition with plurifactorial aetiology, which affects especially young adults. The purpose of the study was to show that alendronate therapy is useful to these patients. We included 34 patients aged 23 to 62 years old, diagnosed in the evolutionary stages II and III, which were divided into two groups. Patients in the first group received treatment with alendronate-70 mg per week plus 5600 IU cholecalciferol for 2 years and conservative treatment. Group II was not treated with alendronate but only conservatively treated. Patients were evaluated from a clinical, imagistic and functional standpoint. In the final evaluation, the imaging aspects improved in patients in the first group. The dual-energy x-ray absorptiometry (DXA) T score, the visual analogue scale (VAS) and the Harris Hip test statistically increased significantly in patients in the first group.

Rezumat

Osteonecroza aseptică de cap femural este o afecțiune invalidantă, cu etiologie plurifactorială, ce afectează cu precădere adulții tineri. Scopul studiului a fost acela de a arăta că terapia cu alendronat este utilă acestor pacienți. Am inclus în studiu 34 de pacienți, cu vârste cuprinse între 23 și 62 de ani, diagnosticați în stadiile evolutive II și III, ce au fost împărțiți în 2 loturi. Pacienții din primul lot au beneficiat de tratament cu alendronat- 70 mg pe săptămână plus 5600 UI colecalciferol timp de 2 ani și tratament conservator. Lotul II nu a primit tratament cu alendronate, ci a beneficiat doar de tratament conservator. Pacienții au fost evaluați clinic, imagistic și funcțional. La evaluarea finală, aspectele imagistice s-au ameliorat la pacienții din primul grup. Scorul T al absorptiometriei duale cu raze X (DXA), cel al scalei analog vizuale a durerii (VAS) și al testului Harris Hip au crescut semnificativ din punct de vedere statistic la pacienții din primul lot.

Keywords: aseptic osteonecrosis, femoral head, alendronate

Introduction

Aseptic osteonecrosis of the femoral head (AVN) is a disabling condition with plurifactorial aetiology, which affects predominantly young adults [12, 19]. The prevalence of the disease is unknown, but between 10000 and 20000 new cases of femoral aseptic osteonecrosis are diagnosed annually in the United States [5, 15, 27]. Although the pathogenesis of the disease is not fully elucidated, it is recognized that the triggering phenomenon is represented by partial

or total disruption of the femoral head vascularization. Lack of vascularity at this level causes death of bone marrow and bone cells [10, 11, 20, 21]. The collapse of bone tissue translates into localized pain and loss of function of the affected coxo-femoral joint, most patients requiring surgery within 3 - 5 years of being diagnosed, in the form of a bipolar or total hip arthroplasty. Because many of the patients diagnosed with this condition are young adults, hip prosthesis must be the last therapeutic option, taking into consideration the fact that they last only a few

years, requiring periodic adjustment and inspection, therefore, when feasible, attempts should be made to save the femoral head prior to collapse with the use of less invasive treatment options [17]. Bisphosphonates (Bps) are potent anti-reabsorbent agents that act by inhibiting the action of mature osteoclasts in the bone, which theoretically normalizes uncoupled bone remodelling, contributing to femoral head collapse [8, 13, 14]. Of different Bps, alendronate is the most widely prescribed and obvious one [15]. Alendronic acid or alendronate is a nitrogen-containing, second generation bisphosphonate, that binds to and inhibits the activity of farnesyl pyrophosphate synthetase, preventing this way the alterations of small GTPase signalling proteins, which have an important role in speeding up the osteoclast turnover. As a result, bone resorption and turnover are reduced.

The purpose of the study was to determine the role that alendronate therapy has in the treatment of the patients diagnosed with this condition.

Materials and Methods

A randomized blind study was conducted over two years (Jan 2015 - Dec 2017). We included 34 patients aged between 23 and 62 years old, diagnosed with aseptic osteonecrosis of the femoral head, in the evolutionary stages II and III (Liver and Arlet staging), admitted in the Physical and Rehabilitation Medicine Department of the Municipal Hospital "Filantropia" Craiova, Romania. The inclusion criteria consisted in a diagnosis for aseptic necrosis of the femoral head, a modified T dual-energy x-ray absorptiometry (DXA) score, and the visualization of an alteration of the femoral head histoarchitecture. The exclusion criteria were represented by a normal T DXA score, as well as minimal changes in bone tissue structure surrounding the affected area, and the pre-existence of another condition that could have caused the loss of bone mass.

The patients were divided into two groups. Group I-16 patients treated with alendronate-70 mg *per* week plus 5600 IU cholecalciferol (vitamin D) for 2 years and other means of conservative treatment - hygiene-dietary measures, lifestyle changes, wearing walking aids, physiotherapy, kinetotherapy. Group II, 18 patients without treatment with alendronate, only with conservative treatment. Patients in both groups also benefited from pain medication if needed. In order to monitor the therapeutic outcomes, patients were clinically and paraclinically evaluated at study inclusion and at the end of the study. Paraclinic investigations were represented by the collection of several common blood tests, blood inflammation markers such as erythrocyte sedimentation rate (ESR), fibrinogen, C reactive protein (CRP), and other blood tests like calcium level, vitamin D, thyroid tests - thyroid-stimulating hormone level (TSH), para-

thyroid hormone level, protein electrophoresis, alkaline phosphatase, performed in the hospital lab and imaging techniques. Commercial kits and biochemical methods used to determine biochemical parameters were the following: for the haematological parameters the hospital lab used automatic blood count BM-800, for fibrinogen STAGO kit was by the coagulometry method, for ESR- graduated sedimentation rack with vertical test tubes. For the biochemical parameters the lab used the KONELAB60I kit, using a spectrophotometric method and for CRP the Manual Imuno kit. The bone mineral density assessment, initially and at the end of the study, was performed using imaging techniques: X-rays, MRI (magnetic resonance imaging), computed tomography (CT) and DXA test. Pain intensity evaluation was performed using the VAS analogue-visual (VAS) pain scale, and the functionality was evaluated using the Harris Hip scale.

The study has obtained approval from the Ethics Committee of the University of Medicine and Pharmacy of Craiova, Romania, number 217/24.11.2017. Each patient signed an informed consent, they were previously handed a form in which they were presented all the information related to the participation in the study. Clinical data and the collection of biological material were achieved after obtaining the written informed consent from the patients.

Results and Discussion

In the two groups, 34 patients were diagnosed with aseptic osteonecrosis of the femoral head with mixed-traumatic and non-traumatic aetiology, Stages II and III, Ficat and Arlet, aged 23 to 62 years old, with an average age of 43.94 years. The study group was composed of 25 men and 9 women with a sex ratio male:female of 3:1. The results of laboratory blood tests were normal in almost all the patients included in the study, except ESR, fibrinogen, alkaline phosphatase, gamma glutamyl transferase, glutamic oxaloacetate transferase (GOT), glutamic pyruvate transaminase (GPT), total cholesterol in 5 patients who showed slightly increased values, without diagnostic value for other conditions that could have triggered loss of bone mass.

Following initial imaging evaluation, changes in bone tissue from the affected hip, in some cases to the contralateral, such as bone loss, increased bone transplanted, and loss of trabecular structure were noted. In the final evaluation, both on X-rays and on MRI images, these aspects improved in several patients from the first group. In patients in whom we noticed an improvement in bone structure, we noticed that the trabecular bone matrix began to recover, gaining more or less regular appearance with the persistence of some of the initial deformities, the

articular space was preserved or subjected to minimal changes.

Imaging investigations are the basis for the diagnosis and subsequent assessment of patients with this condition. Radiographic, aseptic osteonecrosis have a common element - the emergence of a well-defined condensation zone, or isolated through a peripheral area of reduced intensity. MRI is the non-invasive imaging technique with the highest degree of specificity and sensitivity used in the diagnosis of femoral head aseptic necrosis [21].

Being more quantifiable, we compared the distributions of the two groups according to the T DXA score (Figure 1), and we found that in group I there was a statistically significant improvement (p Chi square = $0.026 < 0.05$), while, for group II, the observed differences were not significant (p Chi square = $0.870 > 0.05$).

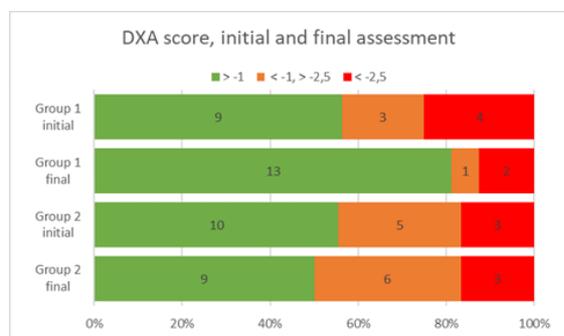


Figure 1.
DXA test, T score values

The DXA test is considered the gold standard in identifying qualitative and quantitative changes in bone tissue, especially in patients experiencing rapid bone loss, being very useful in selecting patients with pharmacological treatment as well as monitoring the effectiveness of anti-resorptive therapy.

Femoral head aseptic osteonecrosis affects especially young adults between the 3rd and 5th decades of life. [8, 12, 14, 24] It is considered that the average age of patients diagnosed with this condition at the time of the first hip arthroplasty is 38 years [8]. It affects 4 times more men than women [14, 24].

The purpose of the treatment in osteonecrosis of the femoral head, based on the evolutionary stage, is to stop the lesion evolution, to prevent femoral head collapse and to prevent the occurrence of arthrosis changes [14]. There is no general consensus regarding the preclinical treatment of femoral aseptic necrosis [16], but patients, regardless of their aetiology, should be encouraged, even at an early stage, to stop drinking and smoking. Pharmacological treatment in the incipient stages is achieved by the use of cholesterol-lowering drugs, anticoagulants, vasodilators and bisphosphonates [9, 17, 25, 26]. In the last decade, many studies have investigated the application of

Bps in the treatment of AVN [1-4, 6, 7, 12, 15, 18, 22, 23, 28]. Alendronic acid seems to be quite effective in preventing early collapse of the femoral head in patients diagnosed early in the disease [3], it has a high affinity for bone mineral and is taken up during osteoclast resorption.

We compared our results with those obtained in similar studies that target patients diagnosed with aseptic osteonecrosis of different aetiologies, stage II and III classified by X-ray and IRM images, according to Ficat and Arlet classification.

In a study conducted by Agarwala *et al.* in 2011, in which patients diagnosed in stage III AVN received alendronate treatment - 70 mg weekly plus calcium and vitamin D, for 3 years, it was demonstrated that alendronate would delay progression of AVN and avoid early indication of surgery in mid-term follow-up [18]. Other studies by Nishii *et al.* two groups of patients were compared - in the first were included patients who received alendronate 10 mg *per day* without any walking assistance *versus* the second group of patients in which patients did not receive alendronate or walking assistance either. They observed that the patients who had received alendronate had less pain and a lower frequency of femoral head collapse when compared to the control group [4].

VAS scores (Figure 2), were similar at the initial evaluation for all the patients included in the study regardless of the group they were in ($p = 0.386$), which allowed us to compare the effect of the two treatments. While both groups showed an improvement in VAS values, the decrease for the first group was greater than the second one ($p = 0.000846$ *versus* $p = 0.000728$), which is also emphasized by the decrease of p values when comparing the VAS scores at the end of the trial ($p = 0.110 > 0.005$ - non-significant difference).

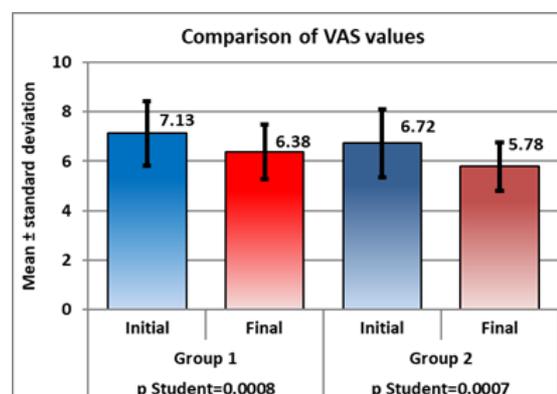


Figure 2.
Comparison of VAS values

As for the Harris Hip Score values, there was no significant difference between the two groups at the initial evaluation ($p = 0.189$), which allows us to

compare the effect of the two treatments. While both groups showed an improvement in the Harris hip score, the incidence for the first group was higher than the second one ($p = 0.000005$ versus $p = 0.042$).

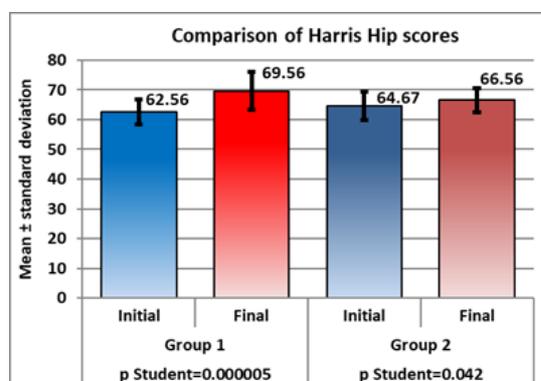


Figure 3.

Comparison of Harris Hip score values

When comparing the VAS values with the Harris hip score, we can conclude that the functional benefits and perceived pain relief were greater for the first group. Chen *et al.* published a study on the clinical efficacy of alendronate treatment of early-stage adult non-traumatic avascular necrosis of femoral head conducted in 2011 in which patients who received 70 mg of alendronate weekly for 3 months showed improved Harris Hip Score and VAS score. They also concluded that alendronate is effective in the treatment of early adult non-traumatic AVN [2]. Another clinical study conducted by Lai *et al.* showed a better Harris Hip Score and VAS score in patients who received alendronate 10 mg *per day* for a period of 2 years. Also, alendronate seemed to prevent the early collapse of the femoral head in the hips [1].

Conclusions

We consider that the treatment with alendronate in patients diagnosed with aseptic osteonecrosis of the femoral head, regardless of age and aetiology, may play an important role in slowing down bone destruction in the affected area and appears to prevent early femoral head collapse in patients diagnosed in the incipient stages of this condition. The treatment with alendronate increases the functionality and reduces the perceived pain of the patients.

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