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PROSPECTIVE STUDY OF USE OF ORAL IBANDRONIC ACID IN AVASCULAR NECROSIS OF FEMORAL HEAD

Orthopaedics

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ABSTRACT

Background: Femoral head avascular necrosis is a severe and crippling condition. Under some pathological situations, such as trauma, steroid consumption, and haemostatic diseases, bone behaves as a closed compartment, and intra osseous bone marrow pressure rises. This increased pressure is communicated to the bone's small venules and capillaries, resulting in ischemia (a reduction in blood flow to the bone). Joint-preserving treatment options have been mainly surgical, with inconsistent results. It has been demonstrated that the use of bisphosphonate medications reduces the prevalence of vertebral compression fractures and may delay the collapse of femoral head avascular necrosis. In patients with nontraumatic avascular necrosis of the femoral head, the aim of this study was to examine the effectiveness of Ibandronate in preventing early collapse of the femoral head in a short term follow up. **Material & Methods:** This is a prospective study of 30 patients with non traumatic avascular necrosis of femoral head (upto Ficat stage –III) meeting the inclusion criteria , treated with oral Ibandronic Acid 150mg/month + oral calcium 500mg -1000mg/day+ Vit-D supplement of 400-800 IU of Vit-D3. For control of pain, analgesics and NSAIDS were given as needed. . Disease progression was evaluated by radiography and magnetic resonance imaging (MRI). The Harris Hip Score was used to rate hip function and quality of life, respectively. **Results:** Average HARRIS HIP SCORE before treatment was 66.7833 (SD- 7.88049), whereas the Average HARRIS HIP SCORE after 12 months treatment = 88.21 (SD = 9.59), p value was <0.01, whereas the Average area of necrosis of femoral head measured by MRI before treatment was 37.5163 % (SD- 9.05374) ,whereas the Average area of necrosis of femoral head measured by MRI after 12 months treatment =38.07 % (SD = 10.23157), p value was 0.113, %. Out of total 30 hip included in study, 2 hips (both were in FICAT AND ARLET STAGE –III before initiation of treatment) progressed radiologically to higher stage. Overall radiological progression rate was 6.66%. **Conclusion:** All clinical and radiological data showed a trend of immediate and significant response to oral ibandronic acid therapy, as well as maintenance of enhanced clinical functioning and radiological result, in a short-term research. Radiographically, the illness advanced but not significantly. These data indicate that Ibandronate is not a cure for AVN, but rather a treatment that delays the disease's progression.

KEYWORDS

Ibandronate , Avascular necrosis

Introduction

A devastating multifactorial illness, osteonecrosis or avascular osteonecrosis (AVN) of the femoral head affects 20 000 people annually in the US [1,2]. Reduced local blood supply and bone loss are two characteristics of AVN, a clinical disorder that progresses but whose pathogenesis is not fully understood [3].Osteoclast-medicated resorption and delayed new bone production create an imbalance during bone regeneration that leads to mechanically weak bone that collapses under weight [4]. The majority of patients need a standard total hip arthroplasty (THA) following collapse because of the severe pain and loss of hip function [5,6]. When possible, efforts should be made to save the femoral head prior to collapse with the use of less invasive therapeutic modalities because a hip replacement cannot be expected to last a patient's lifetime given their young age [7-9] . There is currently no pharmacologic treatment that delays AVN progression and prevents bone collapse that is universally accepted. Unlike other medications, bisphosphonates (Bps) are strong anti-reabsorptive medicines that work by inhibiting the action of mature osteoclasts in the bone . This, in theory, normalises the uncoupled bone remodelling that causes femoral head collapse [10]. It lowers edema and the rate of remodelling, as well as the rate at which bone collapse progresses. Many studies have looked into the use of Bisphosphonates in the treatment of AVASCULAR NECROSIS; however, there are significant differences in Bisphosphonate genre and unclear indication in different stages of AVASCULAR NECROSIS[11,12]. Core decompression has a wide variation in outcomes, even in the short term. The success rates of vascularized fibular grafts from different centres have also varied, ranging from 60% to 90% during short follow-up (less than 3 years. As a result, the outcomes of surgery for early AVN with the goal of stopping or reducing the progression of bone and joint degeneration are mixed. There's also the associated surgical morbidity to consider the unclear indication in different stages of AVASCULAR NECROSIS. As a result, alternate surgical and non-surgical treatments must be investigated. Agarwala et al [13]were the first to demonstrate the efficacy of Alendronate, a Bisphosphonate, in the treatment of Avascular necrosis of the femoral head, demonstrating that it not only improved symptoms but also slowed disease development and lowered the rate of femoral head collapse.

MATERIALS AND METHODS

This study was done as a prospective interventional study in the Department of Orthopaedics in J.A.H Group of Hospitals, Gwalior (M. P.) Inclusion Criteria included Patients with non traumatic AVASCULAR NECROSIS of femoral head (Ficat and Arlet Stage I,II,III) whether unilateral or bilateral with complete clinical records who were ready to adhere to long term oral therapy and excluded cases were Patients with traumatic AVASCULAR NECROSIS of femoral head and with degenerative arthritis (Ficat and Arlet stage IV).Patients with peptic ulceration and hepato renal damage were also excluded.

A regimen of oral Ibandronic Acid 150mg/month + oral calcium 500mg -1000mg/day+ Vit-D supplement of 400-800 IU of Vit-D3. For control of pain, analgesics and NSAIDS were given as needed. Data collection procedure included detailed study variable like, standing time (in minutes), pain and range of motion at hip.

A through history was obtained including demographic data, history of trauma, history of alcohol intake and steroid intake etc. In case of steroid intake, the reason for this was also be recorded. The functional outcomes and clinical results of the patients was evaluated & graded using Harris Hip Score. The radiological outcomes and results of the patients was evaluated & graded using X-RAYS and MRI.

Ficat Stage I represents the earliest clinical manifestation of the

syndrome. The patient complains of pain in the groin, which is worse at night. There is restricted abduction and internal rotation at the hip joint. Radiologically, there is subtle loss of clarity, with poor definition or blurring of the trabecular pattern and patchy osteoporosis. In stage II, there are radiographic changes in the trabecular pattern. Sclerosis may be diffuse, in localized areas, or in a linear arc which is concave superiorly. Decalcification is either generalized or in the form of small cysts. The mixed form includes both sclerosis and cysts. Stage III is characterized by the appearance of sequestrum on the radiographs. A crescentic line appears due to subchondral fracture, representing the transitional form between stages II and III. Joint space is preserved or increased. In stage IV there is progressive loss of articular cartilage and the development of acetabular osteophytes. The radiographic picture is that of osteoarthritis superimposed on a deformed femoral head.

Follow-up

Follow up of the cases was done in a predefined time duration , i.e the 1st follow up was done after 1 month from initiation of treatment, whereas the subsequent follow up was done after at 3rd month, 5th month, 7th month, 9th month and 12th month after initiation of treatment. At each follow up visit, assessment were done on the basis of Average analgesic requirement daily during course of study ,Harris Hip Score ,Standing time, X-rays , MRI of hip joints.

At each visit X-rays of PELVIS WITH BOTH HIP in antero – posterior view with both the lower limbs in 15 degree of internal rotation were taken by standard technologist and techniques. All radiological classification were performed by a single reader. The FICAT & ARLET classification was used for radiological classification & based on X-rays and MRI. At each visit MRI of PELVIS WITH BOTH HIP, were taken in T1, T2, STIR, NON FAT SAT T1, NON FAT SAT PD SEQUENCES, by standard technologist and techniques.

The percentage of femoral head involvement by the necrotic lesions was measured on magnetic resonance images (MRI) using technique described by Kim et al.[14], We measured the largest medio-lateral diameter of the femoral head (R) on midcoronal section and the longest medio-lateral length of the necrotic lesion (A) on coronal magnetic resonance images and the largest antero-posterior diameter of the femoral head (S) on mid saggital section and the longest antero-posterior length of the necrotic lesion (B) on sagittal magnetic resonance images. . The two-dimensional extent of a necrotic lesion was determined with the equation: % area = [(A x B) / (R x S)] X 100 (Figure 1).

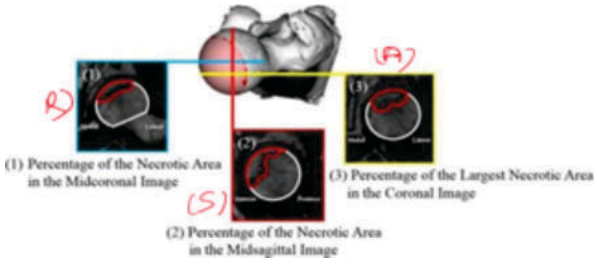

Figure 1: Illustrations Of Parameter Used For Measurement Of Necrotic Area In Femoral Head

RESULT

Data for 24 patients (30 hips) about avascular necrosis of the hip were analysed. There were 60% male patients. The age range was 17–48 yr (Table 1). The follow up period was 1 year for all the hips. The cause of AVN was steroids in 8 patients, Alcohol (6), idiopathic (12), postpartum (2) and post ALL chemotherapy (2). At the end of 1 year, there was significant improvement in all clinical parameters, (standing time, pain and disability (P<0.01).except for increase in area of necrosis of femoral head which was statistically insignificant (p value =0.113).

Table 1: Distribution Of Cases According To Age

Age group (years)	Number	Percentage
15-20	6	20
20-30	12	40
30-40	8	26.66
40-50	4	13.33

Average analgesic intake before treatment was 1.5367 tab/ day (SD= 0.43030), whereas the Average analgesic intake after 12 months treatment = 0.0567 tab/ day.(SD -0.20117) p value was <0.01. Average HARRIS HIP SCORE before treatment was 66.7833 (SD- 7.88049), whereas the Average HARRIS HIP SCORE after 12 months treatment =88.21 (SD = 9.59), p value was <0.01(Table-2). Average standing time before treatment was 17.933 mins (SD- 3.95608) ,whereas the Average standing time after 12 months treatment=37.7667 mins (SD = 5.12387) , p value was <0.01. Average area of necrosis of femoral head measured by MRI before treatment was 37.5163 % (SD- 9.05374) ,whereas the Average area of necrosis of femoral head measured by MRI after 12 months treatment =38.07 % (SD = 10.23157), p value was 0.113, (Table 3) which signifies that the increase in area of necrosis of femoral head measured by MRI , after oral ibandronic acid intake was statistically insignificant.

Table 2: Comparison Of Pre-treatment And Post Treatment Harris Hip Score

S.No.	Duration	Average Harris hip score	P value
1.	Before initiation of treatment	66.7833	
2.	After 1 month	68.37	<0.01
3.	After 3 month	74.083	<0.01
4.	After 5 months	79.2533	<0.01
5.	After 7 months	83.3133	<0.01
6.	After 9 months	86.1933	<0.01
7.	After 12 months	88.2100	<0.01

Table 3: Comparison Of Pre-treatment And Post Treatment Percentage Of Area Of Necrosis Of Femoral Head Measured By Mri

S. No.	Duration	Average percentage of area	P value
1.	Before initiation of treatment	37.5163	
2.	After 1 month	37.5543	0.187
3.	After 3 month	37.6780	0.197
4.	After 5 months	37.8157	0.144
5.	After 7 months	37.9160	0.123
6.	After 9 months	37.9713	0.126
7.	After 12 months	38.0727	0.113

Percentage of hip progressed radiologicaly from FICAT AND ARLET STAGE –I was zero, Percentage of hip progressed radiologicaly from FICAT AND ARLET STAGE –II was also zero, Percentage of hip progressed radiologicaly from FICAT AND ARLET STAGE –III was 18.18 %. (Figure 2 & 3).

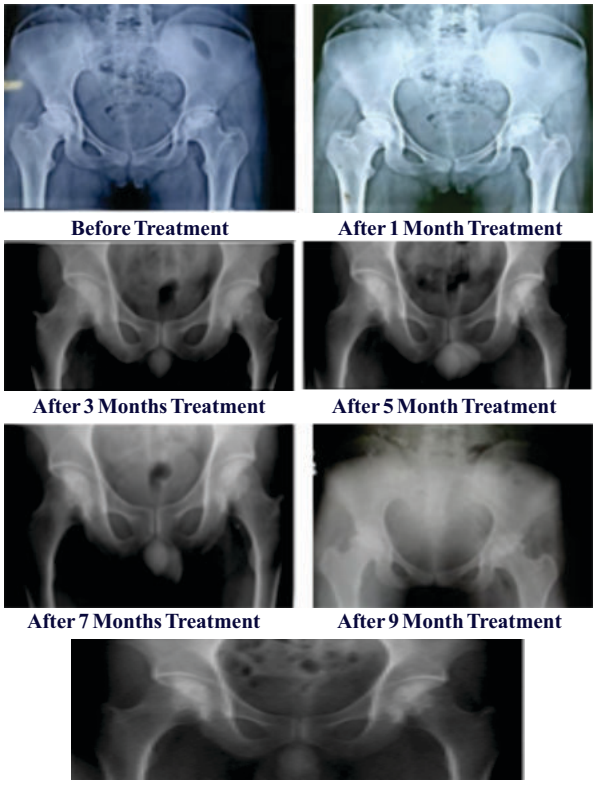

Figure 2: Ficat Stage –ii Before And After Treatment

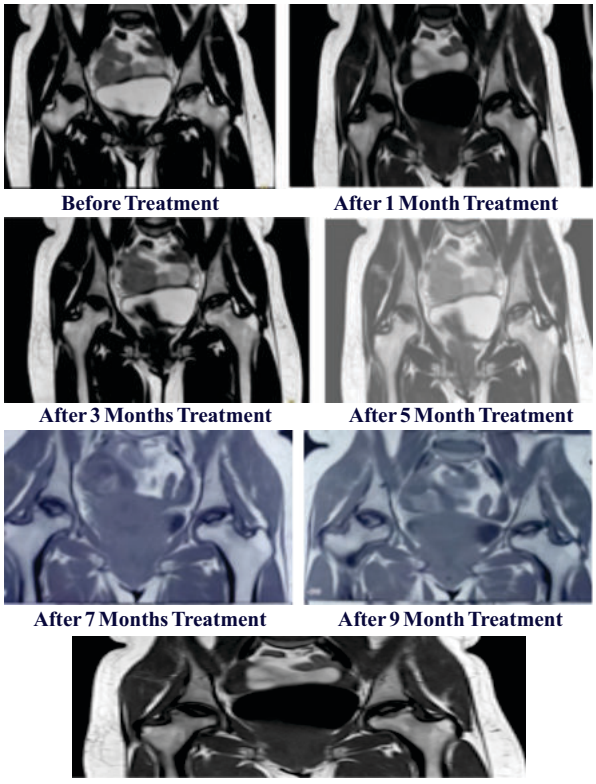

Figure 3: Mri Showing Ficat Stage –ii Before And After Treatment

Out of total 30 hip included in study, 2 hips (both were in FICAT AND ARLET STAGE –III before initiation of treatment) progressed radiologically to higher stage. Overall progression rate was 6.66% (Table 4).

Table 4: Radiological Progression After Treatment

Ficat and Arlet stage on onset	No of hips before initiation of treatment	No of hips after treatment	No. of hips progressed during treatment	Percentage of hips progressed during treatment
I	1	1	0	0
II	18	18	0	0
III	11	9	2	18.18 %
IV	0	2		

DISCUSSION

Avascular necrosis of Femoral head is a devastating condition. Despite advancements in arthroplasty, there are still many issues to be resolved because younger individuals make up the majority of the disease's patients and higher levels of activity are linked to increased rates of failure, loosening, and osteolysis [15,16,17] . A number of surgical techniques, including core decompression, bone grafting, and osteotomy, have been explored with varying degrees of success to stop progressive bone collapse and joint deterioration.

Even in the short term, results of core decompression vary greatly: Ficat [18] reported 89.5% success for the pre-collapse stage while Camp and Colwell reported a 40% success rate [19].

The outcomes of vascularized fibular grafts from various centres have likewise varied, with success rates at short follow-up (less than 3 years) ranging from 60 to 90% [20]. In order to stop or delay the progression of bone and joint deterioration, surgery for early AVN has, at best, mixed success. The accompanying surgical morbidity is another factor.

Agarwala et al [13] in their study found that, before initiation of treatment , Pain which was measured on VAS (visual analogue scale) had a mean value of 6.9 (range 3-10) and after 24 weeks of initiation treatment mean value on VAS was 3 (range 1-7) Agarwala et al [21] stated that the mean VAS score for pain before initiation of treatment was 6.0 (SD- 2.3) and after 1 year of follow up , mean VAS score for pain was 2.2 (SD –1.8), whereas Nishi et al [12] in their comparative study , found that the grade of hip pain in control was unchanged in 6 hips , worsen in seven hips , whereas in group which received alendronate – grade of hip pain unchanged in 15 hips , improved in 4 hips and worsened in 1 hip. Agarwala et al [22] reported that the pain which was assessed by VAS score has average value of 8 before initiation of treatment , after 10 years of follow up was avg VAS score in ficat and arlet stage – I was 4.5 , ficat and arlet stage – II was 6, ficat and arlet stage – III was 4. While evaluating the short term and long term functional outcome analysis of oral bisphosphonates in Avascular necrosis of femoral head, it was observed that apart from RCT conducted by chen et al[23], all the studies provided with data of improvement in functional outcome after the treatment, whether it was decreased in VAS score for pain or decrease in average analgesic requirement during the follow up. Increase in standing time and improvement in HHS (Harris Hip Score), both provided with data of improvement in functional as well improvement in clinical outcome of the disease.

One of the major advantage of oral bisphosphonate therapy, is the excellent improvement in pain associated with the disease, even after 3 months of initiation of treatment. Decrease in pain may be attributed to decrease in bone marrow edema. This decrease in pain, has lead to improvement in day to day activities of life, and overall improvement in quality of life of these patients.

There are many experimental studies done with IBANDRONI C ACID in rats and piglet models . KIM et al [24] in their study concluded that ibandronic acid preserved the trabecular framework of femoral head and prevented femoral head deformity during early phase of repair during following ischemic necrosis of femoral head in piglet model. AYA –AYE et al[25] in their study concluded that local intraosseous administration is an effective route to deliver and distribute ibandronic acid in infacrted femoral head to preserve the femoral head structure .

Agarwala et al [13] in their study found that MRI remained stable in 15 out of 16 patient. Radiological progression after 24 weeks was seen in 1/16 =6.3% Cases. Same author in 2005 in their study recorded that, radiological progression was seen in 10 out of 71 hips (14 %) in 1 year , 12 out of 42 hips (28.5 %) , and 20 out of 37 hips (54 %) > 2 year of follow up. Lai et al [11] found no evidence of reduction or resolution of the necrotic area , on MRI or plain X- rays in any of the femoral head of patients receiving oral alendronate. Chen et al [23] in their Randomised control trail found that radiological progression was seen in 65.6 % hips (21 hips out of 32 hips) in patients of receiving alendronate, 60.6 % hips (26 hips out of 33 hips) in control group.

In short-term study, all clinical and radiological measurements demonstrated a trend of immediate and considerable response to oral ibandronic acid therapy, as well as maintenance of improved clinical functioning and radiological outcome. The disease progressed radiographically, although not considerably. These findings suggest that alendronate is not a cure for AVN; it simply slows the disease's progression. There are certain limitations to this study. After 1 year of follow up, we cant say that we have altered the natural history of disease, because literature states that the average time for collapse of femoral head in Avascular necrosis is 3-4 years. Larger no of patients would have increase the validity of our study results.

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