Hyperbaric Oxygen Therapy in Femoral Head Necrosis

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Abstract: We evaluated hyperbaric oxygen (HBO) therapy on a cohort of patients with femoral head necrosis (FHN). This double-blind, randomized, controlled, prospective study included 20 patients with unilateral FHN. All were Ficat stage II, treated with either compressed oxygen (HBO) or compressed air (HBA). Each patient received 30 treatments of HBO or HBA for 6 weeks. Range of motion, stabilometry, and pain were assessed at the beginning of the study and after 10, 20, and 30 treatments by a blinded physician. After the initial 6-week treatment, the blind was broken; and all HBA patients were offered HBO treatment. At this point, the study becomes observational. Pretreatment, 12-month. and 7 year-follow-up magnetic resonance images were obtained. Statistical comparisons were obtained with nonparametric Mann-Whitney *U* test. Significant pain improvement for HBO was demonstrated after 20 treatments. Range of motion improved significantly during HBO for all parameters between 20 and 30 treatments. All patients remain substantially pain-free 7 years later: none required hip arthroplasty. Substantial radiographic healing of the osteonecrosis was observed in 7 of 9 hips. Hyperbaric oxygen therapy appears to be a viable treatment modality in patients with Ficat II FHN. **Keywords:** hyperbaric oxygen therapy, femoral head necrosis, hip arthroplasty.

Femoral head necrosis (FHN) affects approximately 10 000 to 15 000 patients in the United States annually [1]. The incidence has increased, possibly because of an increase in the use of exogenous steroids, as well as increases in the incidence of trauma and alcohol abuse. Approximately 3% of hip pathology is attributed to FHN. Frequently, this starts between the fifth and sixth decade of life with a male to female prevalence of 3:1. The average age of affected patients is 47 years [2]. This syndrome predominantly affects whites as compared with African Americans with a ratio of 3:1 and is usually unilateral.

It is important to observe that there are 26 studies [3,4] where a declining clinical outcome after total hip arthroplasty in younger patients as compared with older patients has been reported. This apparent discrepancy is not totally understandable; perhaps a role is played by the larger physical activity of younger patients and the possibility of an expected increase of body weight. For these reasons, there is a stream of thinking among orthopedic surgeons that it would be helpful to delay or possibly not perform hip prosthesis especially in the younger population [5-7]. Among all therapies that may delay the requirement for hip arthroplasty, we believe hyperbaric oxygen therapy (HBOT) may show a beneficial effect without the invasiveness of surgery.

In this study, we are demonstrating an effective treatment modality that involves the use of HBOT to treat patients with FHN. In these patients, we describe an overall symptomatic alleviation after a multiple-year follow-up, without necessitating hip arthroplasty surgery.

Methods

This is a double-blind, randomized, controlled, prospective study involving 20 patients (12 men and 8 women) older than 18 years with idiopathic, unilateral FHN. Informed consent was obtained from all patients before the start of the study. Every patient was subjected to an x-ray of the hip in 2 projections (anterior and lateral), after diagnosis was confirmed by magnetic resonance imaging (MRI), to stage their pathology according to the Ficat classification. Only patients without

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any other underlying pathology, those receiving no pharmacologic treatment, and those diagnosed as Ficat stage II were included in this study. Patients with a history of alcohol abuse, trauma to the involved hip, or steroid use were excluded. At the initial presentation, each patient was randomly assigned to either arm of the study. The physician overseeing their daily treatments was aware of their random assignments; however, the physician evaluating their progress after 10, 20, and 30 treatments was blinded to their assignments.

Patients were prospectively randomized to either the HBO or hyperbaric air (HBA) group. There were 10 patients in the HBO group (6 men and 4 women) and 10 patients (6 men and 4 women) in the HBA group; however, one female patient assigned to the HBA group dropped out after the first few treatments for personal reasons and was excluded from the study. Therefore, the study group was completed with 10 HBO and 9 HBA patients. Both groups were simultaneously treated.

Patients were exposed to HBO inside a multiplace hyperbaric chamber (Galeazzi, Bergamo, Italy) with either compressed oxygen or compressed air at 2.5 ATA for 82 minutes, comprising a period of 60 minutes when the patient was continuously exposed to 2.5 ATA without interruption. Each patient was provided with a well-sealed breathing mask from which he or she received either 100% oxygen (HBO) or 100% compressed air (HBA). Oxygen concentration in the mask was measured every 5 minutes to ensure adequacy of the gas supply and the ability of providing a tight seal around the face. The mask was applied at the beginning of the session and was kept in place throughout the 82-minute treatment session without removal.

All patients received 30 treatments of HBO or HBA from Monday through Friday for a period of 6 weeks. After completion of the first 6 weeks, the blind was broken; and all HBA patients were offered 6 weeks of HBO therapy (crossover), which they accepted. At this point, the study becomes an observational study. Furthermore, during the rest of this first year, all 19 patients continued additional HBO exposures as indicated by residual pain complaints. Overall, these patients received 90 HBO treatments in 12 months and underwent an MRI at the 12-month follow-up. After 7 years, a second follow-up was completed; however, 2 patients were lost to follow-up. Only 9 of these 17 patients had the original pretreatment MRI and 12-month follow-up MRI in their possession. All 9 patients underwent a 7-year follow-up MRI and telephone interview.

In both groups, hip flexion, extension, abduction, adduction, stabilometry, and intensity of pain were assessed at the beginning of the study (T_0), after 10 treatments (T_{10}), after 20 treatments (T_{20}), and after 30 treatments (T_{30}) by a team physician blinded to their treatment regimen. Range of motion measurements were made using a goniometer only on the involved hip and were not compared with the uninvolved side. Stabilometry was measured using the platform "BASYS 95-SANITAS ELETTRIC MILANO." In this measurement, the load exerted on each leg (in percentages) is measured independently while standing. This is a more objective and reproducible measurement for load distribution between the right and left leg [8]. We used this test to compare the weight distribution between the right and left side during the initial 30 treatments of both groups.

Table 1. Age Distribution of Patients Who Completed the Study

	n	Mean	Median	Range
HBO	10	49.0	47.5	24-78
HBA	9	48.8	50	38-63

The severity of pain in both groups was adequately assessed before the start of the study and after 10, 20, and 30 treatment sessions. Pain was assessed using the visual analogue score scale: a 0 to 10 scale was used, with 0 representing no pain and 10 indicating the most severe pain. There were no restrictions in weight bearing after completion of the first 12 months of treatment.

Statistical comparisons were executed using nonparametric Mann-Whitney U test to compare HBO vs HBA group because nearly all measured values were not normally distributed (normality was checked using Kolmogorov-Smirnov test). Statistical significance was accepted for P values $< .05$. In addition, α was adjusted for multiple comparisons using a Bonferroni adjustment. The new level of α was < 0.002, indicating that despite the small sample size, the probability of a type I error was reduced.

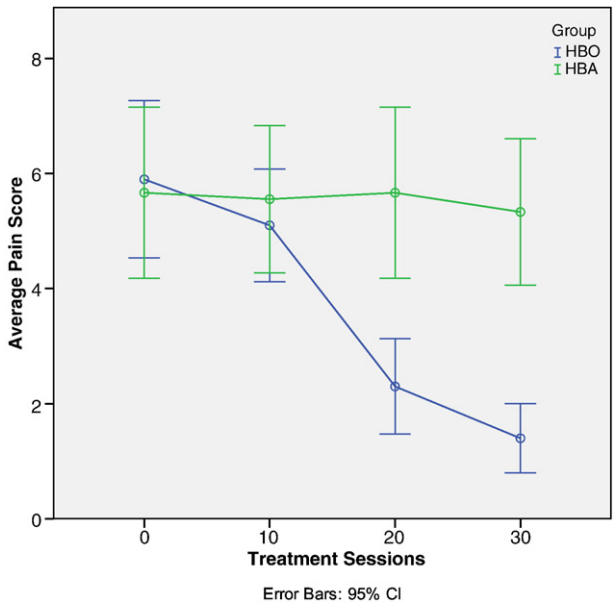

Fig. 1. The severity of pain scale in both groups.

Table 2. Median (and Range) Values for Spontaneous Mobility in Patients in the HBO and HBA Groups

Range of Motion	T_0	T_{10}	T_{20}	T_{30}
HBO group				
Flexion	55.5 (33.0-120.0)	60.5 (38.0-120.0)	64.0 (46.0-120.0)	112.0 (92.0-120.0)
Extension	2.5 (0-20.0)	7.5 (4.0-20.0)	12.5 (6.0-20.0) †	20.0 (15.0-20.0) †
Adduction	1.0 (0-10.0)	4.0 (2.0-10.0)	6.5 (5.0-10.0) †	10.0 (8.0-10.0) †
Abduction	5.0 (0-45.0)	11.5 (6.0-45.0)	18.5 (9.0-45.0) †	35.5 (26.0-45.0) †
HBA group				
Flexion	69.0 (49.0-120.0)	69.0 (48.0-120.0)	86.8 (48.0-120.0)	76.0 (50.0-120.0)
Extension	3.0 (0-6.0)	4.0 (3.0-6.0)	4.0 (0-6.0)	3.0 (0-5.0)
Adduction	0 (0-3.0)	2.0 (0-2.0)	2.0 (1.0-2.0)	2.0 (0-3.0)
Abduction	4.0 (0-8.0)	4.0 (0-10.0)	6.0 (0-10.0)	7.0 (0-10.0)

* Statistical significance vs HBA (P value < .05).
† Statistical significance vs HBA (P value < .001).

Results

Both groups of patients were similar in their demographics; Table 1 shows the mean age distribution, median, and range of both groups. The treatments were well tolerated by both groups. There were no cerebral complications, otalgia, or other complications from the effects of compression or oxygen exposure.

Fig. 1 demonstrates the severity of pain on a 0 to 10 scale in both groups. Although no statistical significance between both groups was noted at the beginning and following 10 sessions (P = .803), the HBO group showed marked improvement and significance after 20 treatment sessions (P = .002 vs HBA) and after 30 sessions (P < .001).

Table 2 represents the median values (in degrees) for the range of motion in flexion, extension, adduction, and abduction for both groups. Although the results for flexion showed marked improvement (nearly doubling after 30 treatments), the statistical analysis failed to show any statistical significance at 10 (P = .335), 20 (P = .356), and 30 (P = .195) treatment sessions. Statistical significance was achieved during extension, adduction, and abduction starting only after 10 sessions (P < .001) and remained significant at 20 (P < .001) and 30 treatment sessions (P < .001) when comparing the HBO and HBA groups.

Table 3 represents stabilometry measurement in both groups before and after 10, 20, and 30 treatment sessions. In the following table, the values for stabilometry correlate to the median value difference between the load on the unaffected limb and the load on the affected limb. Regarding stabilometry, although there was a trend toward HBO having lower differences especially toward the end of the study, the trend failed to reach statistical significance at 10, 20, and 30 sessions (P = .743, .435, and .064, respectively).

At the 7-year follow-up, all 17 patients reported minimal pain with no decrease in activities of daily living; none had received hip arthroplasty surgery or developed contralateral disease. The 9 patients with repeated MRI showed continuing improvement in radiographic appearance, although most of the radiographic improvement was demonstrated between the pretreatment MRI and the 12-month MRI. Seven of the 9 patients, however, demonstrated continuing radiographic improvement between 12 month and 7 years (Fig. 2A-C). Although the other 2 patients had demonstrable bony defect at 7 years, they exhibited minimal symptoms, if any, related to the hip.

Discussion

Femoral head necrosis has no distinguishing clinical features; radiographic findings may appear after a delay of several months to years following the onset of symptoms. Pain is usually the initial presentation and is either sharp, dull aching, or intermittent. Pain may be focal over the hip or radiating to the buttocks, gonads, or knee and is usually precipitated by standing or walking and relieved by rest. The range of motion is usually diminished especially in flexion, abduction, and internal rotation and especially after collapse of the femoral head. A click may be heard when the patient rises from the sitting position or by external rotation of an abducted hip. Patients usually walk with a limp. Trendelenburg sign is usually positive.

Possible causes for FHN include the idiopathic form, alcoholism [9], thromboembolism in a blood vessel feeding the femoral head, or fat embolism [10]. Other

Table 3. Median (and Range) Values for Stabilometry in the HBO and HBA Groups

Stabilometry	T_0	T_{10}	T_{20}	T_{30}
HBO group	25.0 (10.0-38.0)	21.0 (10.0-32.0)	18.0 (10.0-32.0)	12.0 (6.0-22.0)
HBA group	26.0 (10.0-36.0)	22.0 (10.0-36.0)	20.0 (10.0-38.0)	18.0 (10.0-42.0)

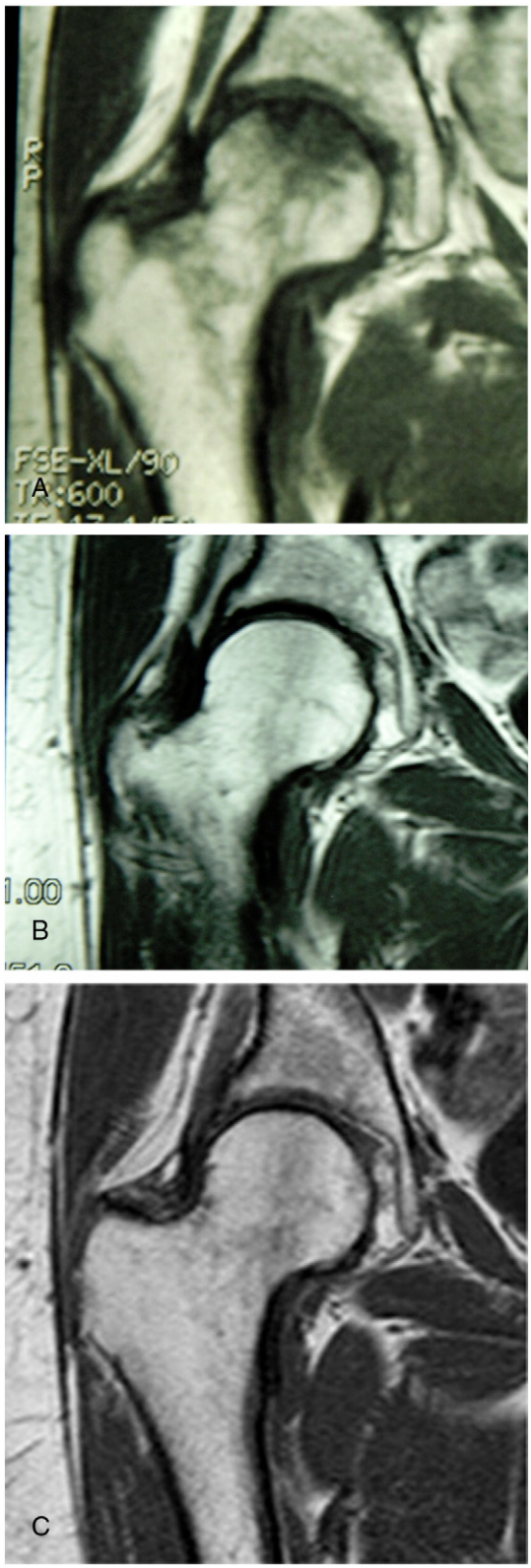

Fig. 2. MRI images of patient treated with HBO. (A) Pretreatment MRI showing bone defect. (B) 12- month MRI showing near complete resolution of bone defect. (C) 7-year follow-up MRI showing no change in bone defect.

causes are gas bubble dysbaric osteonecrosis; [11] anemia, Gaucher disease [12], increased bone marrow pressure [13], impairment of arterial supply to the femoral head [14], obstruction of venous drainage [15], vasculitis [16], intramedullary hemorrhage [17], and hypofibrinogenemia [18].

Bones vulnerable to ischemic necrosis include the femoral head, femoral condyles, head of the humerus, and the proximal parts of the talus and scaphoid bone. These sites lay at the most remote part of the bone's vasculature and are enclosed by cartilage, restricting their access to local blood vessels, and therefore are subsequently liable for ischemic necrosis.

Interruption of blood supply to the affected bone causes osteocytes to begin losing their viability within 12 hours. Later in the course of the disease, bone marrow edema is recognized on MRI. Because remodeling is a slower process, radiographic changes are not evident until 2 months after injury [19]. In the adult, the involved segment usually never fully revascularizes; and the earliest radiographic sign is a separation zone between the bony layer subchondrally and the underlying necrotic bone. This represents the initial collapse of the femoral head. In 90% of cases, this results in total head necrosis because of bone resorption being predominant over neoformation of bone. These areas of resorbed bone are substituted by osteosclerosis and cyst formations; however, it can result in spontaneous resolution of the disease [20].

Many treatment options have been used to alter the natural history of FHN. These include surgical techniques such as core decompression, osteotomy, and bone grafting as well as nonsurgical procedures. These consist of electrical stimulation, pharmacologic therapy to target any underlying coagulopathy, and HBO.

Hyperbaric oxygen therapy acts by targeting the underlying pathophysiology of FHN. During the early stages of the disease, HBO facilitates oxygenation of hypoxic tissue and reduces edema through creating a high concentration of dissolved oxygen and inducing vasoconstriction. This explains the early pain relief noticed in patients treated with this modality. By saturating the extracellular fluid with diffused oxygen, HBO treatment will promote better oxygenation of ischemic bone cells, irrespective of the circulating hemoglobin and without the need for the energy required for dissociation of oxygen from hemoglobin. Later effects of HBO are bone resorption, revascularization, and osteogenesis.

There are at least 4 different methods for staging of FHN including Ficat and Arlet [21], Marcus [22], Steinberg [6], and one proposed by the Association Research Circulation Osseous [23] and the Japanese investigation committee [9]. We will rely on the first staging system in the results of our study. Because outcome differs according to the stage of the disease, staging is an important step in the management of

these patients. In our double-blind, randomized, controlled, prospective study, which included 19 patients with FHN in stage II Ficat classification, we were able to demonstrate significant improvement in the HBO subgroup as compared with the HBA subgroup. As a result of these significant findings, the blind was broken; and patients in the HBA group were crossed over to the HBO group, showing significant improvement. Both groups were subsequently followed for 7 years posttherapy without the need for femoral head arthroplasty.

The theoretical concern about enhanced osteoclastic activity caused by HBOT and, consequently, femoral head collapse has been previously posed. Baxie et al [19] in their HBO series have reported bone collapse in some of their patients; whether this represents increased vulnerability to femoral head collapse from osteoclastic stimulation or simply represents treatment failure cannot be confirmed from the available data. Although most of the published case reports indicate that the outcome of patients with FHN in stages III or IV is poor, this is possibly due to the collapse of the femoral head and advanced hip joint arthrosis [24-26]. We are proposing that this hyperbaric treatment is well suited for FHN patients in stage II Ficat classification.

Based on this analysis, HBO improves outcomes of patients with FHN; and within the 8 years of observation, it is comparable to outcomes from orthopedic interventions. As stated by Strauss et al [27], 83 of 86 patients treated with HBO had satisfactory short-term results, while 83 of 103 patients had satisfactory long-term results. Clearly, this determines that HBO has better outcomes when added to therapy; but the number of combination therapy cases reported is still too small in the literature to draw any meaningful conclusion about the effect of HBO when used as an adjunct to other orthopedic interventions.

One limitation of our study is the small sample size. We only enrolled 17 patients, with 9 patients having their initial MRI at the 7-year follow-up. However, after adjusting the α for multiple comparisons in a small population, our results seem to indicate that the statistical difference between groups remains significant. Furthermore, there have been no other studies reported in the literature with this length of follow-up after HBO treatment of FHN. In addition, after the initial 6 weeks of treatment, the blind was broken; and all control (HBA) patients were offered HBO therapy. This eliminated the control group from our study, making all subsequent evaluations based on an observational study. We report statistically significant differences between the HBO and HBA groups after the initial 6 weeks of treatment; however, the lack of a control groups prohibits us from comparing this therapeutic treatment to the natural course of the disease. Finally, we were unable to do a blinded review of the MRI images at the 7-year follow-up because all patients were ultimately treated with HBO. Because of the inconsistency of how the MRIs were presented at 7-year follow-up, an accurate analysis of the femoral head lesions was not possible.

In conclusion, we recommend that HBO should be considered the primary treatment modality in any patients diagnosed with FHN and stage II Ficat classification and especially in young patients where the goal is to delay total hip arthroplasty as long as possible. Hyperbaric oxygen therapy should also be considered in patients with FHN due to underlying vascular disease, diabetes mellitus, or coagulopathies. In certain circumstances such as Caisson dysbaric osteonecrosis, HBO should be initiated at the onset of symptoms. This study demonstrates in a small series of patients a positive therapeutic result obtained with HBO therapy at midterm follow-up. This therapy has a potential role in the management of avascular necrosis. Further studies to define the frequency and duration of treatment, as well as cost-effectiveness analyses, are indicated.

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