European, multi-centre, randomised, stratified, parallel-group, open-label, phase III, MRI and Radiograph-based study to evaluate the efficacy and safety of Hyperbaric Oxygen therapy in the treatment of patients with Femoral Head Necrosis.

December 2003

Study Personnel

- **Study Chairmen**

Participating Centres

To date, a number of Clinical Centres in Austria, Belgium, Greece, Israel, Slovenia, Switzerland and Italy have agreed to participate. A number of European clinical centres will be invited to join the study.

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- **Statistical Centre**

To be defined

List of Abbreviations

AT	As-Treated
CMC	Co-coordinating and Methods Centre
CRF	Case Report Form
ECHM	European Committee for Hyperbaric Medicine
FHN	Femoral Head Necrosis
HBO	Hyperbaric Oxygen
ITT	Intention-to-Treat
MRI	Magnetic Resonance Imaging
VAS	Visual Analogue Scale

Introduction

Femoral head necrosis (FHN) is a condition in which the blood supply to the femoral head is compromised. This leads to cell death in the marrow and the bone, and interferes with the normal activity of osteoblasts and osteoclasts, and loss of the structural integrity of the femoral head. The progression of the disease implies pain, swelling in the confined space of the femoral head, loss of articular congruity, arthritic changes, and collapse of the femoral head.

The treatment of the FHN is an unresolved orthopaedic problem and multiple approaches are used for its management (Strauss and Dvorak). They include surgical procedures as core decompression, bone grafting, and osteotomy, and non-surgical procedures such as electrical stimulation, magnetic fields, high energy shock wave, pharmacological treatment, and hyperbaric oxygen therapy (HBO).

HBO therapy makes oxygen available to marrow cells and facilitates the bone remodelling processes through oedema reduction and angioneogenesis stimulation.

Currently the number of reported studies of FHN patients treated with HBO remains limited. Despite 15 reports on the efficacy of HBO in FHN, a prospective randomised study is mandatory in order to establish or negate HBO therapy in the treatment of FHN.

As primary endpoint, the current study aims to assessing the effect of HBO on FHN by means of clinical and MRI investigations at short term follow-up. As secondary endpoint long-term response to HBO will be revaluated in the group of patients with partial response at short-term follow-up.

1. Trial Objectives

To evaluate the efficacy and safety of long-term HBO therapy used in addition to conventional non-surgical therapy for patients with FHN.

1.1. Primary endpoint

Patients will be classified as success or failure 5 months after inclusion in each group:

Complete response:

Both of the followings:

- Normal MRI
- Pain free

Partial response:

Any of the followings

- Amelioration in Visual Analogue Scale (VAS)
- No progress to femoral head collapse (from stage 1 or 2 to stage 3 or above)
- Reduction in content of marrow oedema on MRI
- Reduction in joint fluid volume on MRI
- No appearance of femoral head collapse on MRI

Failure:

Any of the followings:

- Worsening or no changes in VAScale
- Radiological progress to femoral head collapse (from stage 1 or 2 to stage 3 or above)
- No change or increase in content of marrow oedema on MRI
- No change or increase in joint fluid volume on MRI
- Appearance of femoral head collapse on MRI
- Any kind of non-conservative treatment.

- **Secondary endpoints**

- Long-term response to HBO will be revaluated in the group of patients with partial response at short-term follow-up.
- Regression at 12-month clinical evaluation of the pain measured through objective evaluation (Harris Hip Score modified) and a visual analogue scale (VAS)
- Regression at 12-month clinical evaluation of analgesic treatment
- Time to surgical treatment if necessary
- Inter and intra observer reproducibility of analysis of the radiographs and MRI images will be assessed.

1.3. Treatment Groups

Eligible patients will be randomised to form the following treatment groups:

- Patients treated with conventional non-surgical therapy and HBO therapy (experimental group);
- Patients treated with conventional non-surgical therapy (control group).

1.4. Primary objective

Primary objective of the study is to compare the rate of success between the two treatment groups within the 5-month study period.

2. Study Design

This will be a randomised, two-arm, open-label, multi-centre, active-control, parallel groups study, Phase III. Patients will be randomised to receive HBO or no HBO for the scheduled number of treatments.

2.1 Study Population

Patients potentially eligible for the study are consecutive in- or outpatients of either sex, 18 to 55 years of age, referring to one of the participating Clinical Centres and diagnosed with FHN. The diagnosis can be referred to as avascular necrosis, ischemic necrosis, aseptic necrosis, or osteonecrosis of the femoral head. Patients diagnosed with FHN will be graded according to the Steinberg Classification (see Appendix 1): only stage 1 and 2 are eligible. Admission to the trial is by MRI and conventional Radiograph to be monitored by the MRI local responsible.

2.1.1 Inclusion criteria

Patients must meet all of the following criteria to be eligible for participation in the study:

- Age between 18 and 55 years;
- Presence of FHN Stage 1 or 2 (Steinberg Classification);
- Written and informed consent to participate in the study;
- Analysis of lesions and quality of imaging on the basis of MRI and Conventional Radiograph

2.1.2 Exclusion criteria

- Age range beyond 18-55 years;
- Presence of focal or diffuse marrow changes (except AVN) at distance from the involved hip.
- Presence of contraindications to MR imaging (pace-maker, cardiac valves, intracerebral or intraocular metallic foreign body, external metallic fixation device, claustrophobia);
- Pregnancy;

- Presence of any condition or disorder of the included hip that could interfere with the study conduct, and specifically: any sign of degenerative hip disease including joint space narrowing and osteophytosis on plain films; abnormal cartilage and/or abnormal subchondral marrow in head or acetabulum on MR images; presence of bone (plain films) or marrow (MR) lesions that are not focused in the subchondral area of the femoral heads; prominent synovial changes those are not consistent with reactive changes to the femoral head disorder;
- Situations where HBO may represent an additional risk: recent (<2 years) spontaneous pneumothorax, eardrum or ossicle chain surgery, acute upper respiratory tract infection, untreated or insufficiently treated epilepsy, concurrent treatment with radiotherapy or chemotherapy, congenital spherocytosis, psychotic disease;
- Concurrent participation in other clinical trials;
- Absence of written informed consent.

2.2 Pregnancy

Women who are able to get pregnant must have a negative pregnancy test before inclusion in the study and before delayed HBO Therapy. A repeat pregnancy test must be done if a patient misses any periods. All potentially childbearing patients are recommended to use an effective birth control method of their choice. If a patient gets pregnant while in this study, she must inform the investigator immediately.

2.3 Patient log

All patients, initially considered for inclusion in the study, should be recorded in a Patient log to document the characteristics of the available patient population in the Clinical Centre. Furthermore, the reason for patient exclusion should be recorded.

2.4 Number of patients

The number of patients needed to detect an increase of the success rate in the conventional plus HBO treatment group equal to 18 % (50-32%) is equal to 128 patients per treatment group (1:1 sampling ratio). Since we expect that about 10% of patients will withdraw or be lost to follow up during the 12 months post randomisation we need a total number of patients equal to 282.

2.5 Randomisation

All eligible patients will be randomly allotted to the experimental group or the control group in order to neutralise potential bias in the comparison of the two groups. The Co-ordinating and Methods Centre (CMC) will generate randomisation centrally and electronically through a randomisation programme (accessible via Internet). Computer-generated randomisation will allocate patients in a 1:1 ratio in variably block-sizes to receive either experimental or control treatment.
Before randomisation an eligible patient will provide written informed consent,

2.6 Stratification

All eligible patients will be stratified by Clinical Centre and stage 1 or 2 according to Steinberg Classification.

2.7 Blinding

Due to the nature of the treatments under investigation, this study is an unblinded (open-label) study. To minimise bias, the following strategies will be adopted:

- *A priori* well-defined criteria for qualifying outcome events
- Assessment of outcome made by two investigators, one MRI Director independently working and blinded to treatment and clinical finding, the second is the local orthopaedic

3. Study medications

All randomised patients will receive the conventional non-surgical therapy. By conventional non-surgical therapy we mean non-weight bearing and pain control. When randomly assigned to the study experimental group, they will receive in addition 60 HBO treatments (2.25 ATA ± 10% - 90 minutes each)[1] within a maximum period of 4 months and according to a time schedule homogeneous across centres. Normal treatment frequency is represented by 5 or 6 treatments per week.

3.1 Compliance

Compliance with the allocated treatment arm will be monitored in all the randomised patients. In experimental group (with HBO), special attention will be given to the level of oxygen pressure reached during the session. In this respect, transcutaneous oximetry of oxygen assessment will be used.
A non-compliant patient will be defined when he receives less than 80% of the planned treatments in a period of 5 months.

[1] **Change in KiloPascal**

3.2 Drop-outs and withdrawals

Patients have the right to withdraw from the study at any time for any reason without prejudice to their subsequent care. A patient is defined as dropout when he is either unwilling or unable to return to the study clinic for regular follow-up visits (Meinert, 1986).

The investigator also has the right to withdraw patients from the study if it is in the best interest of the patient. An excessive rate of dropouts or withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. If patients wish to stop treatment with HBO they should complete the next study visit as planned. If possible, these patients should be followed for the follow-up period. Should a patient decide to withdraw consent to further participation in the trial, all efforts will be made to complete and report data up to the date of discontinuation. A final follow-up visit should be performed if possible. The reasons for patient withdrawal should be reported and, if possible, documented.

4. Study procedures

All eligible patients will undergo baseline examinations including clinical and appropriate radiological assessment at baseline (Radiograph and MRI according to procedure reported in Appendix 2). Variables useful for the evaluation of the disorder and variables representing known risk factors will be assessed. The records will be reported in a structured Case Report Form (CRF).

4.1 Baseline screening visit

The patients must have the following procedures at the baseline-screening visit to be performed within the previous 7 days from the randomisation:

- Physical examination
- History
- Conventional radiological evaluation
- MRI
- Harris hip score
- Visual Analogue Scale
- Steinberg Classification
- Laboratory tests (Sedimentation rate, CBC, Electrolytes)
- Associated therapies
- Inclusion/Exclusion Criteria

4.2 Study period and follow-ups

- 12 - months study period
- Clinical evaluation at baseline, 2, 5, 12 months;
- Conventional radiological evaluation and MRI at Baseline, 5, and 12 months.

5. Data Quality Assurance

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the investigator's records by the study monitor. A set of study specific data entry conventions will be created if appropriate. Data collected will be entered into the study database from the working copy of the original CRF. A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator. As patients complete the study or prematurely withdraw, and their signed CRFs become available, a second data entry will be performed from the original signed CRF. A comparison check will be run to identify and resolve any discrepancies between the first and second data entry.

Once the database is locked, a quality assurance check is performed on 1000 randomly chosen data points that are compared with the original CRFs. This sample size is sufficient to ensure that, with 99% confidence, the true error rate is less than 1% if fewer than 3/1000 discrepancies between the database and the CRF are detected.

6. Statistical considerations

6.1 Statistical Analyses

The rate of success of the treatment groups will be compared by means of logistic regression analysis (Hosmer & Lemeshow, 1989), including in the model as independent variables treatment and type of concomitant therapy, and specific exposure conditions (e.g., alcohol abuse, use of corticosteroids, etc.). The time-to-first-event of the primary outcome (success) will be described using Kaplan-Meier method (Matthews & Farewell, 1988) for each treatment group, and the two groups will be compared using log rank test (Matthews & Farewell, 1988). Statistical significance will be declared if the two-sided P-value for the test falls below 0.05.

6.2 Analysis Sets

Two data sets will be employed in the statistical analysis: the intention-to-treat and the as-treated analysis sets.

Intention-to-Treat Set

The intention-to-treat (ITT) set will include all patients who are randomised, regardless of the treatment received, other protocol deviations or the time of the last follow up.

As-Treated Set

The following patients will be excluded from the as-treated (AT) analysis set:

- Any patient who have violated the inclusion or exclusion criteria;
- Any patient who received less than 80% of the HBO treatments by four months from baseline.

6.3 Sample size

The available literature provides little information on the expected success rate in the conventionally treated control group. On the basis of selected literature, Strauss and Dvorak (2000) report a 24-month (or less) success rate values ranging from 44% to 86% for patients with different modalities of therapeutic intervention or no intervention. Mont and Hungerford (1995) report that most studies show a percentage higher than 85% of patients with collapse of the femoral head at two years when symptomatic hips with stage I or II disease (International Classification) were left untreated. After non-operative treatment, referring to a total of 819 hips, the same authors report that 22% had a satisfactory clinical result, this percentage increasing to 35 and 31% when patient were classified at stage I or II (International Classification), respectively.

We will base sample size calculation on a proportion of successes in the control group equal to 32 % after 12-month study period, as suggested in the meta-analysis by Strauss & Dvorak (1999) for the natural history group. The same authors report a percentage of success equal to 81 % for patients managed with hyperbaric oxygen therapy. In the calculation of the sample size for the present clinical trial, accounting for different stages, duration and treatment received, not cited by the authors, we cautiously decided to consider for the experimental group a value of success equal to 50 %. The sample size needed to detect an increase of the success rate in the conventional plus HBO treatment group equal to 18 % (50-32%) is equal to 128 patients per treatment group (1:1 sampling ratio). We based these calculations on the Fisher exact test (Matthews & Farewell, 1988) and referring to a two-sided type I error of 5% and a statistical power equal to 80%. Since we expect that about 10% of patients will withdraw or be lost to follow up during the 12 months post randomisation we need a total number of patients equal to 282. For these calculations we used the nQuery Advisor software (Elashoff, 2000).

7. Requirements for Hyperbaric Medical Centres Participating in the Study

Every hyperbaric participating centre must be physically or functionally linked to a hospital facility or medical institution and must follow the guidelines of the European Committee for Hyperbaric Medicine (ECHM) regarding personnel, safety and procedures.

8. Publications

Results derived from the present study will be submitted for publication in peer-reviewed, widely recognised, medical journals.

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APPENDICES

Appendix 1: Steinberg Classification

Stage	Description	In the present trial
0	Hip functional and pain free, normal radiograph but considered at risk because of the presence of necrosis in the controlateral hip	Excluded
1	Pain but normal radiograph, abnormal bone scan and MRI	Included
2	Pain and radiographic signs of diffuse porosis, sclerosis, or cyst	Included
3	Crescent sign. Broken contour of the femoral head	Excluded
4	Decreased joint space, flattened contour, collapse of the femoral head	Excluded
5	Involvement of acetabulum	Excluded
6	Severe arthrosis	Excluded

Appendix 2: MRI Procedures

MRI of the hip – (B. Vande Berg)

Part one: Imaging protocol
Part two: Images analysis
Part three: exclusion criteria of hip or patient

1. Part one: imaging protocol

Magnet
Magnet field: any magnetic field (from 0.2 to 1.5 Tesla).
Magnet type: any type (open or closed magnet)

Coil
Coil: Use of the body coil; if available, adaptable body coils or surface coils are recommended.

Patient positioning
Patient lies supine, head or feet first. Both knees are maintained in a neutral position by applying a band around both knees at the level of the patella. A small cushion (maximum 10 cm thick) is placed underneath both knees. Thicker cushion should not be used to avoid hip flexion.
Position of hands is not important.

Imaging protocol (initial and follow-up MR studies)
Scout view images including at least axial images of both femoral heads.
Coronal T1-weighted spin echo (SE) images.
* Comparative images obtained with the body coil (the use of a quadrature coil is allowed if simultaneous imaging of both hips).
* The coronal plane is defined as the plane that is tangent to the anterior aspects of both femoral heads.
* Imaging parameters: TR: 300-600 m/sec; TE: 15-25 m/sec; field of view: 380-500 mm; slice thickness: 4 or 6 mm (5 mm is a good compromise); interslice gap: as small as possible; number of slice: 5-9; scanning matrix >380; reconstruction matrix: 512. If 512 matrix not available, 256x256.
Sagittal T2 Fast SE images
* The body coil may be used but the use of surface coil or adapted body coils is recommended if the local staff is familiar with. Acquisition of sagittal images may be simultaneous on both hips if "multistack" option is available.
* The sagittal imaging plane is defined as the plane that is perpendicular to the

anterior aspect of the femoral neck on localizer images. It is recommended to avoid the femoral artery that should be just medial to the most medial sagittal images.
*Imaging parameters: TR: 2000-4000 m/sec; TE: 80-110 m/sec, field of view: 180-250 mm; slice thickness: 4-5 mm; scan and reconstruction matrix: >180 and 256; echo train length of maximum 6.

These coronal T1-weighted SE and sagittal T2-weighted FSE images are mandatory for inclusion of patients.

Alternative sequences
Fat saturated intermediate-weighted fast spin-echo images are an alternative to T2-weighted FSE images. Fat saturation is obtained by spectral pre-saturation of fat. No STIR images unless good signal to noise ratio are achieved. TR: 2000-4000 m/sec; TE: 25-40 m/sec, field of view: 180-250 mm; slice thickness: 4-5 mm; scan and reconstruction matrix: >180 and 256; echo train length of maximum 6.

Additional sequences
The adjunction of the following sequences is greatly appreciated but their presence is optional.

Sagittal T1-weighted SE images obtained by using the technical parameters of the coronal T1-weighted SE images and the anatomic parameters of the sagittal T2-weighted FSE images.
Coronal T2-weighted FSE images obtained by using the anatomic parameters of the coronal T1-weighted SE images and the technical parameters of the sagittal T2-weighted FSE images.

Follow-up MR studies
The same imaging sequences and parameters should be used in initial and follow-up MR studies.

NB: The following sequences are not part of the protocol: transverse images in any sequences, Gadolinium-enhanced images, and gradient-echo images.

Presentation of images
Images should be printed on 36X43 cm films (standard films) with a maximum of 20 images per film with ideal settings to enable analysis of the signal intensity of the femoral heads.
Only images obtained with reconstruction matrix of 512 may be zoomed. Images obtained with 256X256 matrix should not been zoomed.

Ideally, MR examinations should be stored on any support to enable retrospective analysis.

Radiographic examination

Digitalized or conventional films may be used. If digitalized, photographs should be printed in format equivalent to that of conventional films.

Antero-posterior radiographs of the pelvis: patient lies supine both legs in internal rotation. The X-Ray beam is perpendicular to the patient and is centred on the midline between the umbilicus and the pubis. Spot views of each hip are recommended in the neutral position and in flexion-abduction. No radiographs taken in standing position.

The obtainment of an antero-posterior radiograph of the pelvis with the X-ray beam oriented 30° caudally is highly recommended.

2. Part two: Image analysis

The readings are performed by one or two radiologist that will be blinded to all clinical data including side of pain, date of examination and type of treatment. The films are not read in chronological order.

Results of initial MR studies are classified as follows:

Normal

Abnormal

Well-delimited lesion (or epiphyseal osteonecrosis) defined by presence of subchondral marrow lesion of variable signal on T1- and T2-weighted images delineated from the adjacent marrow by a rim of low signal intensity on T1-weighted sequence and of variable signal on T2-weighted images (the double-line sign is present in 55% of epiphyseal osteonecrosis). Femoral neck marrow may or may not be infiltrated (oedema). Joint effusion may or may not be present.

NB Epiphyseal collapse is defined by presence of marked and focal deformity of the femoral head or by presence of a high signal intensity line parallel to the subchondral bone plate on T2-weighted SE images.

Ill-delimited lesion (or bone marrow oedema) defined by presence of subchondral marrow infiltration (low signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images) that is not delimited from the adjacent marrow by a rim. Joint effusion may or may not be present. Absence of marked epiphyseal deformity and of high signal intensity line parallel to the subchondral bone plate.

Any other feature [exclusion of the involved hip].

Results of initial radiographs are classified as follows

1.Normal

2. Abnormal

Femoral head **infarct** (abnormal femoral head bone structure with preserved femoral head contours and joint space)

Femoral head **osteonecrosis** (abnormal femoral head contour or subchondral fracture with or without abnormal femoral head bone structure or joint space narrowing)

Focal **osteoporosis** (poor visualisation of the subchondral bone plate with preserved joint space and femoral head contours)

Any other feature [loss of joint space, osteophytes, subchondral cysts] will also cause exclusion of the hip.

Results of follow-up studies (gold standard)

Normal (normal marrow signal intensity on coronal T1- and sagittal T2-weighted SE images, normal radiographs)

Abnormal (any changes on conventional radiographs or MR images).

(The use of normal/abnormal instead of healed/not healed is related to the fact that reading of films will be performed blindly. Normal hips at initial study must be excluded).

3. Part three: Additional exclusion criteria

Criteria for exclusion of the hip

Previous total hip replacement.

Any sign of degenerative hip disease including joint space narrowing and osteophytosis on plain films, abnormal cartilage and / or abnormal subchondral marrow in head or acetabulum on MR images.

Presence of bone (plain films) or marrow (MR) lesions that are not focused in the subchondral area of the femoral heads.

Prominent synovial changes that are not consistent with reactive changes to the femoral head disorder.

Normal marrow signal intensity (MR).

Criteria for exclusion of the patient

Patients with known marrow diseases (anaemia, Gaucher disease, etc.)

Presence of focal or diffuse marrow (MR) changes at distance from the involved hip.

Contraindications to MR imaging (Pace-Maker, cardiac valves, intracerebral or intraocular metallic foreign body, external metallic fixation device, pregnancy, claustrophobia).