1. Background and objectives

Sudden deafness (SD) has an incidence of between 5 and 20/100,000 persons per year. Tinnitus and a feeling of increased pressure are often present, vertigo is less commonly associated with the syndrome. Only in approximately 20% of cases, a causal factor can be identified such as: trauma, Ménière's disease, acoustic neurinoma, ototoxic medications, multiple sclerosis. In the remaining 80%, no clear cause can be found and possible etiologies (vascular, viral, round window rupture, autoimmune disease) can be hypothesised:

An original aspect of SD is the possibility of spontaneous complete recoveries which occur in approximately 50% of patients and most of them during the first weeks. No reliable pre-therapeutic outcome predictors are available.

There is general consensus that the sooner any treatment is started, the better the prognosis. This may be related to the rate of spontaneous remissions or to a better response in early stage of the disease. These questions are also still not answered. A prediction of the final recovery seems to be possible from the therapeutic result after 7 days of any given treatment.

There is probably few other disease for which such a variety of treatments have been proposed. According to the pathophysiological findings, the consequence of SD on the inner ear arises from a reduction of the PO2 in the Corti’s organ; thus the treatment is based on the local enhancement of oxygen supply and generally involves: corticosteroids, rheologic substances, Carbogen inhalation, haemodilution. It seems however, that the therapeutic outcome of several proposed drug treatment regimes is in the same range as the spontaneous recovery rate, which itself is still the subject of controversy. So, currently, there is no consensus about these "classical" treatments.

In the same way, the efficacy of hyperbaric oxygen (HBO) for SD has not been conclusively established. Experimental research proves the increase of oxygen partial pressure in the inner ear and the improvement of its function under this condition.

Retrospectively, a large meta-analysis showed a positive effect of HBO in approximately 50% of cases, after failure of classical drug therapy. It was noted however that there was a very large variability in the nature and duration of the classical drug therapy administered prior to HBO. This is to be considered a weakness of these retrospective studies. A French study compared HBO/vasodilator/corticotherapy to vasodilator/corticotherapy alone and to hemodilution therapy. Although the HBO group scored better, the results were not significant.

There have been few published prospective studies. Most of them initiated therapy as soon as possible after the onset of deafness, thereby including the large number of patients who would recover spontaneously, no matter how or even if treated.

In summary, the place of HBO in this disease needs to be clearly evaluated. So, a multicentric (Belgium, Denmark, France, Germany, Italy) prospective and randomised study is started on to establish the clinical efficacy of HBO after failure of classical treatments.

Main objective: enhancement in the auditory function tested by tonal and speech audiometry
Secondary objective: subjective hearing enhancement (intensity and pitch of tinnitus, feeling of fullness to the ear)

2. Material and methods

2.1. Study population

2.1.1. Inclusion criteria

- Sudden (=transition from usual hearing to hearing loss in a period of 1-3 days maximum) unilateral sensorineural hearing loss, with or without tinnitus
- Loss of at least 30 dB in at least three frequencies compared to the contralateral ear
- Mean Hearing Loss (sum of frequencies (250 + 500 + 1000 + 2000 + 4000 + 6000 + 8000) divided by 7) of less than -80 dB (i.e. no complete cophosis)
- No significant compromise of hearing in the contralateral ear, of whatever cause
- Failure to respond (less than 10 dB mean improvement in the 3 most affected frequencies) to a "standard" treatment regimen of at least 7 days, involving the (IV or oral) administration of corticosteroids equivalent to at least 400mg of Methylprednisolone.
The following drugs may be added in various dosages: normo or hypervolemic haemodilution, rheologic and/or vaso-active substances, anticoagulant treatment, Carbogen inhalation
- Delay of < 4 weeks before initiation of HBO. Inclusion in the study should be done as soon as possible after completion of the medical treatment scheme, but not later than 4 weeks after the onset of the SD
- Age limits: >18 years

2.1.2 Exclusion criteria
- Clear etiologic diagnosis: viral infection, trauma (acoustic and barotrauma), Ménière’s disease, acoustic neurinoma, ototoxic medication, multiple sclerosis
- Concomitant embolic or thrombotic arteriosclerotic disease
- Usual contraindications for HBO
- Pregnancy
- Refusal to cooperate or sign the Informed Consent Form

2.2 Intervention
After signing of informed consent form, patients will be randomised according to a computer random number generated list and separated in 2 groups:
- HBO group: 10 HBO treatments, one per day, 2.5 ATA, 100% O₂ (10-15 minutes compression on air, 70 minutes of oxygen breathing, 10 minutes of decompression on air). Treatments will be given in a multiplace hyperbaric chamber, using a demand-system face mask
- non-HBO (control) group: no treatment

After the 10 days study period, each participating team keep the right to treat by HBO patients belonging to the "non treated group" and to perform a 3 months and 1 year follow up according to their feasibility and habits. The results of this secondary follow up, separately recorded will not be included as "study results"

2.3 Patients follow up and evaluation
Evaluation will be done on day 0 (before start of the trial), day 6 and day 11 (the day after the 10th treatment). An anonymous data collecting file will be established for each patient and will contain the following elements:

✓ On day 0
  • Clinical investigations
    Age, general previous history (vascular, smoking habit,...)
    Detailed history of the disease (previous history of SD, medication taken during the week before the onset of deafness)
    Presence of associated signs (mechanical neck problems, rotational vertigo)
    Initial treatment: time, nature and doses
    ENT examination
  Subjective evaluation of symptoms on 3 visual analog scales:
  - Tinnitus:
    "How loud is your tinnitus today ?"
    0 •–––––––––––––––––––––––––––––––––• 10

    "How much is your tinnitus bothering today ?"
    0 •–––––––––––––––––––––––––––––––––• 10

  - Feeling of fullness in the ear:
    "How bad is your feeling of fullness in the affected ear today ?"
    0 •–––––––––––––––––––––––––––––––––• 10

  • Paraclinical investigations
    Mandatory tests:
    Blood cell count, hematocrit, sedimentation rate
    Lues serology (TPHA test)
Mumps antibodies (IgM, IgG)
Tonal audiometry (air and bone), with appropriate masking
Tympanometry with stapledius reflex
Exclusion of a retrocochlear pathology by Brainstem Evoked Potentials or MRI

**Optional tests:**
Other tests or examinations (such as immunologic check up or particular hearing investigations) will be able to be performed according to the experience of each center.

✔ **On day 6 (after the 5th HBO session in the "OHB group")**
Results of tonal audiometry and tympanometry
Reading of the analogic scales
Adverse events due to HBO: ear pain, ear barotrauma, oxygen toxicity, claustrophobia, etc

✔ **On day 11 (after the 10th HBO session in the "HBO group")**
Idem day 6

**2.4 Data analysis**
For each individual patient, the contralateral ear should serve as control.

- Tonal audiometry will evaluate the following frequency range: 250, 500, 1000, 2000, 4000, 6000, 8000 Hz. The Mean Hearing Loss (MHL) will be calculated as the mean of the respective differences between the 3 most affected frequencies and their corresponding contralateral value.

- Evaluation of the effect of HBO treatment and control will encompass:
  - The Mean Hearing Gain (MHG): difference between MHL on day 11/day 6 and on day 11/day 0.
  - The hearing recovery score after the 10 days period of inclusion:
    - "excellent": if the hearing acuity on all three selected frequencies returns to within –10dB or less of the corresponding contralateral control value
    - "good": if the hearing acuity of all three selected frequencies returns to within –20dB of the control value, or if only one or two values return to within –10dB of the control value.
    - "poor": in all other cases

The proportion of patients having obtained a "excellent", "good" or "poor" result will be compared between the two main patient groups, and may be further analysed for subsets of patients according to shape and slope of audiometry curve or abnormality of one or more of the "optional" diagnostic workout tests.

Changes in intensity, pitch of tinnitus and subjective feeling of "fullness" in the affected ear will be analysed by procentual changes in the visual analog scales rating referring to the initial value.

The occurrence of undesirable side effects will be compared as to incidence and severity in both groups.

**2.5 Sample size and statistical data processing**
Because HBO therapy will only be started after more than 10 days (pre-treatment delay), the rate of recovery is probably much lower than the 50% spontaneous recovery rate during the 1" month. As most of the recoveries take place within the first weeks, a 10% probability of having a "good" recovery after the end of an unsuccessful classical drug therapy seems realistic. The success rate of HBO as a secondary treatment, i.e. after unsuccessful drug therapy, according to a recent literature analysis, lies around 50% (hearing gain of at least 20dB in at least 3 frequencies). Because these data come from various retrospective studies, it is safe to underestimate this rate to 30% of "good" recovery with secondary HBO therapy.

Entering these data into a 2x2 table, sample sizes can be calculated as follows: 100 patients in each group can yield a 0.0007 p-value. In order to account for the uncertainties described before, it is proposed to include 200 patients in each group.

**3. References**

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HYPERBARIC OXYGEN IN THE TREATMENT OF SUDDEN DEAFNESS AFTER FAILURE OF PREVIOUS MEDICAL TREATMENT.

START UP OF A MULTICENTRIC, PROSPECTIVE AND RANDOMISED STUDY

BACKGROUND AND OBJECTIVES

Sudden deafness (SD) has an incidence of between 5 and 20/100,000 per year. Tinnitus and a feeling of increased pressure are often present, verifying to keep consistent with the syndrome. Only in approximately 30% of cases, a causal factor can be identified such as: trauma, Ménière’s disease, acoustic neurinoma, systemic medicaments, multiple sclerosis. In the remaining 70%, no clear cause can be found and possible etiologies (vascular, viral, round window rupture, autoimmune disease) can be hypothesized.

An original aspect of SD is the possibility of spontaneous complete recoveries which occur in approximately 50% of patients and most of them during the first weeks. No reliable pre-therapeutic outcome predictions are available.

In summary, the place of HBO in this disease needs to be clearly evaluated.

MATERIAL AND METHODS

Patient population

- Inclusion criteria
  - Sudden hearing loss within 3 days after onset of hearing loss
  - AFB (average bombing frequency) less than 65 db
- Exclusion criteria
  - Previous treatment
  - Neurological disorders
  - Age > 60 years

Intervention

- After informed consent form, patients will be randomized according to a computerized random number generator
  - HBO group: HBO treatment, 10 sessions, 2 x 20 mbar and 90 min.
  - Control group: placebo treatment, 10 sessions, 2 x 20 mbar and 90 min.

Evaluation

- Evaluation will be done on day 0 (before start of the HBO treatment), day 1 and day 11 after the HBO treatment.

Data analysis

- For each individual patient, the outcome of HBO treatment and control will be measured.
- The difference between the 1st and 2nd hearing test will be calculated as the mean difference between the 2 groups.

This multicentric, multinational study provides an unique opportunity to demonstrate the efficacy of HBO therapy in the treatment of drug-resistant Sudden Deafness, while at the same time not withholding HBO from patients.

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