HYPERBARIC OXYGEN IN THE ACUTE TREATMENT OF SUDDEN IDIOPATHIC SENSORINEURAL HEARING LOSS

RANDOMISED, PROSPECTIVE STUDY OF HYPERBARIC OXYGEN THERAPY AFTER FAILURE OF PREVIOUS MEDICAL TREATMENT

PROTOCOL PREPARED BY
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"HYPERBARIC OXYGEN THERAPY"

1. Background

Sudden Sensorineural Hearing Loss (”Sudden Deafness”) has an incidence of between 5 and 20/100.000 persons per year. It can occur at any age but seems to strike more at middle age[1 2 3]. Tinnitus and a feeling of increased pressure are often present, vertigo is less commonly associated with the syndrome[4].

Only in approximately 20% of cases, a causal factor can be identified. This can be a viral infection, such as mumps, trauma, Ménière’s disease, acoustic neurinoma, ototoxic medication, multiple sclerosis. In the remaining 80%, no clear cause can be found. Four possible etiologies can be hypothetised:

- Vascular: since the a. labyrinthi is a terminal artery, any thrombosis or embolus of this artery would lead to a profound deafness with a poor prognosis. In the case of a mainly rheological disturbance, red blood cell sludge and a slowing of blood flow causes a reduction of the partial pressures of oxygen in the inner ear (Corti’s organ)[5]. This reduction would cause the sensory cells to stop functioning, however, cell death would not occur until a critically low oxygen partial pressure is attained [6 7 8].
- Viral: many viral infections could lead to sensorineural hearing loss. Serologic studies are difficult to obtain in a systematic way, are expensive and have a poor chance of positivity. Moreover, some known viral infections, such as mumps, lead to an always irreversible acoustic damage. Some cases of SSHL are accompanied by signs of viral infection, however, a clear viral etiologic origin can seldom be proven [9 10 11].
- Round window rupture: in some cases, the clinical history can give arguments for a rupture of the round window (trauma to the inner ear, heavy weight lifting, intracranial pressure rise)[12 13].
- Auto-immune disease: some authors propose an auto-immune cause for SSHL; however, most known auto-immune syndromes leading to deafness have a slow progressive course of disease[4].

In the literature it is well documented, that irrespective of the source of damage the stria vascularis and the cells of the organ of corti in the inner ear react uniformly[14].
In the cochlea histological findings are swelling and structural damage of the dendrites[15], alterations of mitochondria and the cell-structure, separation of hair-cells from tectorial membrane[16], oedema of the endothelium, oedematous closure of functional endarteries with blocking of the microcirculation. These alterations due to damage or vascular reactions limit the function. That is why improved oxygen supply and enhanced healing processes are seen as the solving keys for dysfunction of the inner ear [13 14 17 18].

Spontaneous complete recovery (return of hearing to within 20dB of the normal or contralateral ear) occurs in approximately 50% of all patients [12 19 20 21 22]. Most recoveries happen during the first weeks. No reliable pre-therapeutic outcome predictors are available, imposing an urgent need for maximal treatment for all patients.

Prognostically negative factors have been identified [1]:

- vertigo
- profound deafness (all frequencies)
- therapeutic delay of more than 10-14 days
- increased blood viscosity[23]
- hypertension

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 [24].

There is probably few other disease for which such a variety of treatments have been proposed, and still today, many different treatment regimens, some more invasive than others, are propagated [25] [26] [27] [28]. Their therapeutic efficacy is very difficult to establish. 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. This is the result of several double-blind prospective trials, where no advantage over NaCl infusion could be established[19] [29].
A significant improvement vs. placebo therapy could however be observed with high-dose intravenous corticosteroid treatment in a degressive scheme [21], as well as with hemodiluton therapy in patients with an increased haematocrit (above 44%)[30]. As these effects have not been reproduced equivocally by other authors, these therapeutic options have not become "accepted standard" in ENT. In fact, not one drug treatment regimen has gained universal acceptance in ENT.

The efficacy of HBO for sudden deafness has not been conclusively established.

Experimental research proves the increase of oxygen partial pressure in the inner ear and the improvement of the function under this condition[31].

Retrospectively, a large meta-analysis by Lamm et al. (1998) [25] 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 [32] compared HBO/vasodilator/corticotherapy to vasodilator/corticotherapy alone and to haemodilution therapy. Although the HBO group scored better, the results were not significant.

There have been few **prospective studies**. Most of these studies 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. Pilgramm *et al.*[33], comparing 37 patients, treated with haemodilution with or without HBO, showed a similar, not significant advantage of adjuvant HBO. Flunkert et al. 2000[34] compared haemodilutive and HBO as a first treatment in early stages of the disease in a prospective controlled trial and saw equal outcome with insignificant advantages for HBO. Many other prospective studies are only presented as communications on HBO congresses, and are never published in peer-reviewed papers.

In summary, there appears to be a need for a large prospective clinical trial to clearly establish the place of HBO in the treatment of SD.

2. Objectives

To establish the clinical efficacy of HBO in the treatment of Sudden Deafness, not responsive to a classical medical treatment. Prospective, randomised, single-blinded controlled study.

Main endpoint:
- changes in auditory function, as tested by tonal and speech audiometry

Secondary endpoints:
- changes in intensity and pitch of tinnitus, if present
- changes in feeling of fullness to the ear
- establishment of the safety of HBO: presence of side effects and complications

3. Study population

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 (loss of >30dB in at least 3 frequencies), of whatever cause

- Failure to respond (less than 10 dB mean improvement in the three most affected frequencies) to a "standard" treatment regimen, of at least 7 days and involving at least a scheme of intravenous or oral high-dose corticosteroids, as detailed in the "Intervention" section below.
- 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 Sudden Deafness

- Age limits: > 18 years

Exclusion criteria:

- Clear etiologic diagnosis:
  - viral infection, such as mumps etc.
  - trauma, including acute acoustic trauma and barotrauma
  - Ménière's disease
  - acoustic neurinoma
  - ototoxic medication
  - multiple sclerosis
- Concomitant embolic or thrombotic arteriosclerotic disease (such as Transient Ischemic Attack, Cerebrovascular Accident, acute coronary occlusion, valvular emboligenic disease)
- Situations where HBO may represent an additional risk: recent (<2 years) spontaneous pneumothorax, ear-drum or ossicle chain surgery, acute upper respiratory tract infection, untreated or insufficiently treated epilepsy, concurrent treatment with radiotherapy or chemotherapy, congenital spherocytosis, psychotic disease
- Pregnancy
- Refusal to cooperate or sign the Informed Consent Form

4. Enrolment of participants

4.a. Baseline examinations

The following baseline examinations are considered mandatory, for they may indicate the presence of a treatable organic disease of which the sudden deafness is a symptom.

Mandatory tests

Clinical examination:

- Detailed history for cardiovascular disease and possible Inner Ear Barotrauma (IEBT)
- Arterial blood pressure
- Clinical ENT examination

Laboratory investigations:

- Blood cell count (incl. differentiation of white blood cells)
- Haematocrit
- Sedimentation rate
- Lues serology (TPHA test)
- Mumps antibodies (IgM, IgG)

Paraclinical examinations:

- Tonal audiometry (air and bone), with appropriate masking
- Tympanometry with stapedius reflex
- Exclusion of retrocochlear pathology, by Brainstem Evoked Potentials or MRI

Other diagnostic tests may be markers of disparate disease entities but change nothing to the therapeutic strategy. It is recommended to collect these data in a standardised way.

Optional tests

Laboratory investigations:

- Auto-antibodies: anti-nuclear antibodies (ANF), anti-endothelial cell antibodies (AECA), anticardiolipine antibodies (ACA), anti-phospholipid, anti-serotonin and anti-ganglioside antibodies
- Other viral antibodies: cytomegalovirus IgM, parainfluenza IgM, adenovirus IgM
- Red blood cell filtrability
- Plasma viscosity

Paraclinical investigations:

- Speech audiometry (proposed standard: DIN Norm)
- Tinnitus matching (tonal quality, loudness, masking level by white noise)
- Spontaneous otoacoustic emissions
- Contrast-enhanced MRI (gadolinium contrast, T1 and T2 weighed images)
- Eye fundoscopy
- Electronystagmography (in case of concomitant vertigo)

4.b. Baseline data recordings

The following information will be collected during the intake, to facilitate analysis of the therapeutic results in subsets of patients with different characteristics.

- Age
- Occupational background
- Previous habitual noise exposure
- History of vascular disease (such as angina pectoris, peripheral arterial disease, thrombosis…)
- Medication taken during the week before the onset of deafness
- Mechanical neck problems in the period immediately preceding the onset of deafness, mandibular joint dysfunction
- Smoking habits (number of Pack-Year smoked)
- Previous history of sudden deafness
- Previous tonal audiometry testing if available
- The presence, or not, of rotational vertigo
- The time to initial treatment
- The nature of the pharmacological treatment received (classified into categories and dosing, such as corticosteroids, vasodilators, haemodilution, anticoagulants in low, medium or high dose)
- Subjective evaluation of symptoms
    - *Tinnitus*: evaluation on two visual analog scales (no graduation, of a length of 10cm) one evaluating the subjective loudness of the tinnitus, the other evaluating the impact of the tinnitus on overall quality of life

      a. “How loud is your tinnitus today ?”

      0 ●——————————————————● 10

      b. “How much is your tinnitus bothering you today ?”

      0 ●——————————————————● 10

    - *Feeling of fullness in the ear*: evaluation on visual analog scale (similar as previous)

      c. “How bad is your feeling of fullness in the affected ear today ?”

      0 ●——————————————————● 10

5. Randomisation

After informed consent, patients will be randomised using a central telephone random number allocation. Patients will be attributed to a given treatment arm according to a (computer) random number generated list. Patient number and randomisation group will be communicated by the telephone operator and recorded in a separate list containing name of patient, birthday and treating center.

Sample size assumptions: The exact rate of recovery after the proposed pre-inclusion period is not known exactly. Because HBO therapy will only be started after more than 10 days (pre-treatment delay), this rate is probably much lower than the 50% spontaneous recovery rate during the 1st 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 (Lamm K. et al. 1998) [28], 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 double the patient sample, i.e. 200 patients in each group (total of 400). An interim statistical analysis (without breaking the code) will be performed after 200 patients.

6. Intervention

All included patients will have received a therapeutic regimen consisting of (IV or oral) administration of corticosteroids in a high, but not extreme dosage. A possible treatment scheme is given below.

Day 1	125 mg IV Methylprednisolon
Day 2	125 mg IV Methylprednisolon
Day 3	80 mg IV Methylprednisolon
Day 4	40 mg IV Methylprednisolon
Day 5	40 mg IV Methylprednisolon
Day 6	32 mg orally Methylprednisolon
Day 7	16 mg orally Methylprednisolon
Day 8	16 mg orally Methylprednisolon
Day 9	8 mg orally Methylprednisolon

In any case, patients will have received at least 400mg of Methylprednisolon during this first week of treatment. According to the preference of the referring ENT specialist (reflecting local or regional treatment strategies), the following drugs may be added in various dosages:

- Normo- or hypervolemic haemodilution: with hydroxy-ethyl-starch (HAES-Steril) (e.g. 6% 250 to 500 ml in 4 hrs / day)
- Rheologic substances (such as Piracetam, Nicergolin, Pentoxifyllin)
- Vaso-active substances
- Anticoagulant treatment
- Carbogen inhalation (e.g. 5% CO_2 in 95% O_2, 8 periods of 30 minutes per day for 5 days)

After randomisation, patients will receive a treatment following one of two modalities:

- HBO group:

  10 HBO treatments, one per day, 2.5 ATA, 100% O_2 (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.
  Oxygen administration in the hyperbaric chamber will be controlled either by transcutaneous oxygen measurements at the subclavicular skin level (at least a five-fold increase, sustained during the whole HBO session), or by measurement of the in- or expired oxygen concentration in the mask (a level of minimum 90% of in- or expired oxygen concentration).

- non-HBO group:

  No treatment for 10 days.

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

7. Blinding

Non-HBO patients will not be submitted to (sham) compression.

Due to the very different nature of the two treatments, blinding of the ENT specialist or audiologist performing the tonal audiometries will be impossible to maintain in all cases.

However, all data will be analysed by an independent university-level researcher unaware of the nature of the treatment given.

8. Evaluation

Evaluation of the patients will be performed on coded evaluation records, devoid of any possible identification of the patient, only the randomisation number.
Evaluation will be done on Day 1 (before start of the trial), Day 6 and Day 11 (the day after the 10^{th} treatment).

Presence of complications and side effects, evaluation of tinnitus, evaluation of subjective "fullness" of ear will be recorded through self-assessment questionnaires. Side effects and complications will independently be recorded by the clinician treating the patient.

Each evaluation will comprise:

a. Performed by ENT physician

- Covering all the items of the mandatory and optional tests performed on this special patient before enrollment.

b. Self assessment questionnaire evaluated by ENT physician

- 2 visual analog scales of tinnitus evaluation (without reference to previous evaluations)
- Visual analog scale of "fullness" evaluation (without reference to previous evaluations)

c. Assessment by treating clinician (to be recorded in the clinical file of the patient, not on the evaluation records)

- Evaluation with regard to side effects of treatment: table of possible side effects, evaluation in three grades: none present, moderately, severe
- Levels of $TcPO_2$ or intra-mask oxygen concentration reached during each treatment session.

All evaluation sets will be sent to a central data gathering and analysis office.

9. Data analysis

For each individual patient, the contralateral ear should serve as control (baseline shift according to age-related presbyacousis and possible chronic noise exposure effects).
If an audiometry test of the affected ear is available that has been taken less than two years before the onset of SD, and without a history of acoustic trauma or hearing disorder in the past two years, this audiogram will be used as a "historic control" of the affected ear.

- 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 three most affected frequencies and their corresponding contralateral value.
- Evaluation of the effect of HBO treatment and control will encompass
    - The Mean Hearing Gain (MHG), defined as the mean gain (in dB) obtained with treatment on the three frequencies that were initially selected as the three worst. It is emphasised here that inclusion in the study requires to have at least three frequencies affected for at least a –30dB loss.
    - a scoring of the "return to acceptable hearing". This value will be defined as follows:
        - "excellent" if the hearing acuity on all three selected ("worst") 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 and pitch of tinnitus will be analysed by procentual changes in the visual analog scales rating referring to the initial value.

Changes in subjective feeling of "fullness" in the affected ear will be analysed by procentual changes in the visual analog scale rating.

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

10. Monitoring and Safety

The Working Group "Sudden Deafness" of the action COST B14 shall act as the Monitoring Committee. All aspects of the study will be monitored by the Monitoring Committee who will review randomly sampled study documents and attention will be paid to protocol violations, missing or incomplete data, and occurrence of severe adverse events.

All centers participating in this study have to follow the code of Good Clinical Practice and to perform the study in accordance to the declaration of Helsinski. All centers have to comply with their own national regulation concerning clinical research. In particular, approval of this protocol by the appropriate organism ruling the ethical aspects of clinical research has to be obtained. It is of the responsability of each center to prepare required documents in their own language in order to obtain this approval.

11. References

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