Hyperbaric oxygen therapy in idiopathic sudden sensorineural hearing loss

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Key-words. Hyperbaric oxygenation; sensorineural hearing loss; sudden deafness; review

Abstract. Hyperbaric oxygen therapy in idiopathic sudden sensorineural hearing loss. Objectives: The pathophysiology of idiopathic sudden sensorineural hearing loss (ISSHL) remains largely unknown. However, it is hypothesized that this disorder may be caused by reduced cochlear blood flow, labyrinth viral infections, intracochlear membrane ruptures or immune-mediated inner ear disease. Hyperbaric oxygen therapy (HBOT) may have a positive effect on ISSHL by raising intracochlear oxygen tension, stimulating angioneogenesis, and having an anti-inflammatory function. The objective of this systematic review was to examine the efficacy of HBOT as a treatment for ISSHL.

Methodology: A systematic approach was applied to search for all clinical studies concerning HBOT in ISSHL in the PubMed database. Nineteen studies met the selection criteria.

Results: Three out of five studies (60%) recommended adding HBOT to monotherapy with corticosteroids (CS). Four out of seven of the included studies (57%) demonstrated that adding HBOT to multi-drug therapies had a beneficial effect. Two out of two studies (100%) concluded that HBOT was significantly more effective than vasodilators. Three out of five studies (60%) showed a positive indication for the use of HBOT as salvage treatment.

Conclusion: HBOT could be useful as an adjunct therapy or salvage treatment for ISSHL, although evidence is still scarce.

Introduction

Idiopathic sensorineural sudden hearing loss (ISSHL) is most commonly defined as a hearing loss of at least 30 dB in three contiguous frequencies in the standard pure-tone audiogram within less than 3 days.¹ Although the pathogenesis of ISSHL remains largely unknown, there are several hypotheses that may explain the origin of this disease. The most commonly discussed hypotheses are decreased cochlear blood flow with cochlear hypoxia, viral infection, intracochlear membrane rupture, and immune-mediated inner ear disease.² These hypotheses explain why current treatment modalities such as corticosteroids, vasodilators, and hyperbaric oxygen therapy are mainly focused on increasing the oxygen supply to the cochlea, reducing inflammation, and counteracting a possible autoimmune mechanism.²³

Hyperbaric oxygen therapy is the administration of 100% oxygen in an environment of elevated pressure. This treatment leads to an increase in the oxygen concentration in the blood and therefore also in the perilymph. In an animal study, the partial oxygen tension of the perilymph rose to 450% of its original value due to the administration of HBOT. The oxygen tension remained high until one hour after the treatment.¹ HBOT may also have a positive effect on the cochlear blood flow by stimulating angioneogenesis and by exerting an anti-inflammatory effect.² These findings support HBOT as a potential treatment option for ISSHL.

The objective of this systematic review was to investigate the efficacy of HBOT as a treatment for ISSHL. This review will also cover the most important factors that could influence treatment.

Materials and methods

The PubMed database was systematically searched by 2 authors independently. Case-control studies, cohort studies, randomized control trials (RCT), and meta-analyses that investigated HBOT as a monotherapy, adjunct therapy, or salvage treatment
<table>
<thead>
<tr>
<th>Study</th>
<th>Publication type</th>
<th>Oxford level of Evidence</th>
<th>Participants</th>
<th>Control</th>
<th>Study group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cekin et al. (2009)</td>
<td>RCT</td>
<td>1b (individual RCT)</td>
<td>n = 57</td>
<td>MT (n=21) HBOT + MT (n=36)</td>
<td>CS, famotidine</td>
<td>2.5 atm 90 minutes 10 sessions</td>
</tr>
<tr>
<td>Cvorovic et al. (2013)</td>
<td>RCT</td>
<td>2b (RCT of poor quality)</td>
<td>n = 50</td>
<td>IT CS (n=25) HBOT (n=25)</td>
<td>IT CS as salvage treatment after initial IV CS</td>
<td>2.0 atm 80 minutes 20 sessions after initial IV CS treatment</td>
</tr>
<tr>
<td>Fattori et al. (2001)</td>
<td>RCT</td>
<td>2b (RCT of poor quality)</td>
<td>n = 50</td>
<td>Vasodilator (n=20) HBOT (n=30)</td>
<td>IV vasodilator</td>
<td>2.2 atm 90 minutes 10 sessions</td>
</tr>
<tr>
<td>Topuz et al. (2003)</td>
<td>RCT</td>
<td>2b (RCT of poor quality)</td>
<td>n = 51</td>
<td>MT (n=21) HBOT + MT (n=30)</td>
<td>CS, diazepam, rheomacrodex, pentoxifylline</td>
<td>2.5 atm 90 minutes 25 sessions</td>
</tr>
<tr>
<td>Yang et al. (2013)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 103</td>
<td>HBOT (n=22) HBOT + IT CS (n=19) IT CS (n=35) None (n=27)</td>
<td>IT CS as salvage treatment after therapy with IV dexamethasone with PO CS</td>
<td>2.5 atm 120 minutes 10 sessions</td>
</tr>
<tr>
<td>Alimoglu et al. (2011)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 239</td>
<td>HBOT (n=58) HBOT + PO CS (n=61) PO CS (n=43) IT CS (n=57)</td>
<td>PO CS: prednisolone IT CS: dexamethasone</td>
<td>2.5 atm 120 minutes 20 sessions</td>
</tr>
<tr>
<td>Aslan et al. (2002)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 50</td>
<td>MT (n=25) HBOT + MT (n=25)</td>
<td>Betahistine hydrochloride, prednisone, stellate ganglion block</td>
<td>2.4 atm 115 minutes 20 sessions</td>
</tr>
<tr>
<td>Callioglu et al. (2015)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 44</td>
<td>IV CS (n=23) HBOT + IV CS (n=21)</td>
<td>Systemic steroids (prednisolone)</td>
<td>2.5 atm 90 minutes 20 sessions</td>
</tr>
<tr>
<td>Capuano et al. (2015)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 300</td>
<td>HBOT (n=100) HBOT + IV CS (n=100) IV CS (n=100)</td>
<td>IV CS</td>
<td>2.5 atm 90 minutes 16 sessions</td>
</tr>
<tr>
<td>Edizer et al. (2015)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 203</td>
<td>HBOT + IV CS (n=53) HBOT + IV CS + LMWH (n=77) IV CS (n=48) IV CS + LMWH (n=27)</td>
<td>IV CS: methyl-prednisolone LMWH: fraxiparine</td>
<td>2.5 atm 120 minutes 20 sessions</td>
</tr>
<tr>
<td>Fujimura et al. (2007)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n = 130</td>
<td>IV CS (n=63) HBOT + IV CS (n=67)</td>
<td>IV CS: dexamethasone</td>
<td>2.5 atm 60 minutes 10 sessions IV CS + HBOT: hydrocortisone-sodium succinate followed by prednisolone</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Publication type</th>
<th>Oxford level of Evidence</th>
<th>Participants</th>
<th>Control</th>
<th>Study group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. (2011)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=465 HBOT+MT (n=112) Steroids (n=76) MT (n=277)</td>
<td>Steroids: IV betamethasone followed by PO prednisolone MT: IV betamethasone followed by PO prednisolone + dextran</td>
<td>2.5 atm 60 minutes 10-20 sessions</td>
<td>Significant recovery with HBOT + MT in patients with severe hearing loss</td>
</tr>
<tr>
<td>Narozny et al. (2004)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=133 MT (n=81) HBOT + MT (n=52)</td>
<td>MT: Procaine, cocarboxylase, vinpocetine, vit B1, B6, pentoxifylline</td>
<td>2.5 atm 90 minutes 16 sessions MT: procaine, methylprednisone, betahistine, dextran, cocarboxylase, vit B1 en B6</td>
<td>Significant recovery with HBOT</td>
</tr>
<tr>
<td>Ohno et al. (2010)</td>
<td>Cohort study (retrospective or prospective was not clearly specified)</td>
<td>2b (individual cohort study)</td>
<td>n = 92 none (n=44) HBOT (n=48)</td>
<td>No intervention occurred after initial CS therapy</td>
<td>2.0 atm 60 minutes 13 sessions as salvage treatment after CS therapy</td>
<td>No significant improvement with HBOT</td>
</tr>
<tr>
<td>Pezzoli et al. (2015)</td>
<td>Prospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=44 PO CS (n=21) HBOT + PO CS (n=23)</td>
<td>PO CS as salvage treatment after initial IV CS therapy</td>
<td>2.5 atm 60 minutes 15 sessions + PO CS as salvage treatment after IV CS therapy</td>
<td>Significantly better recovery with HBOT + PO CS</td>
</tr>
<tr>
<td>Psillas et al. (2015)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=45 none (n=30) HBOT (n=15)</td>
<td>2.2 atm 85 minutes 15 sessions as salvage treatment after initial treatment with dexamethasone and piracetam</td>
<td>No further intervention after initial treatment with dexamethasone and piracetam</td>
<td>Significant recovery after HBOT</td>
</tr>
<tr>
<td>Racic et al. (2003)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=115 IV vasodilators (n=64) HBOT (n=51)</td>
<td>IV vasodilators</td>
<td>2.8 atm 60 minutes 15 sessions</td>
<td>Significantly better recovery with HBOT</td>
</tr>
<tr>
<td>Satar et al. (2006)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=54 MT (n=17) HBOT + MT (n=37)</td>
<td>Piracetam, Vit B complex, Vit C, chlorpheniramine -maleate, metoclopramide, dexamethasone, diazepam</td>
<td>2.5 atm 90 minutes 6 sessions followed by 70 minutes for max 15 sessions + MT</td>
<td>No significant improvement with HBOT</td>
</tr>
<tr>
<td>Suzuki et al. (2012)</td>
<td>Retrospective cohort study</td>
<td>2b (individual cohort study)</td>
<td>n=276 IV CS + IT CS (n=102) HBOT + IV CS (n=174)</td>
<td>IV CS + IT CS</td>
<td>2.5 atm 60 minutes 10 sessions + IT CS</td>
<td>No significant recovery with HBOT</td>
</tr>
</tbody>
</table>

MT = Medical treatment
IV = intravenous
PO = per os
Vit = vitamin
LMWH = low molecular weight heparin

for ISSHL were included. Only studies defining ISSHL as a hearing loss of at least 30 dB over three contiguous frequencies and were of unknown cause were included in this study. We excluded animal studies, case reports, case series, and reviews; articles not written in English or Dutch; and studies for which no online full text was available.

All studies were first evaluated based on the
title and abstract. The full text of articles meeting the selection criteria was further reviewed. The Oxford guidelines were used to score the level of evidence of the selected studies. The details of the included studies with their respective Oxford level of evidence can be found in Table 1. A further assessment of the quality of the methodology used in the included studies was conducted with the National Institute of Health Quality Assessment Tools. The quality was defined as poor, fair, or good by 2 authors independently based on the questions in the quality assessment tool. When the authors’ assessments differed, the study was discussed between them and a conclusion was reached. The consensus between the two authors on the quality of the methodology is represented in Table 2.

The search identified 244 studies of which 45 studies were withheld after a review based on the article’s title. After this step, a further 17 studies were excluded based on the abstract. Of the 27 remaining studies, 8 studies were excluded based on the full text. Finally, 19 studies were included in this review. The flow chart depicting the selection of the studies is shown in Figure 1.

Table 2
Methodological quality assessment using the NIH Quality Assessment Tool

<table>
<thead>
<tr>
<th>Study first author (year)</th>
<th>Quality assessment (poor, fair, or good)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capuano et al. (2015)</td>
<td>Good</td>
</tr>
<tr>
<td>Edizer et al. (2015)</td>
<td>Good</td>
</tr>
<tr>
<td>Liu et al. (2011)</td>
<td>Good</td>
</tr>
<tr>
<td>Narozy et al. (2004)</td>
<td>Good</td>
</tr>
<tr>
<td>Pezzoli et al. (2015)</td>
<td>Good</td>
</tr>
<tr>
<td>Psillas et al. (2015)</td>
<td>Good</td>
</tr>
<tr>
<td>Yang et al. (2013)</td>
<td>Good</td>
</tr>
<tr>
<td>Alimoglu et al. (2011)</td>
<td>Fair</td>
</tr>
<tr>
<td>Aslan et al. (2002)</td>
<td>Fair</td>
</tr>
<tr>
<td>Callioglu et al. (2015)</td>
<td>Fair</td>
</tr>
<tr>
<td>Cekin et al. (2009)</td>
<td>Fair</td>
</tr>
<tr>
<td>Fujimura et al. (2007)</td>
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</tr>
<tr>
<td>Ohno et al. (2010)</td>
<td>Fair</td>
</tr>
<tr>
<td>Racic et al. (2003)</td>
<td>Fair</td>
</tr>
<tr>
<td>Satat et al. (2006)</td>
<td>Fair</td>
</tr>
<tr>
<td>Suzuki et al. (2012)</td>
<td>Fair</td>
</tr>
<tr>
<td>Fattori et al. (2001)</td>
<td>Poor</td>
</tr>
<tr>
<td>Cvorovic et al. (2013)</td>
<td>Poor</td>
</tr>
<tr>
<td>Topuz et al. (2003)</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Performing a meta-analysis from the included studies was impossible due to the heterogeneity of the studies.

Results

Various treatment options are available for ISSHL. The efficacy of HBOT was compared to corticosteroids, vasodilators, and multi-drug therapy separately. The details of all studies and their respective Oxford level of evidence are represented in Table 1. The quality assessment of the included studies is shown in Table 2.

HBOT vs corticosteroids

Five retrospective cohort studies investigated HBOT as an adjunct therapy to corticosteroids (CS). Suzuki et al. found a significant effect in favor of the non-HBOT group. Recovery seemed to be significantly higher in younger patients,
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patients without vertigo, and when treatment was initiated earlier. Fujimura et al. observed no significant difference in full recovery between HBOT and non-HBOT groups, whilst there was a significantly higher rate of recovery in the HBOT-group. An initial hearing threshold of less than 80 dB resulted in a better hearing gain. In the study of Alimoglu et al., a significantly higher percentage of responders were seen in the group receiving HBOT and oral CS compared to those receiving only oral CS, HBOT alone, or intratympanic (IT) CS. Treatment was significantly better when HBOT had been started within the first 15 days post-onset. Capuano et al. noted a significantly positive effect of HBOT on the responder rate and on the rate of complete recovery. Furthermore, hypercholesterolemia, time before initiation of treatment, and audiogram type were significant factors influencing the outcome of treatment. Age, hypertension, vertigo, dysthyroidism, diabetes, and smoking seemed to have no significant effect.

Lastly, Callioglu et al. reported no significant difference between HBOT combined with CS versus CS alone. Age and initial hearing loss seemed to have no significant influence, whilst a shorter time before initiation of treatment seemed to have a significantly positive effect.

HBOT vs vasodilators

One retrospective cohort study by Racic et al. and one RCT by Fattori et al. investigated the efficacy of HBOT compared to vasodilator therapy. Both concluded that HBOT led to better hearing gains than vasodilators. Fattori et al. noted that pantonal hearing loss was correlated with higher mean recovery than hearing loss at higher frequencies. Age and sex were not regarded as significant factors, whilst an initial pure tone average above 70 dB correlated with a greater hearing gain.

HBOT vs multi-drug therapy

Several trials compared the efficacy of HBOT in addition to at least two other pharmacological interventions such as CS, vitamins, and ganglion stellate blockers with lidocaine, diazepam, etc. Two RCTs and five retrospective cohort studies were included.

The RCT by Cekin et al. observed an significantly higher success ratio in the HBOT group and concluded that adding HBOT to standard therapy is not necessary. Age did not have a significant effect on patient recovery. Topuz et al. conducted a RCT in which significant differences in treatment efficacy were found at all frequencies except 2000 Hz. Patients with an initial hearing loss of more than 60 dB and patients younger than 50 years showed significantly better treatment results.

In a retrospective cohort study by Satar et al., no significant difference in average hearing improvement was found. Age did not have a significant impact on hearing gain. The retrospective cohort study of Aslan et al. noted a significantly higher mean hearing gain over five frequencies in the HBOT group. Age was found to be a negative predictor for recovery of ISSHL.

Edizer et al. investigated four groups that received different treatments, but no significant difference was found between treatment modalities. Age, tinnitus, vestibular symptoms, and the audiogram curve had no influence on hearing gain, but patients older than 60 years achieved a lesser extent of full recovery. Hypertension and delaying treatment initiation for more than 10 days were correlated with less hearing gain. In a retrospective study by Liu et al., HBOT was observed to have a significantly positive effect only in patients with an initial hearing level of more than 91 dB. Lastly, Narozny et al. concluded that the hearing gains were better at all frequencies in the HBOT group, which also received multi-drug therapy.

HBOT as salvage treatment

A salvage treatment is considered when standard therapy has failed. Five studies investigated the efficacy of HBOT as a salvage treatment for ISSHL. The RCT by Cvorovic et al. showed no significant differences between HBOT combined with IT CS and monotherapy with IT CS. The authors concluded that both treatments could be used as salvage therapy. Patients younger than 60 years in the HBOT group showed a significantly higher average hearing gain, whilst patients with a hearing threshold above 81 dB showed significantly better results in the IT CS group.

Psillas et al. observed a significantly positive effect of HBOT as salvage treatment. The authors found no significant differences between initiating therapy within or after 20 days. Pre-salvage hearing
threshold did not significantly influence the post-
salvage hearing threshold. Age, sex, and vertigo
had no significant influence on hearing recovery.

In a cohort study by Ohno et al.,22 HBOT as a
salvage treatment was compared to a control group
with no salvage treatment. No significant difference
was found between these 2 groups. Severe initial
hearing loss showed a significant improvement on
mean hearing gain. The time to initiating therapy
showed no significant influence on the results.

A prospective cohort study by Pezzoli et al.23
showed a significant difference in mean recovery
in the HBOT group compared to a control group.
Additionally, patients with severe initial hearing
loss showed significantly better results. Age and
delayed treatment initiation did not seem to have a
significant effect in this study.

Finally, Yang et al.24 investigated the efficacy of
HBOT as salvage treatment in their retrospective
cohort study. The group in which HBOT was
combined with IT CS showed the highest percentage
of patients with a recovery of over 15 dB and a
greater gain in the frequency of 250 Hz.

Discussion

Hyperbaric oxygen therapy is frequently used for
a large variety of diseases and to control many
different symptoms. Nevertheless, the exact
mechanism of and a universal treatment protocol
for the different pathologies is still lacking. Even
more striking, there is not enough evidence to show
that HBOT is even an effective treatment option
for many diseases or symptoms. In this review, we
investigated the use of HBOT for ISSHL.

Treatment options for ISSHL are difficult to study
because of the high rate of spontaneous remission
(45-60%).25 A globally standardized treatment for
ISSHL has yet to be implemented as demonstrated
in the studies included in this review, where the
standard treatments greatly differed.

The current literature shows that HBOT mono-
therapy results are better than vasodilators (2/2
studies, 100%).2,13 HBOT as adjunct therapy with
CS had a positive effect on hearing gain in three
out of five studies (60%) when it was compared
to a CS monotherapy.9-12 Of these three studies,
one showed a positive effect on hearing gain, but
no significant effect on the total recovery rate.9 In
the two remaining studies, however, no significant
improvement in hearing gain or total recovery rate
was found.9,12

When HBOT is used in addition to a multi-
drug treatment, four out of seven studies (57%)
demonstrated a significantly positive effect.6,17-22 In
one of these four studies, the significantly positive
effect was only seen in patients with very severe
hearing loss (> 91 dB).18

Lastly, three out of five studies (60%)
demonstrated a positive role for HBOT as a salvage
treatment.20-24 Based on the NIH Quality Assessment
Tool, the two studies concluding that there was no
significant difference between treatment modalities
were of a lesser methodological quality than the
studies that concluded a significant difference in
favor of HBOT. Thus, when the methodological
quality is taken into account, there is a stronger
argument in favor of HBOT as a salvage treatment
for ISSHL.

The quality assessment of the studies
investigating HBOT as an adjunct therapy with CS
and the studies comparing HBOT with multi-drug
treatment or with vasodilators did not affect the
conclusions.

This modest tendency towards a positive effect
of HBOT in all subcategories suggests a role for
HBOT in the treatment of ISSHL. However,
further investigation in specific patient populations
with a standard protocol for the pressure, time,
and frequency of the treatment is necessary.
Furthermore, the risk of side effects, high cost, and
time-consuming daily sessions with the associated
absence from work to receive HBOT in comparison
with medical treatment should also be considered
in the selection of the most appropriate treatment
for each individual patient.

Factors that could potentially influence the
outcome of treatment for ISSHL were also analyzed
in the studies. First, six studies concluded that age
had no significant effect on hearing gain, while five
studies reported a significant influence.2,3,8,11,14-17,20,21,23
Secondly, four out of eight studies reported a
significantly positive effect when treatment was
initiated soon after symptoms began.3,8-11,14-17,20,21,23
Hearing gain might be higher when treatment
is initiated within two weeks after the onset of
symptoms. Lastly, nine studies discussed the effect
of the initial hearing loss before treatment, five
of which concluded that more severe hearing loss
correlated with a greater hearing gain, which is
also seen in the natural evolution of ISSHL without treatment.  

Conclusion

There is a modest tendency towards a positive effect of HBOT in ISSHL. However, further investigation in specific patient populations using a protocol with a standard pressure, time, and frequency of the treatment is warranted. Age, initial hearing loss, and time between the onset of the symptoms and beginning treatment could influence the outcomes of hearing gain in patients with ISSHL. Furthermore, the risk of side effects, high cost, and time-consuming daily sessions with the associated absence from work due to HBOT should be considered in the selection of the most appropriate treatment for each individual patient.

References


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