

Critical Review:

Does hyperbaric oxygen therapy create greater hearing gains when used as an adjunct therapy to pharmacologic agents for idiopathic sudden sensorineural hearing loss in adults than pharmacologic agents used alone?

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This critical review examines the evidence regarding the effect of hyperbaric oxygen therapy (HBOT) used as an adjunct therapy to pharmacologic agents for idiopathic sudden sensorineural hearing loss in adults compared to the use of pharmacological agents alone. A search of the literature yielded 6 papers with study designs including retrospective cohort studies, case study, and randomized control trials. Overall the literature reviewed supports the use of hyperbaric oxygen therapy as an adjunct therapy for idiopathic sudden sensorineural hearing loss in adults. Clinical implications and future research suggestions are provided.

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a greater than 30 dB sensorineural hearing loss occurring in at least three consecutive frequencies over a period of up to 72 hours (Cvorovic et. al., 2013, Imsuwansri et. al., 2012). ISSNHL affects 5 to 20 per 100,000 individuals (Cvorovic et. al., 2013). ISSNHL is not a distinct disease, but rather a clinical presentation of diverse and uncertain etiologies (Fujimura et. al., 2007, Liu et. al., 2011). Due to the various causative factors many different regimens have been employed as treatment including vasodilators, anticoagulants, corticosteroids, vitamins, plasma expanders, histamine treatment, diet restrictions, antiviral agents, batroxbin, contrast media, stellate ganglion blocks, carbogen treatment, and hyperbaric oxygen therapy (HBOT) (Fujimura et. al., 2007).

Oral steroids are most commonly used to treat ISSNHL to increase circulation to the inner ear but due to their side effects their use may be limited (Alimoglu et. al., 2010). Intratympanic steroids can be injected directly into the ear most often in patients whom oral steroids have not been successful (Imsuwansri et. al., 2012). Although steroids have been most widely used for treatment, overall there is no consensus regarding standard treatment modalities for ISSNHL (Liu et. al., 2011).

Hyperbaric oxygen therapy (HBOT) was first used for the purpose of increasing blood and tissue oxygen to repair damaged tissues in the 1960's for various diseases (Fujimura et. al., 2007). HBOT is the administration of 100% oxygen to a patient under pressures higher than 1 atmosphere absolute inside a

pressure chamber (Korpinar et. al., 2011). In the late 1970's HBOT was first used for ISSNHL (Fujimura, et. al., 2007). Since then, HBOT has gained popularity as treatment for ISSNHL in combination with pharmacologic agents, but still lacks widespread approval (Liu et al., 2011).

Objectives

The primary objective of this paper is to critically review the literature on hyperbaric oxygen therapy as an adjunct therapy to pharmacologic agents for idiopathic sudden sensorineural hearing loss.

Methods

Search Strategy

The sources for this paper were collected using PubMed, CINAHL, and Medline - OVID. The following search strategies were employed:

[Hyperbaric oxygen therapy] or [hyperbaric] AND [idiopathic sudden sensorineural hearing loss] OR [sudden sensorineural hearing loss] OR [sudden hearing loss] OR [sudden deafness].

Selection Criteria

Studies selected for inclusion in this critical review had to involve an investigation into the effects of hyperbaric oxygen therapy as an adjunct therapy to pharmacologic agents in sudden sensorineural hearing loss of adults. No limits of publication year or geographical demographics were placed on the search.

Data Collection

The literature search yielded 6 articles that met the aforementioned criteria: retrospective cohort studies (3), randomized control trials (2), and case study (1).

Results

Retrospective Cohort Studies

The following articles are retrospective cohort studies. Retrospective cohort studies are dependent upon the record keeping of data collectors in the past and therefore cannot control the assessment measures or level of documentation provided. This is problematic because it hinders the researchers' abilities to make comparisons across patients and generalize these results to the general public. This type of study is appropriate for the research question because it looks back at past patients who either did or did not receive HBOT with pharmacologic agents instead of denying treatment to anyone in the studies which may be unethical.

Alimoglu, Inci, Edizer, Ozdilek, and Aslan (2011) examined the files of 217 patients with ISSNHL of 219 ears. Patients were divided into four treatment groups depending on treatment received: (1) oral steroid (prednisolone or equivalent for 3 weeks), proton pump inhibitors (lansoprazole or pantoprazole) and low salt and low carbohydrate diet; (2) oral steroid (same protocol as steroid group) and HBOT (20 sessions); (3) intratympanic steroid (dexamethasone 2 days a week for 3 weeks); (4) and HBOT (same as above). Groups were somewhat unbalanced due to the retrospective nature of the study varying in size from 43-61.

One way ANOVA, Kruskal-Wallis, Chi square, and Mann-Whitney *U* tests were used which are appropriate statistical analyses but they were not fully reported in the study. Mean gain of the oral steroid plus HBOT group was significantly better than the three remaining groups. Twenty-six patients (87%) in the oral steroid and HBOT group completely recovered while no more than 11 (64%) recovered in the remaining groups.

Although the statistical reporting was unclear, this study represents a well-designed retrospective cohort study appropriate for the current question. One limitation is that it was unclear if only the oral steroid plus HBOT group was provided with proton pump inhibitors and advice regarding a low salt and low carbohydrate diet or if all groups obtained this added treatment. Overall, the results of this study provide a suggestive level of evidence that hyperbaric oxygen therapy used in conjunction with steroids have an added benefit than steroids used alone as treatment for ISSNHL.

Fujimura, Suzuki, Shiomori, Udaka, and Mori (2007) examined the medical records of 130 patients with ISSNHL. Sixty-seven patients received HBOT (10 sessions), steroids (dexamethasone for 12 days), and hydrocortisone sodium succinate (14 days). Sixty-three

patients received steroid treatment alone (dexamethasone for 12 days).

Appropriate Chi square test and a two-tailed Student's *t* test were used to statistically analyze the data. Recovery rates (improvement in hearing level ≥ 30 dB or better) in the HBOT group were significantly higher than the steroid group. Patients with initial hearing loss levels of ≥ 80 dB experienced hearing improvement rates that were significantly higher in the HBOT group than in the steroid group. Patients with initial hearing levels of < 80 dB did not have statistically significant hearing improvements compared to other groups. Reported side effects in the HBOT group were as follows: 25% manifested eustachian tube dysfunction, 13% developed otitis media with effusion, myringotomy was required in 6%, and 2% required tympanotomy tube insertion to complete treatment. There were no reported side effects in the other groups.

It should be noted that HBOT group members not only received HBOT in addition to steroids but also received hydrocortisone sodium succinate for 14 days. The added effect of this treatment cannot be teased apart from the treatment of HBOT. As well, no analysis of the side effect or patient history data was provided. Treatment protocols and outcome measures were carefully reported in this study. Overall, the results of this study provide a suggestive level of evidence that hyperbaric oxygen therapy in addition to steroid treatment is beneficial for ISSNHL.

Liu, Kang, Lee, Huang, Liu, Su, Kao, Chu, Chen, and Wang (2011) retrospectively examined the medical charts of 465 patients with unilateral ISSNHL. Among these patients, 76 received steroids alone (betamethasone intravenously for 4 days, prednisolone orally for 8 days); 277 received steroids (same protocol) and plasma expander dextran (intravenously for 6 days); and 112 were treated with HBOT (10-20 sessions), steroids, and dextran.

Pure-tone audiometric results administered before (day 0) and after (day 180) treatment were compared across patients. Appropriate statistical analyses included ANOVA, Pearson chi-square test, and Fisher's exact test as a *post hoc* test.

Patients who initially presented with severe (71-90 dB) or less-severe (less than 70 dB) hearing loss had no additional benefit with HBOT treatment. Patients with initial profound hearing loss ≥ 91 dBHL had significantly greater gains in the HBOT group than the steroid or steroid-dextran group. No significant differences were found for patients in the steroid group compared to the steroid-dextran group.

Although the sample size of this study is large the treatment groups were unbalanced, which is a weakness. The results of this study provide a compelling level of evidence for applying HBOT with steroids for profound ISSNHL.

Case Study

The following is a case study. Case studies often have extremely small sample sizes due to their design. Because of their decreased sample sizes results are difficult to generalize to the general public. Case studies may only have one researcher who collects data and this may lead to bias in data collection and influence results. Case studies may be appropriate as supporting research to other higher level evidence or to direct further research regarding this research question.

Domachevsky, Keynan, Shupak, and Adir (2007) investigated two individual cases. The first case is a 49-year-old man with moderate mid-frequency hearing loss and increased pressure sensation in his left ear. He was prescribed oral steroids (prednisone; 2 times daily for unknown period) and HBOT (2 sessions) 3.5 hours after onset. Resolution of the sensation of pressure resolved after first treatment of HBOT. Audiometry revealed after conclusion of the second treatment that there was a complete resolution of hearing loss. Second case, a 17-year-old female with moderate low-frequency hearing loss, increased pressure, and tinnitus in her right ear. A single episode of vertigo was reported. She was prescribed oral steroids (prednisone; 2 times daily for unknown period) and HBOT (1 session). Audiometric results revealed normal hearing after treatment although specific timing of testing was not specified. The sensation of increased pressure resolved but tinnitus persisted to a lesser degree.

A limitation of this study is that limited medical information was provided regarding the patients' onset and treatment. Symptoms varied from case to case suggesting differences between patients' conditions. The steroid prescriptions and audiometry testing results were not fully reported. Although the results of these two patients are clinically compelling, in that, their hearing losses were completely resolved, the strength of the evidence must be considered equivocal given the design of the study and limited information reported.

Randomized Control Trials

The following are two randomized control trials (RCTs). RCTs may inherently lack external validity, as the results may not be generalizable to the real world given that some studies include procedures that are difficult to achieve outside the study. Additionally, the RCT design does not allow all patients to receive all

possible treatments, which can pose ethical challenges. Nevertheless, RCTs provide a high level of control allowing for a high level of confidence in the findings.

Cekin, Cincik, Uhubil, and Gungor (2009) examined 59 ears of 57 patients with ISSNHL. Subjects were randomly allocated into a study group comprised of 38 ears of 36 patients treated with HBOT (10 sessions) plus steroids (prednisolone for 3 weeks) and famotidine; and a control group comprised of 21 patients with unilateral hearing loss treated with steroids alone. Appropriate nonparametric Wilcoxon signed rank test and the Mann-Whitney *U* tests were used to analyze the unbalanced data, although not fully reported.

Participants were evaluated with pure tone audiometry every second day during the therapy period. Complete and moderate hearing improvement was accepted as the criteria to be determined a successful outcome. The success rate of the study group (79%) was greater than the success rate of the control group (71%), but this rate was not statistically significant ($p > 0.05$). The results of this study do not provide clear evidence that a combination of HBOT with steroids does offer improved outcomes compared with steroids alone in ISSNHL.

Topuz, Yigit, Cinar, and Seven (2004) studied 51 patients with ISSNHL who were randomly divided into two groups. Twenty-one patients received oral steroids (prednisone; for 2 weeks), plasma expander rheomacrodex (infusion for 6 hours for 5 days), diazepam (twice daily for unknown period), pentoxifylline (twice daily for unknown period), and salt restriction (for unknown period). The other 30 patients received the same basic treatment as previously noted with the addition of HBOT. Appropriate Student's *t* test, Mann Whitney *U* test, and chi-square test were used to evaluate the data.

Audiological assessments of patients were performed before and after treatment. The mean hearing gains at 250, 500, 1,000, 2,000, and 4,000 Hz were compared between the two groups. Statistically significant improvement was detected at all of the frequencies except 2,000Hz in the HBOT plus steroid group compared to the steroid only group. The groups were further divided according to age and when age groups and mean hearing gains were compared the average mean hearing gain was found to be significantly higher in patients younger than 50 in comparison to patients older than 50 years. Patients' outcomes of the two groups were also compared depending on initial level of hearing loss. It was found that individuals with initial hearing levels ≥ 60 dB had significantly higher mean

hearing gains at the five frequencies examined than patients with initial hearing levels <60 dB.

The study fails to report the length of treatment for some of the prescriptions and diet restrictions. The study also has significantly fewer patients in the HBOT group than in the steroid group with profound hearing loss (4, 10 respectively). The sample size when the treatment groups were further divided according to hearing loss level and age reduced significantly. These components weaken the validity of the results. This study provides a suggestive level of evidence that the significant gains may be obtained by using HBOT in conjunction with pharmacologic agents and diet restrictions in patients with initial hearing levels >60 dB and younger than 50 years old.

Discussion

The evidence, with fair consistency from the studies reviewed, is highly suggestive of the use of HBOT in combination with pharmacologic agents for improved hearing outcomes in patients with ISSNHL. Within each study limitations were recognized but did not overpower the results reported.

Although all the studies examined the use of oral steroids with HBOT, some studies also included additional variables such as proton pump inhibitors and diet restrictions (Alimoglu et. al., 2011); famotidine (Cekin et. al., 2009); hydrocortisone sodium succinate (Fujimura et. al., 2007); plasma expanders (Liu et. al., 2011); and diazepam, pentoxifylline, and diet restrictions (Topuz et. al., 2004). The addition of these variables decreases the validity of comparing results across groups in the studies. Additionally, HBOT sessions vary in length, frequency, and intensity across studies. Although all the studies restrict their patients to those that were treated within 30 days of onset, the dates of initial treatment in relation to onset of symptoms varies across studies. The nature of idiopathic sudden sensorineural hearing loss lends itself to a heterogeneous population, a challenge of research in this area is to restrict the population enough to determine the conditions in which treatment is most beneficial (i.e. date of onset, date of treatment initiation, severity, additional symptoms – vertigo).

All six studies (Alimoglu et. al., 2011; Cekin et. al., 2009; Domachevsky et. al., 2007; Fujimura et. al. 2007; Liu et. al., 2011; and Topuz et. al. 2004) used pure tone audiometry as pretreatment and outcome measures. The timing of pure tone audiometry administered post-treatment varied depending on the study.

Adverse effects from HBOT are limited and minimal occurrences were reported in the literature (Fujimura et. al., 2007). Although the side effects related to HBOT are limited, they still should be considered along with patient history of these issues when deciding on treatment. The evidence provides clinically compelling documentation of positive outcomes with the addition of HBOT to pharmacologic treatment. Due to the limited adverse side effects of HBOT and compelling positive outcomes stemming from HBOT in the literature it is recommended clinically as an additive therapy for the treatment of ISSNHL.

There is a trend in the literature that HBOT in conjunction with pharmacologic agents provides improvements in hearing thresholds of those with ISSNHL. Ultimately, significant improvements in hearing thresholds were revealed in the HBOT groups of all studies, except in Cekin et. al. (2009) in which improvement was noted but not statistically significant. In Fujimura et. al. (2007), statistically significant improvements in the HBOT group were only noted in patients with initial hearing loss >80 dB. In Topuz et. al. (2004), statistically significant improvements in the HBOT group were only noted in patients with initial hearing loss >60 dB. These results suggest that further research needs to be conducted analyzing groups of individuals with varying severities of ISSNHL. Collectively the studies examined offer a suggestive level of evidence supporting the use of HBOT in conjunction with pharmacologic agents for ISSNHL.

Clinical Implications

The moderate level of evidence provided by this critical appraisal of studies supports the use of HBOT in conjunction with pharmacologic agents in ISSNHL especially in patients with severe to profound hearing loss. Although reports of adverse side effects due to HBOT are limited, professionals should carefully examine patients' history of these issues before recommending HBOT. Further controlled research is needed to provide more definitive guidelines in regards to side effects, intensity, frequency, and duration of HBOT treatment to ensure efficacy.

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