Int. Adv. Otol. 2013; 9:(3) 372-380

ORIGINAL ARTICLE

Including Hyperbaric Oxygen Therapy in Medical Treatment Protocol in Sudden Hearing Loss is not Useful

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Purpose: The purpose of this study is to research the effect of including the hyperbaric oxygen therapy in medical treatment protocol in sudden hearing loss (SHL).

Materials and Methods: Seventy-three patients suffering from SHL with a loss of 30 dB and over in three successive frequencies, who were treated in our clinic were put into two groups, were included in the retrospective study. Thirty-four patients in the first group were given papaverine and corticosteroid treatment. Antiviral therapy was added to 12 patients within this group, due to a history of the existence of upper respiratory infection (URI), which had been present over the previous 14 days. Thirty-nine patients in the second group were given papaverine and corticosteroid treatment, and antiviral therapy was added to 18 patients with a history of URI that had been present over the previous 14 days. Between the 6th and 16th days, patients received hyperbaric oxygen therapy (HBOT). An audiological examination of patients was carried out prior to treatment, and at five days, seven days, one month, and three months after the treatment. Patients in both groups were compared in terms of hearing gain.

Results: In a comparison of the two groups, it was determined that both groups were correlated with each other in terms of age (p=0.55), gender (p=0.39), seasonal distribution (p=0.39), duration of hearing loss (p=0.51), presence of tinnitus (p=0.48), and vestibular symptom existence (p=0.82), and there was no difference between groups. A statistically significant change was determined in hearing following treatment in the first group, in comparison to the pre-treatment period (p=0.01). A statistically significant change was also determined in hearing following treatment in the second group, in comparison to the pre-treatment period (p=0.01).Following the comparison of hearing gain of both groups, a no statistically significant difference could found (p=0.89)

Discussion: It is believed that many factors exist in the etiology of SHL. Among those, vascular, immunologic, and viral factors were discussed in particular in many studies, and the role of these factors in etiology was not elucidated, although they were frequently regarded as responsible for the development of SHL. Therefore, combining the agents directed to vascular, immunologic, and viral etiology in SHL treatment became an acceptable approach. The combined treatment modality based on the principle of simultaneous usage of more than one agent in SHL treatment was also supported with the results of our study, and is thought to be a highly effective practice.

Conclusion: It is believed that the treatment protocol including papaverine, corticosteroid, antiviral agents, and HBOT have a significant effect on the results of SHL treatment. Although including HBOT in medical treatment was observed to provide a hearing gain within the group, following the comparison of both groups, it was determined that it did not cause a statistically significant difference on the results, and more comprehensive and prospective studies are required regarding this subject.

Submitted : 19 February 2013 *Revised : 28 July 2013* *Accepted : 25 September 2013*

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Introduction

Sudden hearing loss (SHL) was first defined by De Kleyn[1] in 1944 as the development of 30 dB or higher sensorineural hearing loss in at least three consecutive frequencies over less than a three day-period. In some recent studies it has been stated that the hearing loss should be accepted as SHL even if it is less than 30 dB and over three successive frequencies[2-5]. It has been stated that a spontaneous improvement can be seen in 32-65% of the cases.[6]

The patient's age, presence of vertigo, the degree of hearing loss, configuration of the audiogram, and the time between the inception of sudden hearing loss and the onset of the treatment are among the factors that affect the prognosis.[7-9]

The etiology of SHL cannot be detected in 88% of the patients.[10] The causes such as vascular insufficiency, autoimmune factors, viral infections and circulatory disorders have been widely discussed in the etiology.[8,11,12]

Agents used in the treatment are generally directed towards improvement of micro-circulation and suppression of the autoimmune damage by decreasing inflammation and edema. In SHL treatment, hemodilution, carbogen gas inhalation, plasmapheresis, thrombolytics, urographin, and many other agents have been used in addition to widely used vasodilators, steroids, antivirals and hyperbaric oxygen therapy (HBOT).[13,14] Usually more than one treatment modality is administered in SHL due to the fact that the etiology of the disease is uncertain.[15]

Materials and Methods

In our study, 89 patients who we hospitalized in our clinic with the diagnosis of SHL were retrospectively analyzed. A total of 16 patients who could not receive corticosteroids for any reason, could not tolerate papaverine treatment, could not be followed up or aborted the treatment were excluded from the study. The study was carried out with the remaining 73 patients. The cases were assessed with their medical history, physical examination, laboratory and audiological examinations, and temporal magnetic resonance imaging. Following the audiological examination on the day of admission, the treatment was initiated on the same day to the patients who had sensorineural hearing loss 30 dB or greater in three successive frequencies.

Patients who were included in our study were divided into two groups:

1st group: All patients received papaverine and corticosteroids. Antiviral therapy was added if an upper respiratory tract infection (URTI) history had been present over the previous 14 days.

2nd group: All patients received papaverine, corticosteroids and hyperbaric oxygen therapy. Antiviral therapy was added if URTI history had been present over the previous 14 days.

Papaverine hydrochloride 300 mg/day, 250 ml in 0.9% saline, and 1 mg/kg/day intravenous methylprednisolone were applied to 34 patients in the first group for five days. On the sixth day, oral methylprednisolone tablets were used, tapered by 10 mg every other day and continued in a manner that would end within 14 days. Acyclovir 200 mg tablets, 1 x 5 tablets/day was given to 12 patients for a period of 5 days if they had an URTI history over the previous 14 days.

The medical treatment protocol for 39 patients in the second group was the same as the one in the first group. In addition to papaverine hydrochloride and methylprednisolone, Acyclovir was applied to 18 patients with URTI history. Moreover, in addition to the medical treatment, HBOT with 2.5 ATM pressure was applied to the patients in this group between the 6th and 16th days, for a total of 20 sessions (a total of 50 hours with each session lasting 2.5 hours).

Both groups were assessed in terms of age, gender, duration of the hearing loss, tinnitus, vestibular symptoms, and the seasons in which the patients were admitted to the hospital. Audiological examinations were repeated on the fifth and seventh days, and in the first and third months. Hearing gain compared to the pre-treatment audiometric values and the audiometric test at the last follow up were recorded in both groups. In the first (in hospitalization, before treatment) and the last (in the third month) audiological examination results, bone conduction measurement values were taken and the hearing gains were calculated separately in each group.

The difference between the two groups in terms of age, gender, seasonal distribution, duration of hearing loss, presence of tinnitus and vestibular symptoms were analyzed statistically. Furthermore, the difference between the two groups in terms of hearing gain was also statistically analyzed.

The SPSS program (Statistical Package for Social Sciences for Windows 10.0) was used for the statistical analyses. Paired sample t-test and Spearman's Rho test were used in addition to descriptive statistical methods (average, standard deviation). The results were assessed at a confidence interval of 95% and at the significance level of $p<0.05$.

Results

There were 34 patients in the first group. They consisted of 19 women and 15 men between the ages of 16 - 79 years with an average age of 50.7 (SD ± 14.3) years. The second group consisted of 39 patients, 16 women and 23 men between the ages of 28 - 63 years with an average age of 45.7 (SD ±10.4) years.

The average duration to the beginning of the therapy (the duration of the hearing loss) was 6.6 days (SD ± 5.3) in the first group while it was 4.5 days (SD ± 5.8) in the second group.

In the first group, tinnitus was present in addition to the hearing loss in 28 (82%) patients while there were 34 patients with tinnitus (87%) in the second group. In the first group 12 (35%) patients had vestibular symptoms and in the second group only 5 patients (12%) vestibular symptoms.

Analysis of the seasonal distribution showed that 13 patients admitted in winter, 10 patients admitted in spring, 8 patients admitted in fall and 3 patients admitted in summer in the first group. In the second group, the numbers of the patients were 14, 13, 6 and 6 for their admission in winter, fall, spring and summer, respectively. When the patients of the two groups were taken together, 38% of the patients admitted in the winter, 29% admitted in fall, 24% admitted in spring and 9% admitted in summer.

HBOT started 6-16 (minimum-maximum) days after the onset of the hearing loss (average 11 days). In the first group, erythrocyte sedimentation rate (ESR) was high in 12 (35%) patients, the fibrinogen level was high in 12 (35%) patients, the thyroid function tests (TFT) were abnormal in 12 (35%) patients, the white blood cell (WBC) count was high in 11 (32%) patients, 6 (17%) patients were anemic, 20 (58%) patients had abnormal lipid profiles, 11 (32%) patients had high blood glucose levels, 6 (17%) patients were positive for ANA and the serum folic acid levels were low in 3 (8%) patients.

In the second group, 14 patients (35%) had elevated ESR, 8 (20%) had high fibrinogen levels, 11 (28%) had abnormal TFT, 10 had 26(%) high WBC counts, 3 (7%) had anemia, 25 (64%) had abnormal lipid profiles and 10 (26%) had high blood glucose levels.

In our study, a total of 73 patients were administered papaverine in both groups (34 patients in the first group and 39 in the second group), and papaverine-induced complications did not develop such as premature heartbeat, atrioventricular block, xerostomia, constipation, elevation of liver enzymes, fatigue, dizziness, somnolence, headache or flushing.

In the first group, the mean hearing thresholds of the patients who were given papaverine, corticosteroid and antiviral therapy at 500, 1000 and 2000 Hz, are presented in Table 1.

In the second group, the mean hearing thresholds of the patients who were given papaverine, corticosteroid, antiviral therapy and hyperbaric oxygen therapy at 500, 1000 and 2000 Hz are given in Table 2.

In the statistical comparison of the two groups performed with the paired sample t-test, it was determined that both groups were correlated with each

Table 1. Audiological examination results of the first group

	BC hearing threshold averages (dB)
Pre-treatment	BC1 51.4
5th day	BC2 59.2
7th day	BC3 42.7
1st month	BC4 40.0
3rd month	BC5 35.4
p value	0.01

BC: Bone conduction

Table 2. Hearing measurement values of second group

	BC hearing threshold averages (dB)
Pre-treatment	BC1 52.8
5th day	BC2 52.1
7th day	BC3 44.2
1st month	BC4 36.3
3rd month	BC5 31.9
p value	0.01

other in terms of age (p=0.55), gender (p=0.39), seasonal distribution (p=0.39), duration of hearing loss (p=0.51), presence of tinnitus (p=0.48) and the presence of vestibular symptoms (p=0.82), and there was no difference between the groups.

Hearing gain average of the first group (the difference of the bone conduction averages) was 16 dB, and hearing gain average of the second group was 20.09 dB. (Figure 1)

A comparison of bone conduction gains of the two groups was done using Spearman's rho test. A statistically significant difference could not be detected following the comparison of bone conduction values before, during, and after treatment between the first and second groups with the assistance of Mauchly's sphericity test (p=0.89). However, a significant intra-group improvement was detected in both groups. A statistically significant improvement in hearing was also detected after the treatment in the first group when compared to the pre-treatment period (p=0.01). A statistically significant improvement in hearing was also detected after the treatment in the second group when compared to the pre-treatment period (p=0.01). Although including HBOT in medical treatment provided an intra-group gain, following the comparison of two groups it was determined that it did not create a statistically significant difference in the results (p=0.89).

Discussion

Since there is no anastomosis among the systems maintaining the blood supply to the inner ear, the inner ear is prone to develop hypoxia, anoxia or a toxic condition.[16]

Although many studies have been carried out on SHL pathophysiology, its etiology has not yet been fully clarified and three most common areas of focus have been vascular conditions, immunological factors and viral infections. Many studies focused on the effects of these factors [8,12]

Although some studies in literature have shown that women had SHL more frequently, [13,17] some others claimed the opposite.[18,19] Hultcrantz et al.[20] reported that females and males had different ABR responses (women had shorter latency times), postmenopausal women who had hormone replacement therapy had better hearing levels compared to the ones who did not have any replacement therapy. The authors emphasized the protective effect of estrogen on hearing. In our study, a small male preponderance was seen (38 males, 35 females).

The time to initiation of the treatment is one of the most important prognostic factors in SHL. It has been reported that the shorter the time period between the onset of the hearing loss and the onset of treatment, the better is the outcome.[13, 21-23] It is usually accepted that a better outcome is obtained if treatment begins in the first 7-10 days of SHL. [24]

Zadeh et al.13 reported recovery in 75% of the patients when treatment was started within three days while this ratio was 67% if treatment started after 3 days. In our study, the mean time to the onset of the treatment was 5.5 days.

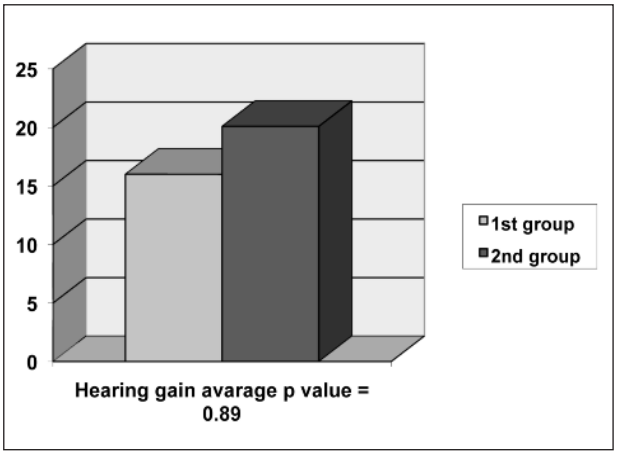

Figure 1. Hearing gain average of the first group (the difference of bone conduction averages) was 16 dB, and hearing gain average of the second group was 20.09 dB.

Some studies in the literature claimed that right ear was affected more by SHL 13 while some others claimed that there was a preponderance for the left ear.[25] However, no studies up to date have investigated the relation of the affected side on etiopathogenesis. In our study, the right ear was affected in 45 of the 73 patients and the left ear was affected in 28 patients.

A number of studies have investigated the relation of seasons and SHL. Megighian et al.[26] reported cyclic changes in the prevalence of SHL in relation to the seasons. On the other hand, some others reported the opposite, and stated that the seasons or the weather conditions had no effect on the SHL prevalence.[27] Wilson et al.[28] reported a seroconversion for mumps, rubeola, VZV, CMV and influenza B viruses in 1983, and the disease occurred more frequently in spring. Another study performed in Taiwan suggested a seasonal relation and reported that SHL occurred most frequently in winter.[29] The seasonal analysis of our patients showed that 27 patients admitted in winter, 37 patients admitted in spring and 9 patients admitted in summer, and most of our patients admitted in spring. Viral infection is one of the most emphasized factors in SHL etiology and the relation between the seasonal transitions and SHL cases may support the viral infection hypothesis [26-29]

Tinnitus is a more common symptom in SHL patients when compared to vertigo.[30] In our study, there was tinnitus in 62 of 74 (84%) patients, and vestibular symptoms in 17 (23%) patients.

DM and HT which cause microangiopathy affect the prognosis adversely and are seen more frequently in SHL patients.[8] In addition, systemic diseases such as DM have been suggested as risk factors for SHL. [21] Microangiopathy due to diabetes may cause decreased cochlear blood flow and eventually hearing loss. In our study, 2 of 73 patients had DM history, however 21 had high blood glucose levels on their inpatient laboratory investigations. Those patients were later consulted with the Endocrinology Clinic and their systemic steroids were administered under the supervision of the endocrinologists. None of the patients had complications due to steroid treatment.

A literature review on SHL etiology revealed the following factors in the etiology of SHL: idiopathic factors in 71%, infectious diseases in 12%, otological diseases in 4%, trauma in 4%, vascular disease in 2-3%, neoplastic factors in 2%, and other factors in 2%.[31]

Various etiological factors raised different treatment modalities. Vasodilator agents are given to improve vascular disorders, steroids are given for their anti-inflammatory, anti-edema and immunosuppressive effects, antiviral agents are given to treat the viral infections. Aforementioned drugs are the most frequently used agents in SHL treatment. Apart from these frequently used treatment modalities, HBOT has been used in SHL treatment, alone or in combination with other treatment modalities. The general opinion is that a combination of the treatment modalities and administering more than one agent is more effective. [7,15]

Papaverine hydrochloride, histamine, nicotinic acid and lidocaine hydrochloride may be preferred for the purpose of vasodilation. In our study, we administered papaverine HCL to all of our patients due to its vasodilator effect. Papaverine shows its effect by inhibiting the phophodiesterase enzyme and increasing intracellular c-AMP concentration and causing a spasmolytic and anticholinergic effect. It also has a direct effect on the smooth muscles causing a decreased tone and vasodilation. It may exert the same effect on coronary and intracranial arteries as well as pulmonary artery and the arterioles. It may cause a mild sedative effect at high doses. It is contraindicated in case of hypersensitivity against the drug and in the presence of atrioventricular block, acute myocardial infarction, liver enzyme abnormalities and glaucoma. Side effects such as tachycardia, premature cardiac beats, atrioventricular block, xerostomia, constipation, elevation of the liver enzymes, fatigue, dizziness, somnolence, headache and flushing may appear during its use.[32]

In their experimental study, Suga et al.[33] determined that cochlear blood flow minimally increased at a rate of 71% after papaverine application. It was stated in experimental and clinical studies that arterial vasospasm can be prevented with the application of papaverine.[32,34]

A study carried out on diabetic patients with SHL by Ensari et al.[32] claimed that papaverine HCL was a safer medicine in terms of not affecting blood sugar levels when compared to the frequently seen symptoms of steroids and histamine. Papaverine HCL, as seen in our study, is a safe and effective treatment method. Papaverine application may cause side effects as such tachycardia, arrhythmia, flushing, headache, and elevation of the liver enzymes. A close follow-up of the patient in terms of blood pressure, pulse, and the number of breaths/per minute, and a slow infusion of the drug can prevent these possible side effects. Papaverine was applied to all patients in our study, and no serious complications developed.

It has been stated that corticosteroid treatment started as soon as possible following the occurrence of symptoms of SHL is highly effective, the Annexin A1 molecule in the cochlea becomes a target for glucocorticoids, and glucocorticoids can play a role as a major mediator in the anti-inflammatory effects.[35] Steroids are stated to increase cochlear blood flow in addition to suppressing inflammation.[36]

As the inner ear can be seen as the primary target in the immune system, it can be secondarily affected in the course of a systemic autoimmune disease. It has been stated in many studies that the presence of auto-antibodies developed against the inner ear antigens may cause this disease, and antibodies develop in the inner ear against 28, 42, 68 kDa inner ear proteins.[37,38] Steroids also have a direct therapeutic effect on the immunological mechanism blamed in the etiology. Furthermore, eliciting a response to steroids used in SHL treatment may cause an association with the autoimmune etiology.[39]

Another method used in SHL treatment is hyperbaric oxygen therapy. Hyperbaric oxygen therapy has been used in the treatment of a number of otorhinolaryngologic diseases (acute acoustic trauma, malignant external otitis, Meniere's Disease, maintenance of head-neck flaps, chronic inflammations, sudden hearing loss, migraines and similar headaches) in addition to air or gas embolisms, carbon monoxide poisoning and necrotizing soft tissue diseases.[40,41]

Due to these effects, HBOT is also used in SHL treatment. HBOT basically regulates microcirculation, inhibits neutrophil adhesion molecule induced by ischemia-reperfusion conditions, and demonstrates its effect on the nitric oxide mechanism. Nitric oxide is known to increase cell strength in the cochlea.[14,42]

One study stated that HBOT caused an improvement in pure-tone hearing levels of patients with SHL, and it can be attempted as a recovery treatment in patients not responding to medical treatment.[14]

In another study carried out with HBOT, patients were divided into two groups and HBOT was administered to one group in addition to standard medical treatment, and the standard medical treatment was applied alone to the other group. A significant difference between two groups could not be found in terms of the results. As the cost of HBOT is high, it has been stated that it can be appropriate to be used only in patients who present contraindications for medical treatment.[43] Another study stated that HBOT supported the treatment with corticosteroids.[44] Some studies indicated that including HBOT in medical treatment for SHL treatment could be beneficial.[45,46]

It was determined in our study that including HBOT in medical treatment did not have a statistically significant contribution to hearing results.

In order to design an appropriate treatment protocol in SHL, the etiological factors should be clarified by the help of medical history, laboratory and imaging methods after the diagnosis. If a certain cause such as infection, neurological causes, ototoxic medications, or endocrine, metabolic, and other systemic diseases are detected, the most appropriate treatment protocol should be planned as directed to the underlying cause. However, an underlying cause cannot be detected in most of the patients. Patients usually receive combined treatments.

It was determined in our study that the multimodal treatment protocol consisting of papaverine, corticosteroids, antiviral agents, and HBOT provides a significant effect on hearing results. However, following the comparison of two groups it was determined that including HBOT in medical treatment

did not make a statistically significant difference in the results.

A combined treatment modality based on the principle of using more than one agent at the same time in SHL treatment is supported with the results of our study, and it is thought to be a very effective practice. A statistically significant difference could not be found regarding including HBOT in SHL treatment. Despite this, a statistically significant difference was determined on hearing after the treatment in both groups when compared to the pre-treatment period. More comprehensive experimental and prospective studies are required in order to clarify the efficiency of HBOT in the SHL treatment.

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