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Original Article

Effect of hyperbaric oxygen therapy on thiol/disulfide homeostasis in patients with idiopathic sudden sensorineural hearing loss

İdiopatik ani işitme kaybı olan hastaların tiyol/disülfit homeostazisi üzerine hiperbarik oksijen tedavisinin etkisi

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ABSTRACT

Introduction: Idiopathic sudden sensorineural hearing loss (ISSNHL) is an otologic emergency that can lead to loss of function in one of the most important human senses. Recently, hyperbaric oxygen therapy (HBOT) has gained popularity with pharmacotherapy in ISSNHL. This study aimed to determine changes induced in thiol/disulfide homeostasis (TDH, a new biomarker of systemic oxidative stress) by pharmacotherapy and HBOT in patients with ISSNHL.

Methods: This prospective study analyzed the albumin, total thiol, native thiol, and disulfide levels and disulfide-native thiol, disulfide-total thiol, and native thiol-total thiol ratios before and after HBOT with standardizing pharmacotherapy using a new colorimetric method in patients with ISSNHL.

Results: 41 patients with ISSNHL including 14 (34.1%) women and 27 (65.9%) men participated in the study. The mean age of the patients was 48.02 ± 13.10 years. Of them, 24 (58.5%) had hearing loss in the right ear and 17 (41.5%) had hearing loss in the left ear. There was a statistically significant decrease in the albumin ($p<0.001$), total thiol ($p<0.001$), native thiol ($p<0.001$), and disulfide ($p<0.001$) levels after treatment compared to baseline. There was no statistically significant difference in the disulfide-native thiol ($p=0.148$), disulfide-total thiol ($p=0.172$), and native thiol-total thiol ($p=0.169$) ratios after treatment compared to baseline.

Conclusion: Consequently, this study demonstrated that the thiol-disulphide balance tended to shift towards the oxidative side after HBOT and pharmacotherapy compared to baseline in patients with ISSNHL and that patients with high oxidation level after treatment had better treatment response.

Keywords: Idiopathic sudden sensorineural hearing loss, oxidative stress, thiol/disulfide homeostasis, hyperbaric oxygen therapy

ÖZ

Giriş: İdyopatik ani sensorinöral işitme kaybı (ISSNHL) en önemli insan duyularından birinin işlev kaybına neden olabilen otolojik acil bir durumdur. Son zamanlarda ISSNHL' nda hiperbarik oksijen tedavisi (HBOT), farmakoterapi ile birlikte popülerlik kazanmaktadır. Bu çalışmada ISSNHL olan hastalarda farmakoterapi ile HBOT'nin sistemik oksidatif stresin yeni bir göstergesi olan tiyol/disülfit homeostrazisinde (TDH) meydana getirdiği değişikliklerin tespiti amaçlandı.

Yöntem: Bu prospektif çalışmada ISSNHL olan hastalarda, çalışma başında ve standart tedaviyle birlikte HBOT uygulandıktan sonra albümin, total tiyol, native tiyol, disülfit düzeyleri ile disülfit /native tiyol, disülfit /total tiyol ve native tiyol/total tiyol oranları yeni bir kolorimetrik yöntem kullanılarak analiz edilmiştir.

Bulgular: Çalışmaya 14'ü (%34,1) kadın 27'si (%65,9) erkek olmak üzere 41 ISSNH' li hasta katıldı. Hastaların yaş ortalaması 48,02±13,10 idi. Hastaların 24'ü (%58,5) sağ kulaktan 17'si (%41,5) sol kulaktan şikayeti vardı. Hastaların başlangıca göre tedavi sonrasında native tiyol ($p<0,001$), total tiyol ($p<0,001$), disülfit ($p<0,001$) ve albümin ($p<0,001$) değerlerinde istatistiksel olarak anlamlı düşme olmuştur. Disülfit /native tiyol ($p=0,148$), disülfit /total tiyol ($p=0,172$) ve native tiyol/total tiyol ($p=0,169$) oranlarında tedavi sonrasında öncesine göre istatistiki olarak anlamlı fark bulunamamıştır.

Sonuç: Sonuç olarak bu çalışmada, ISSNHL hastalarda başlangıca göre HBOT ve medikal tedavi verildikten sonra tiyol-disülfit dengesinin oksidasyon yönüne doğru kayma eğiliminde olduğu ve tedavi sonrası oksidasyonun yüksek olduğu hastalarda tedaviye cevabın daha iyi olduğu görülmektedir.

Anahtar Kelimeler: İdiopatik ani sensorinöral işitme kaybı, oksidatif stres, tiyol/disülfit homeostazisi, hiperbarik oksijen tedavisi

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Introduction

Sudden sensorineural hearing loss is defined as sensorineural hearing loss of 30 dB or greater over at least three contiguous audiometric frequencies occurring within a 72-hr period [1]. It is an otologic emergency that can lead to loss of function in one of the most important human senses. While only 10% of cases with sudden sensorineural hearing loss have specified causes, the remaining cases are defined as idiopathic sudden sensorineural hearing loss (ISSNHL). The causes of sudden sensorineural hearing loss can include infectious causes, circulatory disorders, traumatic injuries as well as immunological, toxic, neoplastic, metabolic, and neurological sources. The pathophysiology of ISSNHL is still not fully understood [2].

In animal studies, reactive oxygen species (ROS) have been shown to play an important role in cochlear hair cell damage caused by ototoxic drugs, inflammatory diseases, acoustic trauma, and radiation [3]. Hair cell and cell mitochondria in the cochlea as well as enzymes such as xanthine oxidase (XO) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase are major sources of ROS. ROS may induce apoptosis by affecting the mitochondrial permeability and can lead to oxidative stress by triggering cytochrome c release and activating p53 and caspases [4]. ROS can directly damage cellular macromolecules such as proteins, lipids, RNA, and DNA [5]. As a result, studies provide evidence for the possible role of oxidative stress in the etiology of ISSNHL [6-8].

The treatment of sudden hearing loss is based on its etiology. Oral corticosteroids are commonly used in patients with ISSNHL. Although intratympanic steroids can be tried in patients with sudden hearing loss since it provides a high concentration in animal models, there are contradictory results [9].

Recently, hyperbaric oxygen therapy (HBOT) has gained popularity with pharmacotherapy in ISSNHL. HBOT is the only known method of increasing oxygen partial pressure in the inner ear fluid. HBOT consists of breathing 100% oxygen at pressures higher than ambient pressure. A pressure of approximately 0.25 MPa is used for the purposes of the treatment [10]. This pressure allows oxygenation of all organs and tissues of the body including the middle ear to resolve hearing loss symptoms besides breathing 100% oxygen with a special mask [11].

The balance between production and removal of free radicals is known as oxidative balance. It is possible that free radical damage is reduced by maintaining oxidative balance. Thiol is one of the most important antioxidant and plays an important role in the elimination of free radicals by enzymatic and non-enzymatic pathways [12-14]. The plasma thiol pool is mainly formed by some protein thiols including cysteine, homocysteine, glutathione, and albumin. Thiol/disulfide homeostasis (TDH) is an indicator of oxidative stress and essential for the regulation of detoxification, apoptosis, signaling pathways, and enzymatic reactions [15, 16].

In this study, we would like to investigate changes in thiol/disulfide homeostasis after hyperbaric oxygen therapy compared to baseline in patients with sudden hearing loss.

Methods

This study was approved by the Ethics Committee of KTO Karatay University Faculty of Medicine (2017/007). This prospective study was conducted in Konya Education and Research Hospital, University of Health Sciences. All patients were informed about the study design. Informed consent was obtained from the patients who agreed to participate in the study. The study was conducted in patients who were diagnosed with ISSNHL and were planned to undergo HBOT between 01.12.2017 and 01.06.2018.

Patients who had cardiovascular diseases such as acute coronary syndrome, myocarditis, left ventricular dysfunction and heart failure, who received antioxidant drug therapy (angiotensin converting enzyme inhibitors, beta blockers with antioxidant properties, or antioxidant vitamins), who had diabetes mellitus, chronic liver failure, chronic renal failure, cancer, Parkinson's disease and Alzheimer's disease, who had an infectious disease within the last 4 weeks, who had inflammatory diseases such as Crohn's disease, ulcerative colitis and rheumatoid arthritis, who smoked cigarettes, and who had claustrophobia were excluded from the study.

Hyperbaric Oxygen Therapy Protocol

All patients who participated in the study were treated with HBOT (MUL 34) for 5 days in a multi-person pressure chamber. They were placed within the hyperbaric chamber for 120 minutes including 20 minutes of compression at 45 feet, three oxygen breathing periods (25 minutes on oxygen followed by 5 minutes on air) and 15 minutes of decompression.

Audiological tests:

The patients were assessed with standardized methods for pure-tone threshold audiometry before and after treatment by approved audiologists. The pure-tone average (PTA) was calculated as an average threshold measured at 250, 500, 1000, 2000, 4000, and 8000 Hz. According to the international standards defined by the World Health Organization (WHO), hearing loss has been classified as follows: 0–26 dB HL=no impairment, 26–40 dB HL=mild impairment, 41-60 dB HL=moderate impairment, 61–80 dB HL= severe impairment, and >81 dB HL= profound impairment [17].

Treatment protocol

All patients were hospitalized and received the standard combined intravenous treatment protocol for 10 days. This protocol contains 1 mg/kg prednisolone, 200 mg pentoxifylline, 500 mg vitamin B1, and 500 mg vitamin B6 per day.

Treatment response

The patients with a hearing gain lower than 15 dB in PTA between the first and sixth week audiograms were considered to be unresponsive to treatment. The patients with a hearing gain more than 15 dB in PTA between the first and sixth week audiograms were considered to be responsive to treatment. Treatment responders were divided into three groups: (1) recovering to within 10 dB of the hearing level of the unaffected ear (complete recovery), (2) recovering to at least 50% of the maximum possible recovery (good recovery), and (3) recovering under 50% of the maximum possible recovery (poor recovery). We used contralateral ear as the baseline for normal hearing, and reaching the hearing level of the contralateral ear was accepted as maximum possible recovery [18].

Blood Sampling and Laboratory analysis

5 ml of blood sample was collected into into serum separator tubes for thiol-disulfide homeostasis tests before and after hyperbaric oxygen therapy. The blood samples were centrifuged at 1500×g for 10minutes. The separated serum samples were kept in -80°C after coding. Thiol/disulphide homeostasis were evaluated using an automated clinical chemistry analyser (Roche, cobas 501, Mannheim, Germany) by a novel automatic and spectrophotometric method that measures the exact thiol/disulphide status. First, free functional thiol groups (–SH) are extricated by decreasing disulphide bonds (–S–S–) by sodium borohydride (NaBH4). The unused NaBH4 remnants are completely removed by formaldehyde. So, this prevents further reduction of 5,5′-dithiobis-2-nitrobenzoic acid (DTNB) as well as any disulfide bonds resulting from the reaction with DTNB. Total thiol groups involving reduced and native thiol groups were determined after reaction with DTNB. The disulfide parameter is a value which can be calculated automatically as half of the native thiol content and total thiol content. After the native and total thiols were determined, the disulphide amounts, disulphide/total thiol percent ratios, native thiol/total thiol percent ratios and disulphide/native thiol percent ratios were calculated [19].

Statistical analysis

Statistical analyzes were performed with SPSS 21 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY) software. Numbers, percentages, means, and standard errors were used for data presentation. The normal distribution of the data was assessed by the Shapiro-Wilk test. The Paired samples t-test was used if the data were normally distributed. The Wilcoxon signed-rank test and Kruskal–Wallis test were used if the data were not normally distributed. All analyzes were performed as two-sided hypotheses with a 5% significance level and a 95% confidence interval.

Results

41 patients with ISSNHL including 14 (34.1%) women and 27 (65.9%) men participated in the study. The mean age of the patients was 48.02 ± 13.10 years. Of them, 24 (58.5%) had hearing loss in the right ear and 17 (41.5%) had hearing loss in the left ear. The mean duration of symptoms before admission was 11.78 days (max=30, min=3). Of them, 14 (34.1%) had moderate hearing loss before treatment, 12 (29.3%) had severe hearing loss before treatment, and 15 (36.6%) had profound hearing loss before treatment (Table 1). Patients taken to the study received a mean of 18.0 ± 8.3 (Min = 5, Max = 40) sessions of hyperbaric treatment. Of them, 8 (19.5%) had complete recovery, 14 (34.1%) had good recovery, 12 (29.3%) had poor recovery, and 7 (17.1%) did not respond to treatment (Table 1).

Table 1. Clinical data of patients

	n (%)
Affected ear	
Right	24 (58.5)
Left	17 (41.5)
Hearing impairment	
Moderate	14 (34.1)
Severe	12 (29.3)
Profound	15 (36.6)
Treatment response	
No response	7 (17.1)
Complete recovery	8 (19.5)
Good recovery	14 (34.1)
Poor recovery	12 (29.3)

There was a statistically significant decrease in the albumin (p<0.001), total thiol (p<0.001), native thiol (p<0.001), and disulfide (p<0.001) levels after treatment compared to baseline. There was no statistically significant difference in the disulfide-native thiol (p=0.148), disulfide-total thiol (p=0.172), and native thiol-total thiol (p=0.169) ratios after treatment compared to baseline (Table 2).

The effect of post-treatment levels of oxidative stress markers on treatment outcome is shown in Table 3. Treatment outcome was not significantly associated with the albumin (p=0.585), total thiol (p=0.381), native thiol (p=0.201), and disulfide (p=0.310) levels and disulfide/native thiol (p=0.420) ratio after treatment. On the other hand, treatment outcome was significantly associated with the disulfide/total thiol (p=0.045) and native thiol/total thiol (p=0.039) ratios after treatment.

When the effect of time elapsed between the onset of symptoms and the initiation of treatment on treatment success was examined, no significant difference was found (p=0.256). The average elapsed time was respectively 16±3.25 days in the non-responder group, 12.25±2.53 days in the poor recovery group, 11.07±1.82 days in the good recovery group, and 8.42±2.37 days in the complete recovery group (Figure 1).

Table 2. Plasma thiol/disulfide levels at baseline and after treatment

	Baseline Mean±SD	After treatment Mean±SD	*p*
Native Thiol (µmol/L)[1]	524.14±86.09	425.77±77.47	<0.001
Total Thiol (µmol/L)[1]	584.94±92.07	477.11±74.77	<0.001
Disulfide (µmol/L)[1]	30.40±7.00	25.67±7.35	<0.001
Disulfide/Native Thiol (%)[1]	5.86±1.44	6.33±2.51	0.148
Disulfide/Total Thiol (%)[1]	5.22±1.12	5.54±1.89	0.172
Native Thiol/Total Thiol (%)[1]	89.55±2.26	88.90±3.79	0.169
Albumin (g/dL)[2]	5.33±0.97	4.49±0.50	<0.001

[1]Paired Samples Test
[2]Wilcoxon Signed Ranks Test

Table 3. Effect of post-treatment levels of oxidative stress markers on treatment outcome

	n=41	Albumin	Native Thiol	Total Thiol	Disulfide	Disulfide/Native Thiol	Disulfide/Total Thiol	Native Thiol/Total Thiol
No response	7	4.64±0.22	471.12 ±17.42	519.22 ±18.05	24.04 ±1.03	5.11±0.26	4.65±0.22	90.68±0.42
Complete recovery	8	4.61±0.23	422.25 ±33.64	487.86 ±33.33	32.78 ±3.08	8.03±1.04	6.83±0.74	86.26±1.49
Good recovery	14	4.52±0.15	426.78 ±21.39	476.69 ±21.07	24.96 ±2.43	6.06±0.66	5.33±0.51	89.33±1.03
Poor recovery	12	4.35±0.10	426.63 ±20.70	474.59 ±17.60	23.99 ±1.95	6.03±0.87	5.78±0.65	89.44±1.30
P value		0.585	0.201	0.381	0.31	0.42	0.045	0.039

Kruskal-Wallis Test

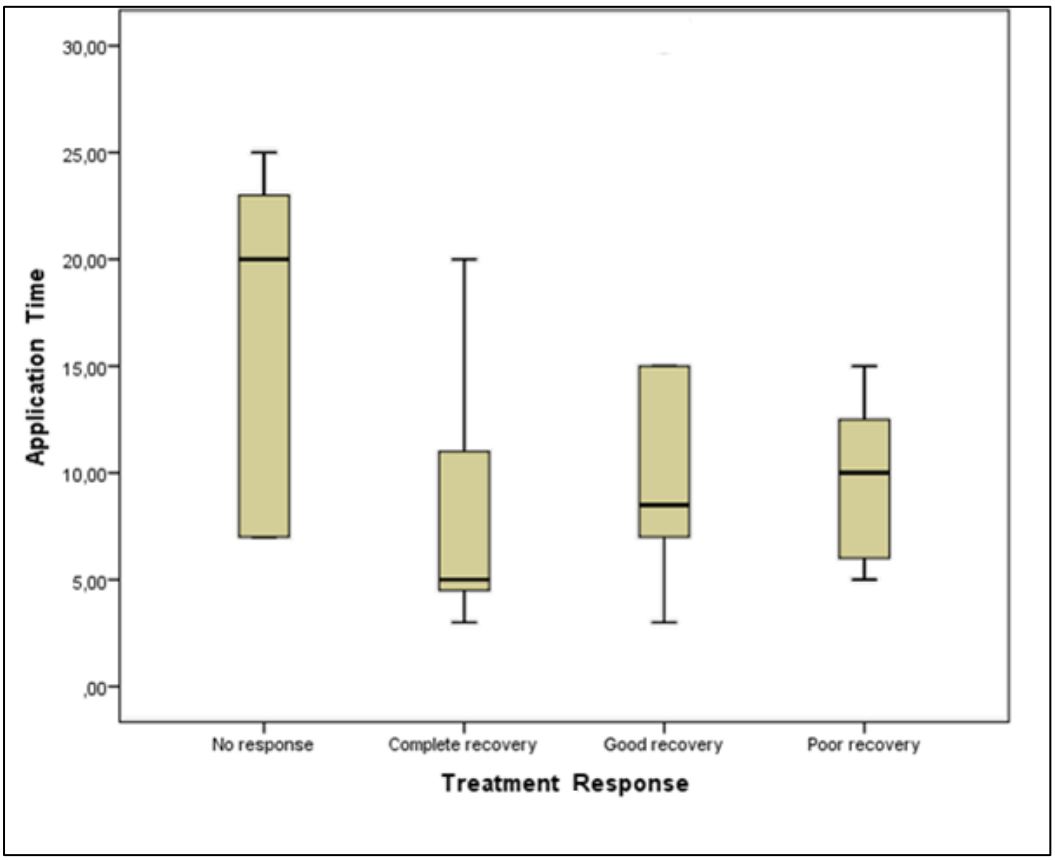

Figure 1. Relationship between admission time and treatment response

Discussion

This study investigated changes in thiol/disulfide homeostasis after treatment compared to baseline in patients with ISSNHL who underwent HBOT and pharmacotherapy. To our knowledge, this study is the first study on this field in the literature.

Oxidative stress is defined as a condition where oxidant levels are higher than antioxidant levels and which causes an imbalance in the oxidant/antioxidant systems and leads to free radical damage [20]. Breathing 100% oxygen during HBOT can increase the formation of reactive oxygen species in the body and affect the oxidant-antioxidant balance.

The plasma thiol pool is mainly constituted by albumin thiols and protein thiols and to a lesser extent by low-molecular-weight thiols such as cysteine (Cys), cysteinylglycine, glutathione, homocysteine, and p-glutamylcysteine [21]. Dynamic thiol disulphide homeostasis has critical roles in antioxidant protection, detoxification, signal transduction, apoptosis, regulation of enzymatic activity and transcription factors, and cellular signalling mechanisms [19, 22].

Quaranta et al. reported that patients with ISSNHL had high oxidative stress levels and low antioxidant levels [23]. Gul et al. found that the disulfide level and disulfide/native thiol and disulfide/total thiol ratios were significantly lower and the native thiol/total thiol ratio was significantly higher in patients with ISSNHL compared to controls [18]. However, it was determined that the native thiol and total thiol levels showed no significant difference between the two groups. It was also reported that the oxidative stress index was higher in the patient group than in the control group. In our study, the native thiol, total thiol, and disulfide levels significantly decreased following HBOT. Albumin is the major source of thiols and disulfides. The native thiol, total thiol, and disulfide levels decreased because there was a reduction in albumin level after treatment. When the disulfide/native thiol ratio that represents the proportion of oxidized thiols (disulfides) to non-oxidized thiols (native thiols) was examined to evaluate these results independently of albumin, this ratio increased after treatment although not significant. The increase in the disulfide/native thiol ratio after treatment indicates that the thiol-disulfide balance tends to shift towards the oxidative side.

Gul et al. reported that increased TOS levels increased the likelihood of ISSNHL and increased disulfide levels reduced the likelihood of ISSNHL according to the results of logistic regression analysis [18]. In our study, when the relationship between post-treatment levels of TDH parameters and treatment outcome was examined, treatment outcome was significantly associated with the disulfide/total thiol and native thiol/total thiol ratios after treatment. The disulfide/total thiol ratio was found to be the highest in the complete recovery group and the lowest in the non-responder group. The native thiol/total thiol ratio was found to be the lowest in the complete recovery group and the highest in the non-responder group. Treatment outcome was not statistically significantly associated with the albumin, total thiol, native thiol, and disulfide levels and disulfide/native thiol ratio after treatment. However, it was determined that the complete recovery group had the lowest native thiol level and the highest disulfide level and that the non-responder group had the highest native thiol level and the lowest disulfide level. These results showed us that patients with ISSNHL having high oxidation level after HBOT had better treatment response.

Paprocki et al. reported that the effect of HBOT on oxidation-reduction processes was not clearly elucidated and might be associated with many factors [11]. In the same study, the authors indicated that the antioxidant response after HBOT might depend on the age of the subjects [11].

In the study of Aslan et al. involving 55 patients with sudden hearing loss, they reported that HBOT was effective in patients younger than 50 years of age and was ineffective in patients over 50 years of age [24]. Similarly, Topuz et al. indicated that that HBOT was more effective especially at lower frequencies in younger patients [25]. In our study, the mean age of the patients was 48.02 ± 13.10 years.The high mean age of patients in our study may have affected treatment success.
Paprocki et al. indicated that oral glucocorticoids affected the oxidant-antioxidant balance [11]. Cavaleriu et al. reported that steroid treatment markedly increased production of endogenous antioxidants [26]. Although we know that steroids can affect study outcomes, steroids found in the treatment protocols for ISSNHL were used in this study due to the ethical issues. Thus, steroid treatment may have reduced HBOT-related oxidative stress in patients.

Ohno et al. compared the patient group treated with conventional therapy for the first 4 weeks with the patient group undergoing HBOT after 4 weeks of conventional therapy and found no statistically significant difference in hearing gain between these two groups [27]. This may be due to delayed initiation of HBOT (4 weeks after initiation of ISSNHL). Khater et al. have suggested early and concurrent administration of HBOT with clinically approved medicines [28]. In our study, the time elapsed between the onset of symptoms and the initiation of HBOT had no significant effect on treatment success. However, the fact that this time was the longest in the non-responder group and the shortest in the complete recovery group suggests that early initiation of HBOT may be beneficial in patients with ISSNHL.

Conclusion

Consequently, this study demonstrated that the thiol-disulphide balance tended to shift towards the oxidative side after HBOT and pharmacotherapy compared to baseline in patients with ISSNHL and that patients with high oxidation level after treatment had better treatment response.

Conflict of interest: None
Financial disclosure: None

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