The Treatment of Idiopathic Sudden Sensorineural Hearing Loss Using Phlebotomy: A Prospective, Randomized, Double-Blind Clinical Trial

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Abstract- This randomized clinical trial aimed to assess the efficacy of phlebotomy on improvement of hearing loss. 71 patients with sudden sensorineural hearing loss were enrolled in this randomized clinical trial study. They were divided into two groups: group A received steroid and hydration therapy plus phlebotomy, while group B received the same regimen without phlebotomy. They were matched according to sex, age, Hb, and Htc. Pure tone audiometries were administered to examine the hearing levels before and after treatment. Statistical analysis showed higher improvement in 250-1000 Hz in patients whit phlebotomy (P<0.001). However, there was noticed no significant difference in hearing improvement in 2000-8000 Hz between two methods. The number (%) of patients who had improvement was 29(85.3%) in phlebotomy group and 21(56.8%) in non-phlebotomy group. On the other hand, the number (%) of patients who showed no improvement in A and B group was 5(14.7%) and 16(43.2%), respectively (P=0.008). Using phlebotomy accompanied by steroid and hydration therapy leads to higher improvement in hearing loss especially in 250-1000 Hz. We think that this method has the ability to achieve better result in the management of patients with SSNHL.

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Introduction

Most otolaryngologists define sudden sensory hearing loss as a loss greater than 30dB in three contiguous frequencies occurring over a period of less than 3 days. Usually, it is unilateral and frequently accompanied by tinnitus and vertigo. The degree of hearing loss may vary from mild to profound, involving a part or all of the frequency range. About one third of these patients wake up in the morning with a hearing loss (1).

The incidence of SSNHL has been reported to be approximately 5 to 20 per 100,000 persons per year. Because of the high (45-65%) spontaneous recovery rate and low incidence, study of SSNHL is difficult. Indeed, SSNHL is a medical emergency that viral infections, vascular compromise, autoimmune process, and labyrinthine membrane ruptures have been proposed as its possible etiologies. Seen from other way round, bilateral sudden deafness is uncommon. If bilateral SSNHL is found, we must consider it an immunomediated inner ear disease (2,3). SSNHL patients with mid-tone loss have the best prognosis and the audiogram pattern of patients with SSNHL allows us to predict its outcome better (4). Recently, with the increasing widespread application of magnetic resonance imaging, an expected higher rate of acoustic neuroma has been detected in patients with sudden hearing loss (5). Steroid therapy has been known as the mainstay of treatment for SSNHL (1). Many otolaryngologists empirically administer a treatment battery consisting of any combination of corticosteroid, vasodilators, plasma expander, calcium channel blocker, and so on, and the use of all these drugs is based on improving the blood circulation and restoring oxygen tension of the inner ear (6). The aim of this study was to investigate whether phlebotomy can be an effective treatment for patients with SSNHL. We could not find any data in the literatures about use of phlebotomy modality on SSNHL.

Patients and Methods

A randomized clinical trial study was designed for 71 patients over 18 years old with idiopathic SSNHL and performed between November 2007 and July 2008. The

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study was approved by the Institutional Review Boards of Hamadan University of Medical Sciences (Hamadan, Iran). All patients signed an institutional review board approved consent form. A total of 71 patients having a clinical diagnosis of SSNHL were enrolled in the study, assigned via a randomization code (according to random table) to two groups: A and B. The study was single blinded relative to the certified audiologist. According to author's experiment on this procedure and review of previous studies on SSNHL treatment, we thought this style of treatment can be effective 25% better than usual modality. Therefore, by using this data approximately we have needed 30 cases for this study.

The onset time of SSNHL for all patients was less than 1 week. The patients of each group received hydration, oral intake and intravenous (1000 ml Ringer serum and 2000 ml Normal Saline Serum) and oral steroid (prednisolon, 5mg tablet) that was used on the schedule 20 mg bid and tapered to 8 days. All patients discharged on fourth day and continued oral therapy until the end of study eighth day. Only in group A, 1 unit (450 ml) of blood was taken from each patient (phlebotomy) on the first day. Safety of phlebotomy was mentioned to our patients, because we accepted lower limit of 13 g/100 ml hemoglobin for phlebotomy. Our medical staff was trained to perform phlebotomy properly. All patients underwent a history-taking, physical and audiologic examination, syphilis serology, autoimmune tests (CBC, diff, Serum igA, igM, igG, ANA, RF), and magnetic resonance imaging (MRI). Exclusion criteria included: trauma, syphilis, meniere`s, tumors, autoimmune diseases, middle ear infection, cardiovascular diseases, hypertension, systemic diseases (for example: diabetes mellitus) and fever. Since there is no reliable test to show the presence of prilymphatic fistula and also for menier,s disease, the history of patient is an important clue. Use of any other drug was not allowed during the study.

On the first day, the patients of group A were referred to Blood Bank and they were kept under controlled conditions in hospital after phlebotomy, but patients of group B were hospitalized directly. The patients could not visit each other during the stay period in the hospital.

Audiometry tests (P.T.A., S.D.S.-S.R.T.) were performed by certified audiologist on the baseline, 8th and 15th day. All patients were discharged on the 4th day, and the treatment was followed by steroid and low-salt diets in their homes. Hearing improvement was defined as a decrease threshold average of 20 dB in the four-frequency (0.5, 1, 2, and 3KHz) pure-tone. Statistical analysis was performed using t-test, paired t-test and $(chi)^2$ test. Significance was determined to be at the confidence level of $p<0.05$.

Results

Seventy one patients (38 men and 33 women) with a mean age of 44.8 years (range 18-73 ys) participated in our study. Group A (undergoing phlebotomy) consisted of 19 men and 15 women, and group B (without phlebotomy) consisted of 19 men and 18 women. There was no significant statistical difference in age, sex ratio, Hb, Htc, and initial hearing level between the two studied groups (Table 1).

The mean of hearing loss threshold before and after therapy and in different range of frequency in both groups is shown in Table 2, indicating good improvement in hearing loss in both groups in the same range of frequencies. As this table shows, the mean (±SD) of hearing loss improvement (in 250-1000 Hz) in phlebotomy and non-phlebotomy groups was 48(±34) and 28(±32) respectively, that indicates a higher improvement in phlebotomy group (P=0.01).

Table 1. Baseline characteristics of patients in two studeid groups.

Factor	Group A (n=34)	Group B (n=37)
Age (year)	42.86 ± 33.3	46.5 ± 15.1
Sex ratio (M/F)	19/15	19/18
Hb (g/100ml)	15.3 ± 1.4	16.0 ± 2.6
Htc (%)	45.9 ± 5.3	47.6 ± 8.7
Hearing Threshold (dB)		
250-1000 Hz	68.5 ± 33.3	57.3 ± 34.9
2000-8000 Hz	71.1 ± 32.5	69.5 ± 31.1

Table 2. Hearing loss thresholds in different ranges of frequency in two studeid groups.

Frequency Hz	A with phlebotomy dB		B without phlebotomy dB	
	Before	After	Before	After
250-1000 *	68.5 ± 33.3	20.6 ± 18.6	57.3 ± 34.9	29.2 ± 30.5
2000-8000	71.1 ± 32.5	28.0 ± 20.9	69.5 ± 31.1	37.9 ± 32.6

* P=0.01

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Table 3. Comparison of the number and percentage of the patients with and without improvement in phlebotomy and non-phlebotomy groups.

Frequency Hz	A with phlebotomy n (%)		B without phlebotomy n (%)	
	improvement	no-improvement	improvement	no-improvement
250-1000 *	29 (85.3)	5 (14.7)	21 (56.8)	16 (43.2)
2000-8000	25 (73.5)	9 (26.5)	24 (64.9)	13 (35.1)

* P=0.008

Efficacy of the phlebotomy method compared to non-phlebotomy approach is expressed as the percentage of patients who had improvement in their hearing threshold. The results of this comparison which are shown in Table3 (phlebotomy group 85.3% and control group 56.8%) indicate higher efficacy of phlebotomy (P=0.008). Furthermore, the frequency of vertigo and tinnitus in patients who underwent phlebotomy was significantly lower than in subjects without phlebotomy (P<0.05).

Discussion

The etiology of SSNHL is not proven yet in otology, although several causes have been suggested, including vascular lesions, labyrinthine membrane breaks, and viral lesions. There are some data that strongly support the viral theory (1,2). On the other hand, there was no increase in antibody titers to cytomegalovirus, human herpesvirus (HHV)-6 and HHV-7 in the majority of patients with SSNHL. This led to the conclusion that these viruses, which are highly prevalent in the adult population, are not the direct cause of SSNHL in most patients (7). As demonstrated by Perlman and colleagues (in the article of Schweinfurth J, et al.) the cochlea is intolerant of short term ischemia, so cochlear microphonics and action potentials are lost after 60 seconds of anoxia and permanently depressed after 30 minutes. This implies that irreversible cochlear damage has taken place long before any directed therapy can usually be instituted (8). Patients who develop sudden hearing loss tend to have obstructive sleep apnea more frequently than those in the control group owing to the similar risk factors for cerebral infarction (decreasing PO_2 and increasing PCO_2 during cessation of airflow and vasospasm, thrombosis, embolism, hypercoagulation and sludging.) and sudden hearing loss (9). With close attention to this concept and according to the results of this study we suggest that phlebotomy not only reduces blood viscosity but also promotes circulation and perhaps this procedure affects the emotional state of patients and results in adjustment of stress that always exists. In this experience, hearing improvement was noticed in 29(85.3%) of 34 ears of participants who were phlebotomized, and 21(56.8%) of 37 ears in the control group, in the range of 250-1000 Hz frequencies. Differences in the high frequencies were less prominent, and however steroid therapy has been known the mainstay of treatment for SSNHL (1), the results after phlebotomy are believed to be better.

Unfortunately we could not find similar study to compare the results. More recently laser Doppler Flowmetry has been used to study cochlear perfusion and has shown no increase in cochlear blood flow with carbogen therapy. Several other studies have incorporated vasodilators (8). The empirical use of all these drugs is mainly based on improving the blood circulation and restoring oxygen tension of the inner ear. Sudden hearing loss can developed by autoimmune disorders localized to the inner ear or secondary to systemic immune diseases. In patients with SSNHL, immune-mediated vascular damage can have a pathogenetic role while anti-endothelial cell antibody (AECA) might represent a serological maker of vasculitis (10). Nevertheless, a systemic disease could produce bilateral rather than unilateral ear symptoms over time, but as in ocular autoimmune diseases, the microvascular damage may be unilateral. It has been proposed that glucocorticoids are a mainstay of medical therapy for SSNHL (11). Herr B.D. and colleagues in their study on treatment of SSNHL instead of systemic steroid administration, via micro wick or catheter near round window, used dexamethasone drop, and prevented patients from suffering possible complications (12). Also, this method was applied by other investigators, Xenellis J. et al reported, from the 19 patients who received intratympanic treatment, in 9 patients, the PTA threshold improved more than 10 dB, in 10 patients there was no change greater than 10 dB (13). The treatment of idiopathic SSNHL using pulse therapy has been employed by Westerlaken, Boris O et al. in 2007 (14). They indicated that pulse therapy was equally effective and safe as standard-dose prednisolon and hearing improved from 71 dB HL to 36 dB HL in the patients

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group and from 75 dB HL to 42 dB HL in the control group.The effect of prostaglandin E1 (PGE1) in the treatment of idiopathic sudden SNHL has been evaluated, and no significant benefit has been observed (15). Chang NC and colleagues found that the best prognosis was with the midtone or low-tone pattern in the Sheehy classification. Also, the older patients, those with vertigo, or those treated after 6 days, had a poor prognosis (4). A patient with tinnitus accidentally had noticed his ear's noise reduced after phlebotomy. In the preliminary period of our study several years ago we thought to this subject and advised our patients who complained of tinnitus to have phlebotomy. Usually, these patients had high viscosity and their hemoglobin and hematocrit were upper than normal limit. Most of these patients reported us that they felt well after phlebotomy and intensity of their tinnitus had been reduced. In the present study, we have investigated whether phlebotomy may be an effective treatment for patients with SSNHL. This is the first systematic investigation on the effectiveness of phlebotomy for patients with SSNHL. Compared to conventional (steroid) therapy, the presence of satisfaction status in our patients after phlebotomy and replacement with plasma expander (hyper hydration by water intake and serum therapy) increased, and improvement of hearing levels was apparent. Also it supports the hypothesis that elevated blood viscosity may be an important causal factor for SSNHL. Furthermore, following lowering the plasma viscosity by phlebotomy and sufficient hydration, most of the participants did not complain from tinnitus, at least for a limited duration. Benefits of phlebotomy and replacement by hyper hydration are obvious, because the circulation of microvascular system of inner ear is achieved with easier flow. Interestingly, the patients whose hemoglobin and hematocrit were nearly at normal level expressed their satisfaction sense. In conclusion, as a result of this intervention (phlebotomy), the patients feel better and by reducing their blood viscosity and replacing it with hydration, the unknown mechanism of SSNHL will be controlled. Additionally, in the stay period in hospital they are worked up. According to these results, we suggest that all patients with SSNHL diagnosis should be hospitalized immediately and undergo hyper hydration after phlebotomy.

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