



## Our Experience in Patients with Sudden Sensorineural Hearing Loss

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### Abstract

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### Introduction

Sudden sensorineural hearing loss is defined as the development of sensorineural type hearing loss of 30 dB or more in 3 consecutive frequencies in 72 hours [1] Its annual incidence in the population is 5-20 cases in 100,000, and this condition is generally idiopathic and unilateral, with an equal distribution among genders. Although it may be determined in all age groups, it is most commonly reported in between the ages of 40-53 years [2]. Usually, the cause can't be identified; hence, it is called idiopathic. Although various theories have been suggested to explain the cause, no exact conclusion was made. Vascular disorders, viral infections, and autoimmune disorders are some of the most accepted hypotheses [3, 4].

The degree of hearing loss, time period from the onset of hearing loss and beginning of treatment, audiometric configuration, comorbidities (hypertension, diabetes), and presence of vestibular symptoms and tinnitus may influence the course of ISSNHL [5, 7].

Treatment protocols for ISSNHL, aim to decrease the inflammatory state of the inner ear and to increase the blood supply and oxygenation [6]

We aimed to compare the efficacy of dexamethasone and citicoline combination versus methylprednisolone in patients with sudden sensorineural hearing loss.

The exact mechanism of how steroids may improve hearing is still unknown. It has been thought that steroids act mainly by reversing the inflammation in the internal ear. Moreover, they may have the effects of stabilizing endolymph hemostasis by a mineralocorticoid effect, improving stria vascularis functions and potentially cochlear blood flow [8].

Citicoline is a of choice for treatment of cerebrovascular diseases. To sum up, citicoline interferes positively with the brain energy metabolism, stimulates central neurotransmission, activates cell repair mechanisms, decreases ischemic lesion size.

### Methods

#### Study design and study population

This was a single center, retrospective observational cohort study. We included of 98 consecutive patients with idiopathic sudden hearing loss who were admitted to "Astghik MC" clinic during the period 2015 to 2019 and received either dexametasone & citicoline combination (hereafter referred as an intervention group, n=65) or methylprednisolone (hereafter referred as a control group, n=33).

Those patients with an identified cause were excluded, and only idiopathic cases were investigated. The youngest patient was 12 years old,

and the oldest was 73; the mean age were 46,88 (12,80) in control and 48,45 (14,08) in intervention group respectively

The age, gender, affected side, blood tests including complete blood count and basic treatment, treatment modalities, associated symptoms (vestibular and auditory), and comorbidities were recorded. Cranial and temporal bone magnetic resonance imaging (MRI) was performed for all patients. Those with a lesion known to be associated with SSNHL on imaging (vestibular schwannoma or inner ear malformation) were excluded. After clinical examination, pure tone audiometry with tympanometry was carried out, and pure tone average (PTA) was calculated as the arithmetic mean of the hearing thresholds (HT) at 500, 1000, 2000 and 4000 Hz. Patients with hearing loss (HL) of 20 dB or more in at least 3 subsequent frequencies, which developed in less than 3 days, were included.

### Interventions/procedures

We compared the efficiency of two treatment schemes: dexamethasone followed by cyticoline and methylprednisolone as a monotherapy. The patients were divided into two groups. The first group received dexametason 8mg/2ml/3days, then 4mg/1ml/ 3 days and 2mg/0,5ml/ 1day, respectively. After 7 days the patients of first group continue received citicoline 500mg/100ml 0.9% NaCl intravenously 10 days. The patients of second group received methylprednisolone 48mg/7days, then reduced to 4 mg daily until the end of the drug/10days. The first group reduced the duration of steroids, thereby preventing their side effects.

### Data Collection and Study Outcomes

We used “Astghik MC” database to identify patients for inclusion in the study. From the medical records we extracted study related information, specifically demographic and clinical characteristics, received treatment, PTA score during three visits (0, 7 and 17 days).

The study primary outcome was the effect of treatment on changes in PTA score. The PTA score was computed as the average of the measured thresholds at 500,1000, 2000 and 4000 Hz frequencies. Generally, a minimum 20-dB gain in pure-tone average (PTA) is regarded as significant success in studies [9]. In times, this study a minimum

20-dB gain in PTA, determined in different times, was regarded as a positive response to the treatment.

We checked the PTA score at baseline (Day 0) before starting the treatment, then at Day 7 and Day 17 after the treatment according to recommended standard procedure in our clinic.

As a secondary outcome, we assessed the proportion of patients who at the end of treatment experienced significant or complete recovery (changes in PTA score  $\geq 9$  unit between baseline and Day 17th) vs no recovery (changes in PTA score  $< 9$  unit, between baseline and Day 17th) in hearing score.

### Statistical Analysis

The statistical analyses were conducted using R version 3.4.1 [2]. Categorical variables were summarized using counts and frequencies, and compared between two intervention groups using chi-square test. Continuous variables were presented as means and standard deviations and were compared using Student t- test.

To estimate changes in PTA scores over time we used linear mixed effects models (incorporating both fixed and random effects) using residual maximum likelihood methods. These models take into account the correlation within subjects' repeated responses at each time point. In this model, both the baseline and post-baseline values modelled as dependent variable. In the initial model time treated as continuous variable, treatment group and interaction term between time and intervention were modeled as fixed effects and each subject as random effect. The models were further adjusted for disease severity and age. Residuals were plotted to check the model diagnostics.

In subsequent model, we re-coded time as categorical variable to test the dose effects at each time points. We used Tukey method to adjust for multiple comparisons across all time points between the treatment groups.

All response observations, including information from subjects who did not complete all sessions, were included in the analyses. Results expressed as differences in mean change from the baseline with 95% CI at 7 and 17th days. All statistical tests were two sided and were performed at 0.05 significance level.

## Ethical Considerations

The “The Ethics Committee of YSMU” Research Ethics Board approved the study and granted a waiver of consent for the abstraction of de-identified medical records data.

## Results

From 2015-2018 in “Astghik” clinic and 65 patients received a combination of dexamethasone & citicoline and 33 patients - methylprednisolone. The mean age of study participants was  $48 \pm 13.6$  and 61% were males with no statistical difference observed

between groups. Two thirds of participants in both group had moderate to severe hearing loss (Table 1).

The primary analysis compared changes in patients’ mean PTA scores over treatment period between the groups. At time of treatment initiation (Day 0) the mean PTA scores were comparable between control ( $53.4 \pm 18.7$ ) and intervention ( $51.8 \pm 19.6$ ) groups. In both groups the PTA score improved over treatment period. The mean scores at day 7 and day 17 after the treatment initiation were  $40.9 \pm 17.4$  and  $30.9 \pm 18.8$  in control and  $42.2 \pm 20.1$  and  $34.4 \pm 22.0$  in intervention group respectively (Figure 1).

## Tables

**Table 1. Baseline characteristics**

	Control (n=33)	Intervention (n=65)	p-value
<b>Age (mean (sd))</b>	46.88 (12.80)	48.45 (14.08)	0.590
<b>Female (%)</b>	22 (66.7)	38 (57.6)	0.513
<b>Severity (%)</b>			
<b>Low</b>	11 (33.3)	22 (33.9)	
<b>Intermediate</b>	10 (30.3)	25 (38.4)	0.577
<b>Severe</b>	12 (36.4)	18 (27.7)	

**Table 2: Estimates from linear mixed model regression**

	Point estimate	95% CI	p-value
<b>Intercept</b>	35.60	29.3 to 37.9	0.000
<b>treatment</b>	1.38	-2.79 to 5.56	0.512
<b>days</b>	-1.18	-1.34 to -1.03	0.000
<b>factor(severity)2</b>	12.75	8.36 to 17.1	0.000
<b>factor(severity)3</b>	39.52	34.8 to 44.3	0.000
<b>age.c</b>	0.20	0.06 to 0.34	0.005
<b>treatment:days</b>	0.18	-0.01 to 0.38	0.066

Linear mixed models showed that in both groups the PTA score reduced over treatment period on average by 1.18 per day for control group and by 1.00 per day for treatment group. Difference in daily score reduction of 0.18 (0.01 to 0.38,  $p=0.066$ ) between groups failed to reach statistical significance (Table 2).

At the end of treatment (Day 17<sup>th</sup>) 84.8 % (n=28) patients in control and 80.0% (n=52) patients in intervention group had experienced significant to complete recovery (p=0.757).

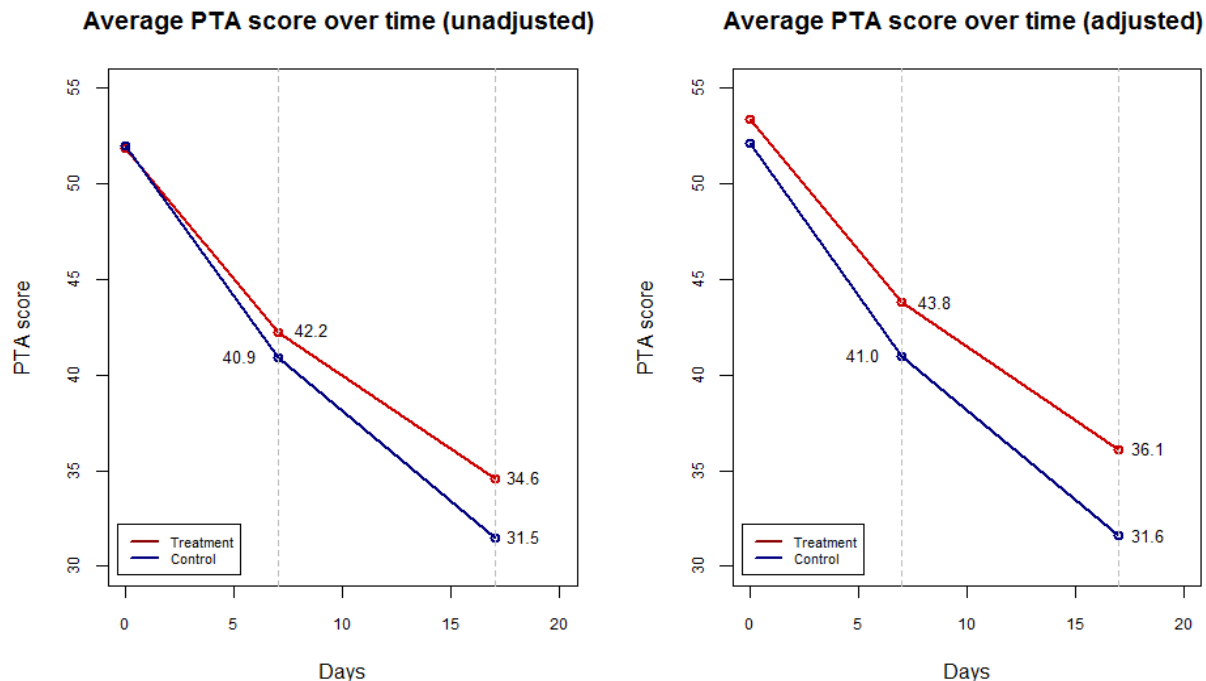


Figure 1: Average PTA score over time unadjusted and adjusted for age and hearing loss severity.

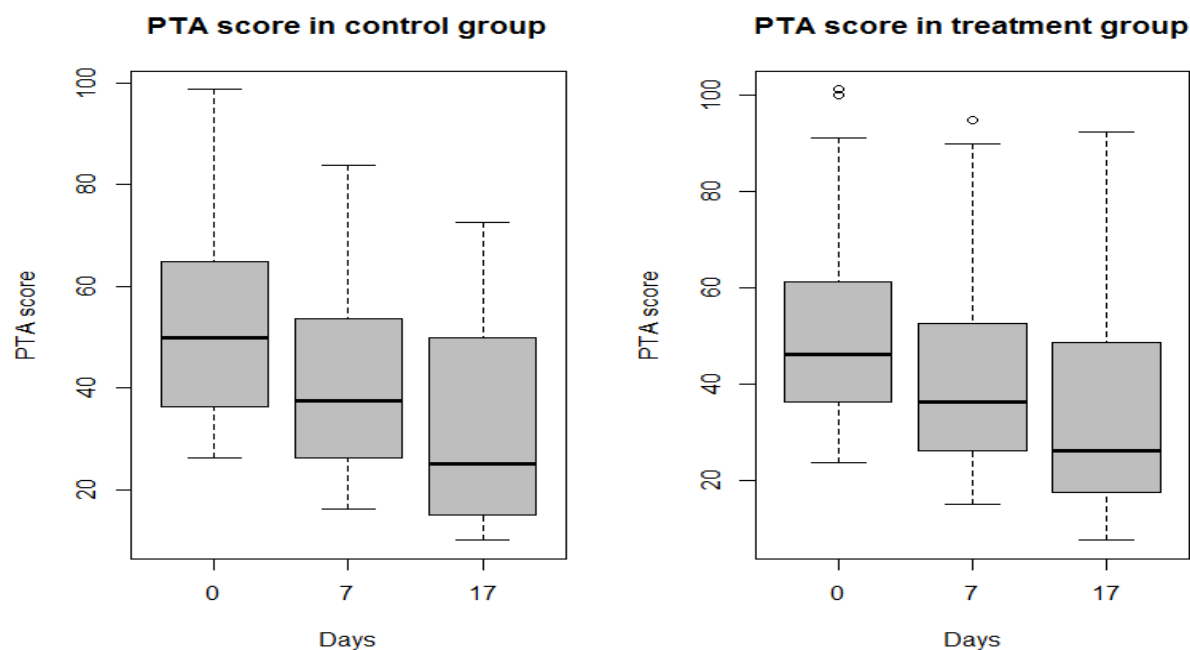


Figure: PTA score over time

Discussion

Although the definition of ISSNHL requires a reduction of at least 30 dB in 3 subsequent frequencies, we also included patients with less than

30 dB of hearing deficit if they complained of serious debilitation of everyday life because of the hearing loss. We therefore included patients with a hearing loss of 20 dB or more in at least 3 subsequent frequencies, which developed in less than 3 days.

The etiology, pathophysiology, and treatment of ISSHL still continue to be discussed currently, and ISSHL is one of the most challenging issues of otolaryngology. With many different treatment modalities studied at present, systemic steroid treatment has been the most commonly used modality [8, 9].

Between the cell and the environment there are constant metabolic processes. Various nutrients, bioregulators, hormones, etc., enter through the outer membrane. With age, the membrane loses its liquid properties due to an increase in the specific gravity of cholesterol molecules in it and a decrease in phospholipids, and this explains the aging process—the cells become more rigid and stable. Transport properties deteriorate, so the cell reacts worse to various anabolic stimuli, hormonal signals [10].

Phosphatidylcholine is a phospholipid that supports the fluid and plastic properties of the cell, slows down the aging process. It is part of lecithin, contains fatty acids and choline. Since the main role of this substance is structural, phosphatidylcholine ensures the normal formation of biomembranes and affects numerous cell functions. Phosphatidylcholine is involved in the transport of fats, cholesterol, fatty acids. It is a kind of "solvent" for cholesterol [11].

Citicoline is a medicine, which is an intermediate in the formation of phosphatidylcholine from choline. Studies show that the medicine increases the density of dopamine and acetylcholine receptors [12, 13].

Citicoline is a of choice for treatment of cerebrovascular diseases, it interferes positively with the brain energy metabolism, stimulates central neurotransmission, activates cell repair mechanisms, decreases ischemic lesion size. Citicoline affects the synthesis of adrenocorticotropic hormone and cortisol. Citicoline lowers increased glutamate concentrations and raises decreased ATP concentrations induced by ischemia [14, 15].

We compared the efficiency of two treatment schemes: a combination of dexamethasone & citicoline and methylprednisolone. The patients were

divided into two groups. The first group received dexametason i/m 8mg/2ml/3days, then 4mg/1ml/3 days and 2 mg/0,5 ml/ 1 day, respectively. After 7 days the patients of first group continue received citicoline 500mg/ 100ml 0,9% NaCl intravenously 10 days. The first group reduced the duration of steroids, thereby preventing their side effects.

At the end of treatment (Day 17 -th) 84.8% (n=28) patients in control and 80.0% (n=52) patients in intervention group had experienced significant to complete recovery (p=0.757).

Studies show that this treatment also gives good results and significantly reduces the side effects of steroids

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