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Running Head: Stress Impacts Sudden Hearing Loss Recovery

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Abstract

Purpose: This paper investigates the possible connections between the level of chronic stress and success of steroid therapy in patients with sudden sensorineural hearing loss (SSNHL).
Method: A single-center retrospective longitudinal cohort study on 55 patients in a tertiary referral otology center. Patients diagnosed with SSNHL between 2014 and 2017 were asked to complete a Measure of Perceived Stress (MPS) questionnaire. Inclusion criteria were patients >18 years of age, SSNHL diagnosed within 4 previous weeks, completed steroid treatment, and complete documentation.
Results: There were 30 patients (55%) that showed significant improval in their pure tone audiogram (PTA) hearing threshold average (≥15 dB) after steroid treatment. Two-step cluster analysis identified three clusters based on average PTA hearing threshold recovery and average MPS scores. The difference between pre-treatment and post-treatment hearing levels was significantly higher in the cluster with moderate stress compared to clusters with mild and high stress levels (Kruskal-Wallis test, Friedman test, $P<0.001$). There were no significant differences in average PTA hearing threshold recovery after steroid therapy between groups of patients with mild and severe stress.
Conclusions: Patients with moderate stress levels show significantly better results after steroid treatment for SSNHL than patients with low or high stress levels.

Key words: sudden sensorineural hearing loss; chronic stress; treatment; steroid resistance

Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as idiopathic hearing loss greater than 30dB on at least three contiguous hearing frequencies lasting more than three days (Merchant, 2005). There are many theories concerning the cause of SSNHL. Most prominent are vascular, immune, viral, trauma and combination of these; however in most cases the real cause of SSNHL remains unknown (Merchant, 2005). Genetic factors may contribute to the SSNHL, with significant associations reported for polymorphisms in genes related to blood vessels, circulation, or inflammation (Capaccio, 2009, Hiramatsu, 2012).

Many therapies have been proposed for treatment of SSNHL, but most of them were ultimately found to be unsuccessful (Conlin, 2007). Steroid treatment is currently regarded as standard therapy for SSNHL and has been used since the 1950s, although its pathophysiological role in hearing recovery is not completely clear. Most studies showed a statistically significant improvement after steroid treatment, while others did not provide statistical evidence that steroid treatment lead to measurable improvement (Conlin, 2007, Stachler, 2012). Steroid resistance is a well-known phenomenon in treatment of chronic inflammatory disorders like asthma and COPD (Barnes, 2013). Some studies have found that moderate exposure to stress increases the secretion of stress hormones and results in favorable physiological adaptations (Tahera, 2006, Cohen, 2007). However, stimuli that cause prolonged exposure to high levels of stress, may lead to under or over activation of physiological adaptation mechanisms, including glucocorticoid receptor expression (Schmitt, 2000, Lopez-Gonazalez, 2009, Byl, 1984). It is not known whether steroid resistance contributes to the poor therapeutic response to steroid treatment in SSNHL, but there is considerable evidence suggesting that in response to chronic psychologic stress, key

physiologic systems might operate at higher or lower levels than in normal homeostasis. The disturbed balance of these integrated systems may translate into adverse health outcomes (Wright, 2009).

Psychological stress affects the hypothalamic-pituitary adrenal axis (HPA) which is mediated by cortisol. The idea that stress levels may modulate steroid resistance has been already proposed, suggesting that stress-induced increases in glucocorticoid levels protect not against the source of stress itself but rather against the body's normal reactions to stress, preventing those reactions from overshooting and themselves threatening homeostasis (Munck, 1986). Endogenous glucocorticoids are released following stress-related events such as acoustic trauma in an effort to maintain homeostasis (Canlon, 2007). In accordance to the Arndt-Schultz law, short term stress may benefit recovery, but prolonged periods of stress may be detrimental to recovery (Canlon, 2007, Arndt-Schultz, nd, Trune, 2010). Glucocorticoid receptors have been found in many organs including the cochlea (mostly in spiral ganglion cells and in smaller numbers in outer hearing cells) and they are subject to either up-regulation or down-regulation, depending on cortisol levels in the body. Hypotheses linking stress associated diseases in females rely on gender-biased differences in the corticotropin-releasing factor subtype 1 receptor (CRF1) signaling pathway (McEwen, 2007). Also, interactions between chronic stress and severity of chronic rhinosinuitis (CRS) have shown significant association between CRS severity and chronic stress levels. (Tomljenovic, 2018).

Our hypothesis is that response to steroid therapy may be affected by the severity and duration of psychological stress. Early prediction of therapeutic outcome could reduce number of ineffective treatments and possible side effects due to administering large doses of corticosteroids. This paper investigates the possible connection between the level of chronic stress and success of steroid therapy in patients with SSNHL.

Patients and Methods

This single-center retrospective longitudinal cohort study included patients with SSNHL treated with steroid therapy between 2014 and 2017 in a tertiary otology referral center, with data collected from our department's data base. Written informed consent was obtained from all of the eligible patients, and they were asked to score symptoms in a Measure of Perceived Stress (MPS) questionnaire (Brajac, 2003). Inclusion criteria were patients od 18 years of age and older, a positive diagnosis of SSNHL within 4 weeks prior to starting steroid therapy, completed corticosteroid treatment protocol, complete follow-up during the first month after steroid treatment and complete documentation and questionnaires. A total of 73 patients with SSNHL were enrolled in this study. MPS scale measures emotional, behavioral, and cognitive aspects of distress. Our scale modification consisted of 48 statements with which patients indicated their perceived stress on a 5-point Likert-type scale. The scale was validated in the Croatian language on a sample of 165 healthy adults and previously validated to be correlated to biological markers of stress (Brajac, 2003, Walvekar, 2015). In order to stratify patients according to the severity of stress level we performed a cluster analysis using a two-step cluster test. Two-step cluster analysis was performed to reveal natural groupings (or clusters) within our dataset that would otherwise not be apparent. The algorithm employed by this procedure has several desirable features that differentiate it from traditional clustering techniques; A) It can handle categorical and continuous variables: by assuming variables to be independent, a joint multinomial-normal distribution can be placed on categorical and continuous variables. B) Automatic selection of number of clusters: by comparing the values of a model-choice criterion across different clustering solutions, the procedure can automatically determine the optimal number of clusters. We used MPS scores as continuous

variables, and gender and stress class as categorical variables (high vs. low stress, above and below than median of the whole population). We excluded patients that had previous stapedectomy surgery, acoustic neurinoma, Meniere disease, patients receiving chemotherapy, and patients with psychiatric diagnoses in their medical history (4 patients post stapedectomy, 5 patients with Meniere disease, 9 patients were diagnosed more than 4 weeks prior to treatment start). All of the patients met the criteria of sudden hearing loss: sudden onset of sensorineural hearing loss, unknown cause of hearing loss, average hearing level greater of 30 dB at 500, 1000, 2000, 4000 and 8000 Hz. Pure tone audiometry (PTA) average was measured on the same day that patients started steroid therapy and on the day they completed their treatment. Patients received steroids (240 mg of intravenous methylprednisolone sodium succinate (Solu-Medrol, Pfizer Manufacturing, Belgium) for two days with tapering the dose down every 2 days until reaching 80 mg, and then continuing with oral steroid therapy for six days). The improvement in PTA was regarded as being significant if an average ≥15 dB shift in PTA was recorded when averaging PTA shifts at 500, 1000, 2000, 4000 and 8000 Hz. Pre-treatment PTA levels were used to match patients from all three clusters, and then used the average improvement in PTA at 500, 1000, 2000, 4000 and 8000 Hz >15 dB as a cut-off level to designate whether the patient improved or not. We used this cut-off value to form a categorical variable of 0/1, that was used as a dependent variable in analyzing the differences in improvement levels between the clusters, alongside the average PTA improvement on all frequencies in dB. Using both variables added to the strength of our analysis, and used both the Kruskal-Wallis test and Friedman's test used presented identical results.

In order to exclude the impact of baseline hearing loss on the outcomes after treatment (hypothesizing that greater loss at baseline is more likely to have greater improvement in dB after treatment), a matched pair analysis according to baseline hearing loss was performed. Each patient in the moderate stress cluster was attributed a matched pair from the mild stress

cluster and from the severe stress cluster, which have identical or similar baseline hearing loss. This created a subset of 30 participants included in the secondary analysis using the Friedman's test.

The study was approved by the Ethics Committee of University Hospital "Sestre milosrdnice," Zagreb School of Medicine and School of Dentistry. Patient characteristics that were analyzed with regard to hearing recovery were: presence of vertigo, age in years, duration between initial hearing loss and initiation of treatment, hearing loss patterns on pure tone audiogram and hearing loss severity. We also evaluated gender as a possible prognostic factor since cellular and molecular sex differences in stress response have been reported. Other tests, such as tympanometry, acoustic reflex and otoacoustic emission tests were not analyzed in this study.

The data distribution was calculated using the Kolmogorov–Smirnov test. Internal consistency was measured with Cronbach's alpha, a statistic calculated from the pairwise correlations between items used to measure the reliability of our psychometric test – the MPS score, confirming that the questions were not redundant. Statistical analysis was performed depending on the normality of the distribution using the Kruskal-Wallis test to compare outcomes between clusters with post-hoc analysis with Wilcoxon signed rank test, and Mann–Whitney *U* two-tailed tests for unpaired comparisons. The patients between clusters were matched according to their pre-treatment PTA hearing loss levels, so that every moderate stress cluster patient was paired with a patient from the mild and severe stress patient cluster. Friedman test for paired samples was then performed to assess correlations (the non-parametric alternative to the one-way ANOVA with repeated measures). All tests of statistical significance were performed using a two-sided 5% type I error rate.

Statistical analysis was performed using MedCalc software (Version 11.2.1 © 1993-2010. MedCalc Software bvba Software, Broekstraat 52, 9030 Mariakerke, Belgium), and SPSS

(Version 22.0., 2013. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) using standard descriptive statistics and frequency tabulation as indicated.

Results

The patient demographics are displayed in Table 1. Pure tone hearing level thresholds before and after steroid therapy were measured and the differences were correlated with patient data. There were 30 patients (55%) that showed significant improvement in their PTA hearing threshold average (≥15 dB). Three clusters according to stress levels were identified with good separation and a silhouette measure of cohesion and separation >0.65. Predictor importance of MPS scores was 0.6, indicating high relative importance of each predictor in estimating the reliability of each predictor in making a clustering prediction. The two-step cluster method included MPS scores and patient gender, as it is known that gender is a possible confounding variable in perceived stress scores (female patients have higher stress level at baseline).

The cluster analysis divided patients into 3 clusters, according to MPS stress level scores (low, intermediate and high) and gender. The moderate stress cluster differed significantly in both variables from the other two; it had 10 patients (18.2%), with an average PTA hearing recovery of 43.8 dB and an average MPS score of 43.8 (moderate stress). The mild stress cluster encompassed 28 patients (50.9%) and showed an average PTA hearing recovery of 6.39 dB, with an average MPS score of 31.46 (mild stress). The severe stress cluster had 17 patients (30.9%), showed an average PTA hearing recovery of 8.18 dB, and an average MPS score of 94.94 (severe stress).

There are several questions dealing with vertigo symptoms in the MPS questionnaire, and we analyzed its possible impact by designating a categorical variable to it in our data analysis – 0/1, and then performed the Kruskal-Wallis test to see whether it had any impact on cluster

formation and whether it could impact the overall MPS scores unevenly among the clusters. It did not prove to be statistically significant, so we ruled it out as a possible confounding factor (Kruskal-Wallis test, $\chi2 = 2.97$, df=1, P=0.294). Vertigo did not increase stress levels on the MPS scale. The recovery rate in the group of patients with vertigo did not differ significantly from patients without vertigo. We performed Mann-Whitney's U test to see whether age could be a confounding factor, but its distribution was not significantly correlated to hearing recovery in our sample (P=906) and there was no significant age difference between the clusters (P=0.436).

Prior to therapy, there were no significant differences in average PTA hearing loss thresholds between patients with severe and mild stress. The cluster with moderate stress had a significantly higher hearing loss at 500, 1000 and 2000 Hz, but not at 4000 and 8000 Hz (Kruskal-Wallis test, df =2, $\chi2 = 7.375$, P=0.025 for 500 Hz, $\chi2=7.565$, P=0.023 for 1000 Hz, $\chi2 = 3.090$, P=0.213 for 4000 Hz, $\chi2 = 0.316$, P=0.854 for 8000 Hz). Hearing level improvement was measured in all groups but only the patients with moderate stress the hearing improvement showed significant improvement.

To avoid test-retest variability, we used a ≥15 dB PTA post-treatment threshold shift as a cut-off value, and performed a ROC curve analysis of PTA pre-treatment and post-treatment shifts on 500, 1000, 2000, 4000 and 8000 Hz, and on the average PTA shift on all frequencies. The analysis showed AUC (area under curve) of 0.999, P<0.0001, and a cut-off value of 5 dB (Youden J index) with a 100% sensitivity and 96% specificity.

When analyzing hearing recovery as a categorical variable, using the ≥15 dB post-treatment PTA threshold as a cut-off value, patients with moderate stress levels respond significantly better to treatment (Kruskal-Wallis test, $\chi2 = 20.407$, df =2, P<0.001, Figure 1). The difference between pre-treatment and post-treatment hearing levels was significantly higher in the cluster with moderate stress compared to clusters with mild and high stress levels

(Kruskal-Wallis test, $\chi 2 = 20.407$, df =2, P<0.001, Figure 2). There were no differences in hearing levels after steroid therapy between groups of patients with mild and severe stress.

We then paired patients between cluster groups according to their basal level of hearing loss (prior to therapy), where we matched patients from all 3 clusters to have the closest possible level of basal hearing loss. Every moderate stress cluster patient was paired with a patient from the mild and severe stress patient cluster. We then performed Friedman's test for paired samples with the average improvement in PTA after therapy designated as the dependent variable. The analysis showed that the cluster with moderate stress levels shows a significantly higher level of improvement compared to clusters with mild and severe stress levels (Friedman test, $\chi^2 = 18$, df =2, P<0.0001, Figure 3).

Discussion

Stress is a process of increased arousal with the primary biological function of maintaining homeostasis. Short-term stress with sufficient recovery is beneficial, whereas long-term stress exposure without sufficient recovery may lead to various detrimental health effects, in accordance to Arndt-Schultz law and Hans Selye's stress syndrome theory (Arndt-Schultz, nd, Trune, 2010 Selye, 1936). Chronic stress is associated with a greater risk of diabetes, cardiovascular disease, autoimmune diseases and many other disorders (Trune, 2010). Several studies have shown links between psychosocial distress and vascular disorders, diabetes, increased blood clotting, and decreased fibrinolysis (Cohen, 2012, von Känel, 2001). During viral infections, patients with higher levels of chronic stress exhibit glucocorticoid receptor resistance and failure in inflammatory response downregulation (Nouwen, 2009, Toda, 2011). Prolonged activation of the HPA and sympathetic-adrenal medullary system axes, might elicit a counter response in stimulated lymphocytes and downregulate the expression and function

of glucocorticoid receptors, leading to functional glucocorticoid resistance (Miller, 2002). This has already been identified in pediatric asthma patients, where subjects who perceived greater stress were more resistant to hydrocortisone's effects on cytokine expression and activation of eosinophils relative to asthmatic subjects reporting lower stress levels (Miller, 2009). Previous research has suggested that it is imperative to have background information about the individual's stress levels before administering glucocorticoid therapy (von Känel, 2001). After long term restraint stress in rats, modulation of the expression of glucocorticoid receptor (GR) and hypoxia-inducible factor 1 alpha (Hif1a) genes was observed in auditory tissues (the inferior colliculus, spiral ganglion, and the organ of Corti) (Trune, 2001). Also, the expression of an outer hair cell marker prestin was significantly up-regulated. This animal experiment indicated that that 24-h stress induced transient hypersensitivity of the auditory system and modulated gene expression in a tissue-specific manner (Tahera, 2007, Curtis, 2006). Additional studies in both primate and murine models link social status and chronic social stress to hypercortisolism and steroid resistance (Trune, 2001, Cohen, 2012, von Känel, 2001). Although stress in humans has been considered as a factor in pathophysiological mechanisms of SSNHL, several other recent studies could not confirm a correlation between stress levels and hearing recovery following steroid therapy (Nouwen, 2009, Toda, 2011). However, depression, the most common stress-related disorder, was linked with sudden sensorineural hearing loss onset (Tahera, 2007).

Steroids have been widely used for the treatment of hearing loss for more than 60 years, ever since the association between inner ear and systemic autoimmune diseases was first reported. Nowadays, steroids are still the most commonly used in SSNHL treatment although in most cases no autoimmune disorders can be diagnosed. In autoimmune disorders in mice, steroid therapy improves the stria vascularis function (Trune, 2010). Stria vascularis is an important part of the cochlea involved in ion homeostasis and its malfunction could be one of the

principal factors in SSNHL occurrence (Trune, 2010). The protective role of steroids against acoustic trauma has been previously demonstrated (Canlon, 2007). It was shown that intratympanal application of dexamethasone prior to noise exposure prevented hearing loss by restoring glucocorticoid receptor expression in guinea pigs (Heinrich, 2016). Steroids are used in many immune disorders and their major action in suppression of immune response is to switch off inflammatory genes for cytokines, chemokines, adhesion molecules, inflammatory, enzymes, and receptors. Their immunosuppressive effect is widely considered as the most likely explanation of positive effects in hearing recovery (Conlin, 2007, Stachler, 2012, Barnes, 2013).

Many factors have been reported as possible prognostic factors for SSNHL: age, the presence of vertigo, the severity of hearing loss, the shape of PTA thresholds, and the time from symptoms to the initiation of treatment (Roh, 2017). A recent study in military veterans from Iraq and Afghanistan has shown that comorbid posttraumatic stress disorders and depression were significantly associated with increased rates of hearing loss, tinnitus, or both conditions together (Swan, 2017). Lifestyle stress can play a role in pathophysiological mechanisms of SSNHL (Caldirola, 2016). In a recent study, depression, the most common stress-related disorder, was considered a risk factor for sudden sensorineural hearing loss (Lin, 2016). There are other reports regarding psychological correlation with SSNHL (Ghiadoni, 2000, Mazurek, 2010, Tahera, 2006).

Recent studies found no correlation between the level of stress and hearing recovery following steroid therapy (Roh, 2017). Depression, the most common stress-related disorder, was the only factor associated with a worse response to steroid treatment. Patients with mild depression responded better to steroid treatment while patients with severe depression were marked as non-responders to steroid treatment. Our results showed that patients with moderate stress levels respond better to steroid therapy than patients with high or mild stress

levels. As previously stated, stress is often associated with other disorders, principally vascular that could explain why patients with high stress levels did not respond well to steroid treatment. Moderate exposure (e.g. exercise or testing) increases the secretion of stress hormones and results in favorable physiological adaptations (Tahera, 2006, Cohen, 2007). However, stimuli that cause mild and short stress episodes, or on the other hand prolonged exposure to high levels of detrimental stress, may lead to under or over activation of physiological adaptation mechanisms (Schmitt, 2000, Lopez-Gonazalez, 2009, Byl, 1984). This could explain why both patients with mild levels of stress and with high levels of stress did not respond well to steroid therapy.

A hypothesis related to the difference in prevalence of stress associated diseases in females relies upon the gender-biased corticotropin-releasing factor subtype 1 receptor (CRF1) signaling pathway (McEwen, 2007). Conditions associated with chronic stress exposure are more common in females (Neuser, 1986, Saeki, 1994, Bangasser, 2014). Recent research of the interaction between chronic stress and severity of chronic rhinosinuitis (CRS) in a disease specific questionnaire, has shown significant association of CRS severity and chronic stress. (Tomljenovic, 2018). We, however, were unable to confirm these previously reported gender differences in stress induced inflammatory responses in this paper.

We recognize that there are limitations of our study, principally regarding our sample size, despite the fact that high levels of statistical significance was demonstrated in our tests. Adjusting for confounding factors such as age, vertigo, and configuration of hearing loss was not entirely possible, but measures were taken to ensure that they do not influence the reproducibility of the results by pairing patients according to pre-treatment hearing loss and enforcing strict exclusion criteria. This is a single-center study, which also may add bias to patient selection. We cannot consider our analysis flawless, but would also point out that our data seem to indicate a significant interaction between hearing recovery and stress levels,

which support the Arndt-Schultz law elegantly, ecpecially when translated into Selye's Syndrome - an expression of Claude Bernard's milieu intérieur. (Selye, 1936).

There is a clear clinical need to be able to predict which patients will benefit from steroid therapy. Our results suggest that patients with moderate stress levels show significantly better results after steroid treatment for sudden sensorineural hearing loss than patients with low or high stress levels. Unfavorable results in these patient groups may be explained by the detrimental effects of chronic stress exposure on physiological adaptive mechanisms of the auditory system.

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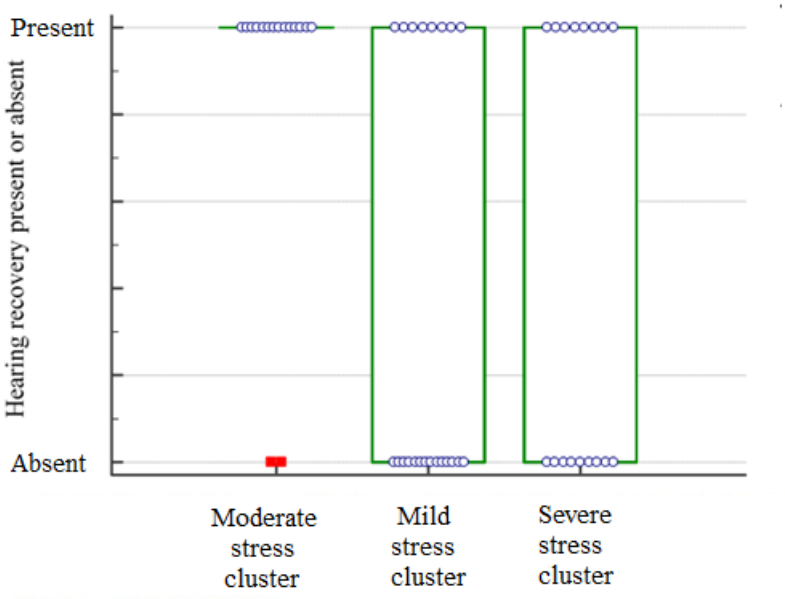
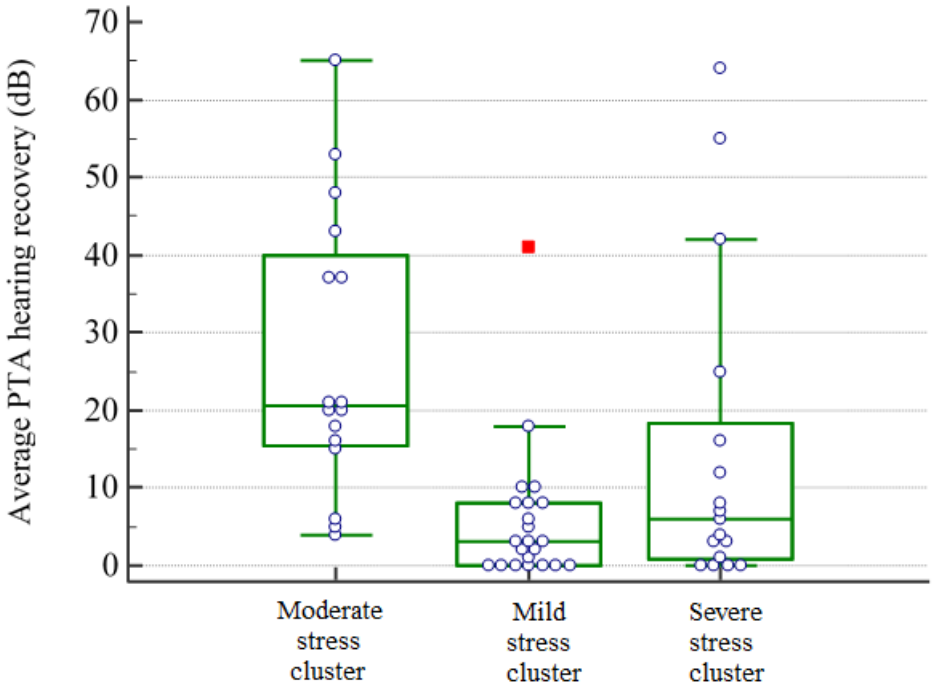
Figures and Legends

Figure 1. Patients with moderate stress levels respond significantly better to treatment when analyzed as a categorical variable (Kruskal-Wallis test, $P<0.001$, $N=10$, using the $\geq$15 dB post-treatment PTA hearing threshold recovery as a cut-off value).

Figure 2. Patients in the moderate stress cluster showed a significantly higher difference between pre-treatment and post-treatment hearing levels compared to clusters with mild and severe stress levels (Kruskal-Wallis test, $P<0.001$, $N=55$)

Figure 3. Patients in the moderate stress level cluster showed statistically higher post-treatment average PTA hearing recovery thresholds at all frequencies when matched to the patients in the other two clusters according to pre-treatment PTA hearing levels (Friedman test, $P<0.0001$, $N=30$).


Present
Hearing recovery present or absent
Absent
Moderate stress cluster
Mild stress cluster
Severe stress cluster


Average PTA hearing recovery (dB)
70
60
50
40
30
20
10
0
Moderate stress cluster
Mild stress cluster
Severe stress cluster

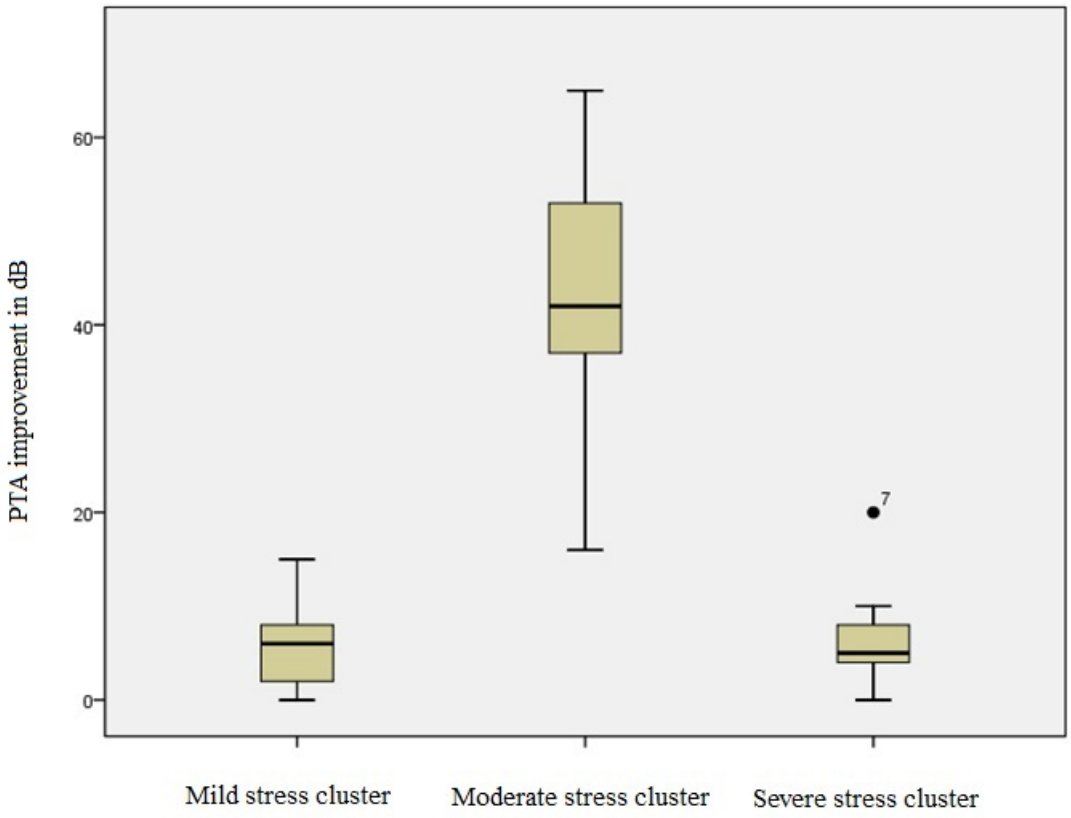

PTA improvement in dB
60
40
20
0
7
Mild stress cluster
Moderate stress cluster
Severe stress cluster

Table 1. Patient demographics, MPS scores and post-treatment PTA shifts among the patient clusters

	Mild stress cluster	Moderate stress cluster	Severe stress cluster	Total	P value and test
Number of patients	28	10	17	55	
Age (years)	49.25	44.6	53.5	50.54	Kruskal-Wallis test p>0.05
Gender	12 male, 16 female patients	5 male, 5 female patients	6 male, 11 female patients	23 male, 22 female patients	Kruskal-Wallis test p>0.05
Vertigo present	8 patients	2 patients	5 patients		Kruskal-Wallis test p>0.05
Average MPS score	31.46	43.8	94.94	56.1	Two-step cluster analysis
Average post-treatement PTA shift on all frequencies	6.39 dB	43.8 dB	8.18 dB	14.6 dB	Kruskal-Wallis test, $\chi2$ = 20.407, df =2, P<0.001, Friedman test, $\chi2$ = 18, df =2, P<0.0001