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RESEARCH ARTICLE
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The Effect of Vocal Rehabilitation on Patients with Vocal Cord Paralysis

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ABSTRACT

Objective: The aim of this study is to examine voice characteristics by perceptual assessment of voices of patients with vocal cord paralysis before and after vocal rehabilitation.
Materials and Methods: 80 subjects participated in the study, of which 40 belonged to the experimental group and 40 to the control group. A subjective assessment of the voice using the GRBAS scale was performed. This instrument assesses the quality of the voice, that is, it determines the degree and severity of the disorder. Measures of central tendency, measures of variability, one-factor analysis of variance, t-test for independent samples, chi-square test and interclass correlation coefficient were applied in statistical data processing.
Results: Before vocal rehabilitation, severe (S) and moderate (G, R, B and A) voice changes were present in patients with vocal cord paralysis. After the vocal rehabilitation was completed, there was an improvement in voice quality on all subscales, i.e. in moderate (G, R, B and A) there was a noticeable absence of changes in the voice and in severe (S) there was a slight change in the voice.
Conclusion: Vocal rehabilitation aims to improve glottic occlusion without causing hyperkinesia, which is assisted by the abdominal breathing technique and improving the function of the internal muscles of the larynx. Vocal therapy is an indispensable part of the treatment of patients with paralysis of the vocal cords, and very often it is sufficient for a complete cure.

Keywords: Vocal cord paralysis, Perceptual assessment, Vocal rehabilitation

INTRODUCTION

Paralysis of the vocal cords is a pathological condition where one or both vocal cords are limited in mobility or immobile. The immobility of the vocal cords can be the result of nerve damage or fixation in the cervical artenoid joint (1) as well as injury or scar changes in the larynx, especially on the back wall of the glottis. The number of patients with vocal cord paralysis is constantly increasing (2). Damage to the central and peripheral nervous system can cause unilateral or bilateral paralysis of n. vagus, its branches, or upper or lower laryngeal nerve (3). Paralysis of the vocal cords can occur in both children and adults. In children, it is most often a congenital malformation of the larynx, which is often associated with a congenital malformation of the central nervous system (4) or is a consequence of trauma during childbirth (5). In adults, paralysis can be caused by trauma (surgical and non-surgical), tumors (pressure on the vagus nerve or laryngeal nerves), neurological and systemic diseases and causes of idiopathic origin (6). Paralysis of the vocal cords most often occurs as a symptom of some disease (5). It most often occurs after thyroid gland surgery, moreover it can be caused by factors of idiopathic origin, head and neck surgery, endotracheal intubation, tonsillectomy and various neurological disorders (5, 7, 8).

Unilateral paralysis of the vocal cords most often occurs after thyroidectomy (surgical intervention of the thyroid gland,

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one or both lobes), where the nerve is often cut or crushed. Paralysis of the left vocal cord occurs much more often than the right, the reason for this is the anatomical position of the left laryngeal nerve, i.e. the left recurrent nerve is longer and therefore more prone to injuries (9). With unilateral paralysis, the vocal cord is not able to occupy an intermediate position, which means that neither adduction nor abduction of the vocal cord is achieved during phonation (10, 11). Dysphonia is the leading symptom of unilateral vocal cord paralysis. The voice is characterized by hoarseness, especially in the early stages of paralysis, the range is narrowed, the intensity is reduced and the duration of the tone is shortened, which leads to vocal fatigue (7).

Bilateral paralysis of the vocal cords occurs much less frequently than unilateral paralysis of the vocal cords, and is most often caused by damage to the recurrent laryngeal nerve or a lesion of the nucleus of the n. vagus in the brain stem (6).

The treatment modality should be determined taking into account the time of injury, the patient's expectations, the status of fluid or solid aspiration, and the compensation provided by the uninjured vocal cord. In some patients, recovery can be spontaneous in the first six to twelve months (12), and while in some patients surgical compensation is performed with a healthy vocal cord, some patients cannot recover with any of these techniques (6). In bilateral paralysis of the vocal cords, the general view is that surgical treatment is the only option. However, it has been shown that vocal and kinesitherapy give significant results, especially if it is a paramedian position of the vocal cords which did not reduce the breathing space to the level when tracheotomy is indicated. It is considered as the decisive choice of the patient (from a willingness and motivational aspect), building a pleasant atmosphere and trust.

The aim of this research was to determine voice characteristics by perceptual assessment of voices of patients with vocal cord paralysis before and after vocal rehabilitation.

MATERIALS AND METHODS

80 respondents participated in the research, of which 40 belonged to the experimental group and 40 to the control group (Table 1). The experimental group consisted of 32.5% male respondents and 67.5% female respondents, and the control group consisted of 42.5% male and 57.5% female respondents. The groups were equal according to gender (p>0.05). The average age of subjects in the experimental group was M=58.2±16.7, and in the control group M=53.2±14.8 years. Otherwise, considering the age of the respondents, the groups were equal (p>0.05).

Table 1: General characteristics of the respondents

	N=80	Groups		p
		Experimental N=40	Control N=40	
Gender, n (%)				
Male	30 (37.5%)	13 (32.5%)	17 (42.5%)	0.356[a]
Female	50 (62.5%)	27 (67.5%)	23 (57.5%)	
Age (AS±SD)	55.7±15.9	58.2±16.7	53.2±14.8	0.165[b]

The research was conducted in the period from November 2019 to April 2022. All subjects were examined by an otorhinolaryngologist using the method of indirect laryngoscopy. After the established diagnosis, they were referred to the speech therapy clinic. The time of inclusion of patients in speech therapy treatment was after two months if caused by an injury and after one month if it was of idiopathic origin. Vocal rehabilitation was carried out individually, twice a week, lasting 30 to 45 minutes. The average duration of vocal therapy was from one month to three months. The aim of vocal rehabilitation was for the patient to master the technique of proper breathing, to remove tension in the neck and shoulder area, to establish adequate voice volume and pitch, and to provide and adopt guidelines for maintaining vocal hygiene.

The examination was conducted using the GRBAS scale (auditory – perceptual scale) designed in Japan. This instrument is standardized and reliable, and describes the quality of the voice through five qualitative parameters, which enables monitoring and comparison of the voice before and after vocal rehabilitation, as well as comparison with subjects of the control group. The instrument describes: the degree of hoarseness (Grade - G), roughness of the voice (Roughness - R), hoarseness in the voice whose source is turbulence caused by an irregular glottal wave (Breathiness - B), weakness in the voice, i.e. the auditory impression of hypokineticity or hypofunctionality in spontaneous phonation (Asthenia - A) and tension in the voice, that is, the auditory impression of excessive effort and tension in spontaneous phonation (Strain - S) (13). The parameters were assessed on a four-point scale with a grade from 0 to 3 (grade 0 - no changes in voice quality; grade 1 - mild changes in voice quality; grade 2 - moderately changed voice; grade 3 - pronounced changes in voice quality). The voices of the subjects were evaluated by three vocal therapists (speech therapists with many years of experience). The vocal therapists were in direct contact with the subject, at a distance of one meter, and evaluated the voice independently of each other. The subjective evaluation of voice quality using the GRBAS scale represents the analysis of the voice with one's own sense of hearing, which is characterized by simplicity in application and economy.

Table 2 shows the results of the agreement test of three independent experts (speech therapists and vocal therapists who evaluated the voice of the subjects). Excellent agreement between raters was recorded, expressed by the interclass correlation coefficient. For the total score of the GRBAS scale, the values of the interclass correlation coefficient were very high (ICC=0.999, CI: 0.999, 1.000), as well as for the scales: G (hoarseness in the voice) (ICC=0.998, CI: 0.996, 0.998), R (roughness in voice) (ICC=0.994, CI: 0.991, 0.996), B (loudness in voice) (ICC=0.990, CI: 0.986, 0.993), A (weakness in voice) (ICC=0.997, CI: 0.995, 0.998) and S (voice tension) (ICC=0.999, CI: 0.999, 1.000).

Table 2: Results of the inter-examiner GRBAS scale test

	Estimated interrater reliability (95% CIs)
GRBAS total score	0.999 (0.999, 1.000)
GRBAS subscale	
G - Grade	0.998 (0.996, 0.998)
R - Roughness	0,994 (0.991, 0.996)
B - Breathiness	0.990 (0.986, 0.993)
A - Asthenia	0.997 (0.995, 0.998)
S - Strain	0.999 (0.999, 1.000)

The interclass correlation coefficient (ICC) was used to assess the reliability of the instrument itself. Among the methods of descriptive statistics, the arithmetic mean with associated standard deviation, measures of central tendency, measures of variability, as well as minimum and maximum were used. Frequency and percentages were used. In analytical statistics for testing differences between parameters, One-factor analysis of variance (ANOVA), t-test for independent samples, and chi-square test were used to examine the relationship between two categorical variables. Statistical processing and analysis were done in the computer program SPSS ver. 20 (Statistical Package for the Social Sciences).

RESULTS

80 respondents participated in the research, 40 respondents belonged to the control group, and 40 to the experimental group. Paralysis of the vocal cords in the experimental group was most often present after thyroid gland surgery (45%), followed by unknown or idiopathic origin (45%) and after carotid artery surgery (10%) (Table 3).

Table 3: Experimental group: comorbidities

Cormobidities percentages	Percentages
After thyroid surgery 18 (45.0%)	18 (45.0%)
After carotid artery surgery 4 (10%)	4 (10%)
18 (45%) of idiopathic origin	18 (45%)
Total	40 (100%)

Paralysis of the left vocal cord was present in 25 patients, right vocal cord in nine patients and bilateral paralysis in six patients (Table 4).

Table 4: Paralysis of the vocal cords

Vocal cord paralysis	Percentages
Right vocal cord	9 (22.5%)
Left vocal cord	25 (62.5%)
Both side	6 (15%)
Total	40 (100%)

Table 5 shows the results of the experimental and control groups on the GRBAS scale before vocal rehabilitation. All parameters between groups on the GRBAS scale were statistically different. The control group had a mean value (zero), which was expected because the control group had a normal/unchanged voice quality that is associated with a 0 (zero) value of all assessed GRBAS scale parameters, (M=0.00 (0.00)), p<0.0001. The experimental group showed worse overall results on the GRBAS scale (M=2.90 (0.14)) compared to the control group (M=0.02 (0.05)), p<0.0001. The GRBAS scale parameter G (hoarseness in voice) was, as expected, more present in the experimental group (M=2.96 (0.13)) compared to the control group (M=0.00 (0.00)), p<0.0001. A statistically significant difference between the two groups also existed on the R scale (voice roughness) (p<0.0001), where the experimental group had worse results (M=2.79 (0.34)) compared to the control group (M=0.00 (0.00)). The difference was also noted on scale B (loudness in the voice), where the subjects of the experimental group had worse results (M=2.75 (0.35)) compared to the control group (M=0.02 (0.07)), p<0.0001. The subjects of the experimental group (M=2.99 (0.05)) compared to the control group (M=0.08 (0.22)), p<0.0001, achieved a higher score on scale A (voice weakness). The results on the S scale (voice tension) were less favorable for the experimental group (M=3.00 (0.00)) compared to the control group. The results of the research of the experimental group showed the presence of severe and moderate changes in voice quality.

After the vocal rehabilitation was completed (Table 6), there were no statistically significant differences between the

Table 5: Results of the GRBAS scale for the experimental and control groups before vocal rehabilitation

	N=80	Groups		p*
		Experimental N=40	Control N=40	
Total score of GRBAS scale	1.46 (1.45)	2.90 (0.14)	0.02 (0.05)	<0.0001
GRBAS subscale				
G - hoarseness in voice	1.48 (1.49)	2.96 (0.13)	0.00 (0.00)	<0.0001
R - roughness in gas	1.40 (1.43)	2.79 (0.34)	0.00 (0.00)	<0.0001
B - hoarseness in voice	1.38 (1.4)	2.75 (0.35)	0.02 (0.07)	<0.0001
A - voice weakness	1.53 (1.48)	2.99 (0.05)	0.08 (0.22)	<0.0001
S - voice tension	1.50 (1.51)	3.00 (0.00)	0.00 (0.00)	<0.0001

*: statistical significance

Table 6: Results of the GRBAS scale for the experimental and control groups after vocal rehabilitation

	N=80	Groups		p*
		Experimental N=40	Control N=40	
Total score of GRBAS scale	0.02 (0.05)	0.01 (0.04)	0.02 (0.05)	0.625
GRBAS subscale				
G - hoarseness in voice	0.00 (0.04)	0.01 (0.05)	0.00 (0.00)	0.320
R - roughness in gas	0.01 (0.06)	0.03 (0.09)	0.00 (0.00)	0.079
B - hoarseness in voice	0.01 (0.06)	0.01 (0.05)	0.02 (0.07)	0.562
A - voice weakness	0.05 (0.18)	0.03 (0.12)	0.08 (0.22)	0.208
S - voice tension	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	

*: statistical significance

experimental and control groups on the GRBAS scale. Vocal rehabilitation was carried out individually, and lasted from one to three months. The values of the experimental group were measured after vocal rehabilitation, while the control group had one measurement.

Table 7 shows the average achieved results of the experimental group before and after treatment. There was a statistically significant improvement in the GRBAS total score after treatment (M= 2.9 (0.14) vs. M= 0.01 (0.04)), p<0.0001. Before the treatment, the achieved score on the G scale (hoarseness in the voice) was M= 2.96 (0.13), and after the treatment M=0.01 (0.05), p<0.0001. Before the vocal treatment on the R scale (roughness in the voice) the respondents had an average score of M=2.79 (0.34), and after the treatment M=0.03 (0.09), which is statistically significant (p<0 ,0001). Improvement after treatment was also noted on scale B (voice hoarseness) (p<0.0001), where the score decreased from M=2.75 (0.35) to M=0.01 (0.05). The average achieved value on scale A (weakness in the voice) before the vocal treatment was M=2.99 (0.05), and after the treatment M=0.03 (0.12), p<0.0001. And on the S scale (voice tension), a statistically significant improvement was achieved after the treatment (M=0.00 (0.00)) compared to the initial values (M=3.00 (0.00)), p<0.0001.

Table 7: Results of the GRBAS scale for the experimental and control groups before and after vocal rehabilitation

	Before vocal rehabilitation	After vocal rehabilitation	p*
Total score of GRBAS scale	2.9 (0.14)	0.01 (0.04)	<0.0001
GRBAS subscale			
G - hoarseness in voice	2.96 (0.13)	0.01 (0.05)	<0.0001
R - roughness in gas	2.79 (0.34)	0.03 (0.09)	<0.0001
B - hoarseness in voice	2.75 (0.35)	0.01 (0.05)	<0.0001
A - voice weakness	2.99 (0.05)	0.03 (0.12)	<0.0001
S - voice tension	3.00 (0.00)	0.00 (0.00)	<0.0001

*: statistical significance

DISCUSSION

Paralysis of the vocal cords means the inability to move one or both vocal cords due to dysfunction of the innervation of the larynx. The leading symptom is dysphonia of varying degrees, the voice is weak, monotonous, narrowed in range, and over time the patient feels tired in the voice (14). These voice disorders can negatively affect an individual's emotional and physical functioning, i.e. their quality of life.

In this observational study, mostly female subjects were represented, that is, vocal cord paralysis occurs more often in women than in men, which is compatible with previous research (15, 16).

Thyroidectomy without identification of the recurrent nerve causes 5.4% of paralysis, half of which is irreversible (17), and surgery with identification of the nerve causes 3-8% of paralysis, but only about 1% is irreversible (18). Given that surgically caused paralysis of recurrence is most often not recognized at the time of injury, today the identification of the return nerve for thyroidectomy is mandatory. A large number of patients in our study with paralysis of the vocal cords were after thyroid surgery, but also of unknown etiology, i.e. idiopathic origin (11, 8). Paralysis of the left vocal cord is much more common than the right one (9, 10), the left recurrent nerve is longer and more prone to injury, while bilateral paralysis of the vocal cords is very rare and usually results from an injury to the upper laryngeal nerve (19, 8).

The GRBAS scale describes the characteristics of the voice and also the effectiveness of vocal rehabilitation. Analyzing the results of the perceptual assessment before vocal rehabilitation, we found that there was a statistically significant difference between the two groups of subjects on all the examined parameters. The values of the parameters of the GRBAS scale were statistically significantly higher in subjects with vocal cord paralysis, compared to subjects in the control group. Based on the obtained results, we can conclude that the code in patients with paralysis of the vocal cords, a greater degree of hoarseness, tension, hoarseness, weakness and hoarseness was observed in the voice. That is, severe (S) and moderate (G, R, B and A) voice changes were present in the patients. The results of research by the authors' group (20) showed more severe changes in voice quality in patients with vocal cord paralysis on subscales G, R and B, while in another study (21) more severe changes in voice quality were also present on subscale S.

Before vocal rehabilitation, the parameter with the highest values was S (voice tension), which could also be observed in the study (22). Parameter A (weakness in the voice) had a high value, which was noticed by other authors (23, 24, 21, 25). Due to paralysis of the vocal cords, there is an incomplete closure of the glottis, which creates an excess of air during phonation, that is, hoarseness in the voice (B), which is also noticeable in other studies (26, 20). Roughness in the voice (R) as a consequence of irregular cycles, i.e. low mobility or immobility of the vocal cords also had a high value, which is compatible with other researches (24, 27). The parameter G (hoarseness in the voice) also had a high value, which was related to other parameters and varies depending on the voice disorder and is compatible with other researches (28, 29, 26, 30, 27, 32).

After the vocal rehabilitation was completed, the voice quality of the subjects of the experimental group improved, that is, there were no negative changes in voice quality. The control group had good results on all subscales of the GRBAS scale, as expected, because the control group had no pathological changes in the voice. In a study by other authors (32), patients with vocal cord paralysis recovered after vocal rehabilitation, and were able to achieve intelligible speech production. Hoarseness (G), tension (S), and weakness in the voice (A) improved and went from severe disturbance to mild or no voice changes. A significant voice improvement in patients with unilateral paralysis of the vocal cords after vocal therapy by subjective evaluation of the voice was found in a study by Santos et al. (33).

In a large number of studies in patients with vocal cord paralysis, vocal therapy improved the voice quality of these patients (34, 35, 14, 36), which positively affected their quality of life.

CONCLUSION

With this study, we concluded that paralysis of the vocal cords has a negative effect on the general health and quality of life of the individual. However, vocal therapy as one of the treatment segments for patients with vocal cord paralysis can lead to significant improvement and even complete recovery. Team cooperation between the speech therapist - vocal therapist and phoniatrist, i.e. laryngologist is very important. Vocal rehabilitation aims to improve glottic occlusion without causing hyperkinesia, which is assisted by the abdominal breathing technique and improving the function of the internal muscles of the larynx. Each person, considering the age, etiology, duration of the paralysis, requires an individual approach, often involving several modalities of therapy simultaneously or individually. Success in the treatment of vocal cord paralysis is based on a very studious and dedicated approach, patience, superior care and prevention of complications, the main goal of which is to correct or restore the patient's voice to be loud enough, pleasant to listen to, so that it can be adequately used during daily life activities, which positively affects the quality of life.

Ethics Committee Approval: This study was approved by the Ethics Committee of Sveti Vračevi Hospital (Date: 07.09.2022, No: 4315-8-2/22).

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REFERENCES

1. Cheetham J, Witte TH, Rawlinson JJ, Soderholm LV, Mohammed HO, Ducharme NG. Intra-articular stabilisation of the equine cricoarytenoid joint. Equine Vet J 2008;40(6):584-8.
2. Kardogan T, Seifert E. Influence of Aging and Sex on Voice Parameters in Patients With Unilateral Vocal Cord Paralysis. Laryngoscope 2005;115(4):655-60.
3. Milutinović Z. Klinički atlas poremećaja glasa, teorija i praksa. Beograd: Zavod za udžbenike i nastavna sredstva, 1997.
4. Bumber Ž, Katić V, Nikšić-Ivančić M, Pegan B, Petrić V, Šprem N. Otorinolaringologija. Zagreb: Ljevak, 2004.
5. Katić V, Prgomet D. Otorinolaringologija i kirurgija glave i vrata: priručnik. Zagreb: Ljevak, 2009.
6. Bothe C, Lopez M, Quer M, Leon X, Garcia J, Lop J. Aetiology and treatment of vocal fold paralysis: retrospective study of 108 patients. Acta Otorinolaringol Esp 2014;65(4):225-30.
7. Schindler A, Bottero A, Capaccio P, Ginocchio D, Adorni F, Ottaviani F. Vocal improvement after voice therapy in unilateral vocal fold paralysis. J Voice 2008;22(1):113-8.
8. Brake M, Anderson J. Bilateral vocal fold immobility: a 13 year review of etiologies managment and the utility of the empey index. J Otolaryngol Head Neck Surg 2015;44(1):27.
9. Ahmed S, Muzamil A, Lateef M. A study of incidence and etiopathology of vocal cord paralysis. Indian J Otolaryngol Head Neck Surg 2002;54(4):294-6.
10. Finck C. Laryngeal dysfunction after thyroid surgery: diagnosis, evaluation and treatment. Acta Chirurgic Belg 2006;106(4):378-87.
11. Chandrasekhar SS, Randolph GW, Seidman MD, Rosenfeld RM, Angelos P, Barkmeier-Keaemer J, et al. Clinicalpractice guideline: Improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg 2013;148(6):S1-S37.
12. Boone DR, McFarlane SC. (2000). The voice and voice therapy, (6th ed). Pearson: Allyn & Bacon, 2000.
13. Isshiki N, Okamura H, Tanabe M, Morimoto M. Differential diagnosis of hoarseness. Folia Phoniatr 1969;21(1):9-19.
14. Bunijevac, M., Čolić, G., Čvorović, R. Objective assessment of voice quality in patients with one-sidedvocal paralysis. In V. Ilic (Ed.), Latest developments in speech therapy, occupational therapy and social work: Implementations of theoretical models in practice: possibilities and limitations. Beograd: Visoka škola socijalnog rada. 2020, pp 387-97.
15. Jakelić A, Bonetti A, Šimunjak B. Akustička procjena i samoprocjena gasa žena s bolestima štitnjače. Logopedija 2015;5(1):9-14.

16. Blatančić G, Bonetti A, Živković-Ivanović T. Objektivna i perceptivna procjena kvaliteta glasa kod osoba sa jednostranom paralizom glasnica. Logopedija 2017;7(1):1-5.
17. Gisselson L. Laryngeal paralysis following in thyreoidectomy. Acta Chir Scand 1949;99:154-62.
18. Widstrom A. Vocal cord palsies following surgery for benign non toxic boitre. Acta Otolaryngol 1973;75:370-1.
19. Rubin JS, Sataloff RT, Korovin GS. (Eds.). Diagnosis and treatment of voice disorders. San Diego: Plural publishing, 2014.
20. Little MA, Costello DAE, Harries MN. Objective dysphonia quantification in vocal fold paralysis: comparing nonlinear with classical measures. J Voice 2011;25(1):21-31.
21. Bielamowicz S, Stager SV. Diagnosis of unilateral recurrent laryngeal nerve paralysis: laryngeal electromyography, subjective rating scales, acoustic and aerodynamic measures. Laryngoscope 2006;116(3):359-64.
22. Rosenthal AL, Lowell SY, Colton RH. Aerodynamic and acoustic features of vocal effort. J Voice 2014;28(2):144-53.
23. Baylor CR, Yorkston KM, Eadie TL, Strand EA, Duffy J. (2006). A systematic review of outcome measurement in unilateral vocal fold paralysis. J Med Speech Lang Pathol 2006;14(1):1-33.
24. Sulica L, Blitzer A. Vocal Fold Paralysis. Eur Arch Otorhinolaryngol 2006;968-9.
25. Blitzer A, Brin MF, Ramig LO. Neurologic disorders of the larynx. New York: Thieme, 2009.
26. Hartl DM, Hans S, Vaissière J, Riquet M, Brasnu DF. Objective voice quality analysis before and after onset of unilateral vocal fold paralysis. J Voice 2001;15(3):351-61.
27. Pinho CMR, Jesus LMT, Barney A. (2013). Aerodynamic measures of speech in unilateral vocal fold paralysis (UVFP) patients. Logoped Phoniatr Vocol 2013;38(1):19-34.
28. Takahashi H. Assessment of auditory impression of dysphonia. In: The Japan Society of Logopedics and Phoniatrics, editor. Voice Examination Methods. Tokyo: Interna, 1979.
29. Hirano M, Hibi S, Terasawa R, Fujiu M. Relationship between aerodynamic, vibratory, acoustic and psychoacoustic correlates in dysphonia. J Phonet 1986;14(3-4):445-56.
30. Yu P, Garrel R, Nicollas R, Ouaknine M, Giovanni A. Objective voice analysis in dysphonic patients: new data including nonlinear measurements. Folia Phoniatr Logop 2007;59(1):20-30.
31. Jesus LM, Martinez J, Hall A, Ferreira A. Acoustic Correlates of Compensatory Adjustments to the Glottic and Supraglottic Structures in Patients with Unilateral Vocal Fold Paralysis. Phoniatr 2015, 704121.
32. Lu QY, Zhang B, Jin KX, Jiang WL, Li X, Gao CY. Rehabilitation Therapy for Vocal Fold Paralysis Caused by Lung Cancer: A Case Report. Phys Ther 2020;100(12):2198-204.
33. Santos M, Vaz Freitas S, Santos P, Carvalho I, Coutinho M, Moreira da Silva Á, et al. Unilateral Vocal Fold Paralysis and Voice Therapy: Does Age Matter? A Prospective Study With 100 Consecutive Patients. Ear Nose Throat J 2021;100(5_suppl):489S-494S.
34. Kaneko M, Hitomi T, Takekawa T, Tsuji T, Kishimoto Y, Hirano S. Effects of Voice Therapy on Laryngeal motor units during phonation in chronic superior laryngeal nerve paresis dysphonia. J Voice 2018;32(6):729-33.
35. *Caçador* M, *Papoila* AL, *Brás-Geraldes* C, Garcia CS, Constantino T, Almeida M, et al. Is Computerized Dynamic Posturography Analysis in Dysphonic patients different after vocal rehabilitation treatment? A Longitudinal Study. J Phonosurg Laryngol 2019;9(2):30-5.
36. Heikkinen M, Penttilä E, Qvarnström M, Mäkinen K, Löppönen H, Kärkkäinen JM. Perceptual Assessment and Acoustic Voice Analysis as Screening Tests for Vocal Fold Paresis After Thyroid or Parathyroid Surgery. Scand J Surger 2021;45(3):767-73.

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Can Osteotomes Be Sharpened in the Operating Room Inexpensively and Effectively? An Experimental Study on Sandpaper Versus Arkansas Stone

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ABSTRACT

Objective: The maintenance of surgical instruments is an ongoing problem for surgeons, especially in operations such as rhinoplasty where instrument sharpness is very important. This study aims to investigate the effectiveness of two inexpensive and easily accessible sharpeners that can be used in the operation room immediately before surgery.
Materials and Methods: Three new Cinelli osteotomes were subjected to base sharpness measurements and then used to cut same-sized artificial bone blocks by applying hammer blows with equal force. The three osteotomes were placed into different groups as follows: the no-sharpening (NS) group, the Arkansas stone (AS) group, and the sandpaper (SP) group. Sharpness measurements were repeated in all groups after the 1st, 4th, 7th, and 10th osteotomies.
Results: No significant difference was found between the initial measurements with the sharpness values measured after the 10th osteotomy in the NS and AS groups (p>0.05). The dullness in the SP group, however, increased significantly through the process.
Conclusion: Using new osteotomes without resharpening them after their first use until they have become blunt may be appropriate. If sharpening is to be done, an Arkansas stone will likely provide better results than sandpaper.

Keywords: Osteotome, sharpness, sandpaper, arkansas stone

INTRODUCTION

The sharpness of an osteotome is extremely important in external nasal surgery for obtaining acceptable results and avoiding complications in nasal hump reduction, with greater sharpness providing more controlled bone cuts. Blunted osteotomes can cause the separation of larger bone fragments instead of only those in the desired area, as well as soft tissue damage. In addition, bone fragment ruptures that occur near the base of the skull can cause serious complications (1-3).

Because medical centers generally have no devices for checking instrument sharpness, the falls on the surgeon to have sharp, well-functioning instruments (1). In addition, no consensus currently exists regarding what materials to use or how often surgeons should sharpen their osteotomes. While some surgeons prefer to sharpen them themselves before or after each case, others have professional manufacturing companies perform the sharpening at certain intervals (e.g., every four months). However, professional sharpening results in large amounts of erosion of the steel, and this has been reported to reduce the life of osteotomes (4, 5).

Ceramic stones, diamond stones, Arkansas stone, Indian stone, aluminum oxide stones, stone engines, and sandpaper are among the materials that can be used in the sharpening process (1, 5). Comparisons of the sharpening results of fine-particle stones (e.g., Arkansas, aluminum oxide) and larger-particle stones (e.g., India and diamond stones) have shown

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fine-particle stones to provide more successful results in terms of sharpness (6). An inexpensive alternative to sharpening stones is to use sandpaper made from silicon carbide, which can then be glued to a piece of wood and used as a sharpening stone (7). Although sandpaper is not a frequently used material in osteotome sharpening, the study has chosen it due to being an inexpensive and easy method that is frequently preferred in daily life for knife sharpening.

Surgeons generally decide when to sharpen instruments by feel (4, 5). Most facial plastic surgeons tend to sharpen their instruments themselves when needed. Therefore, this study aims to compare the effectiveness of Arkansas stone and sandpaper, two different and easily accessible materials that can be used for sharpening under operating room conditions.

MATERIAL AND METHODS

Study Design

This prospective study received exemption approval from the institutional review board of Samsun Training and Research Hospital, a tertiary hospital in Turkey, as the study does not use human tissue. Following the approval from the ethics committee, the study and all measurements were carried out at the Samsun Training and Research Hospital. This study has been funded by the Samsun Training and Research Hospital (Date: 26.09.2019, no: KAEK 219/2/24).

Method for Measuring Sharpness

This study has used three new identical 10 mm Cinelli Osteotomes (Karl Storz, Tuttlingen, Germany; Figure 1c). To realistically simulate nasal osteotomies, a 90-degree complete vertical cut was made to an artificial bone (4 mm wide, 4 cm thick) with a density of 40 PCF (pounds per cubic foot; Sawbone, Sawbones Europe AB, Malmö, Sweden) by applying hammer blows of equal force to all the osteotomes (Figure 1b). A crank-based hammering system was designed, with a latch under the hammer crank that always allowed the crank to drop and hit the osteotome from the same height. A load cell with a touchscreen (Centor Star Touch, Comten Inc., Florida, USA) was used to measure the force transmitted to the osteotome (Figure 2b). The first author (C.B.) hammered the osteotomy three times, and 80 pounds (lb) of effective force was seen to be transferred on average. The height from which to drop the free hammer to create the same force was determined, with the hammer being consistently released from this height. Meanwhile, the mallet strokes made on the artificial bones were performed at equal strength (Figure 2a; Supplemental Video 1).

Figure 1: a) Sandpaper with 500 and 1,000 grit, cut into 10 mm thin strips and waiting to be bonded to wooden blocks for sharpening; b) Fine and c Arkansas stones (shown as >>) with 500 and 1,000 grit and artificial bone blocks (*); and c) 10 mm Cinelli osteotome (Karl Storz, Tuttlingen, Germany).

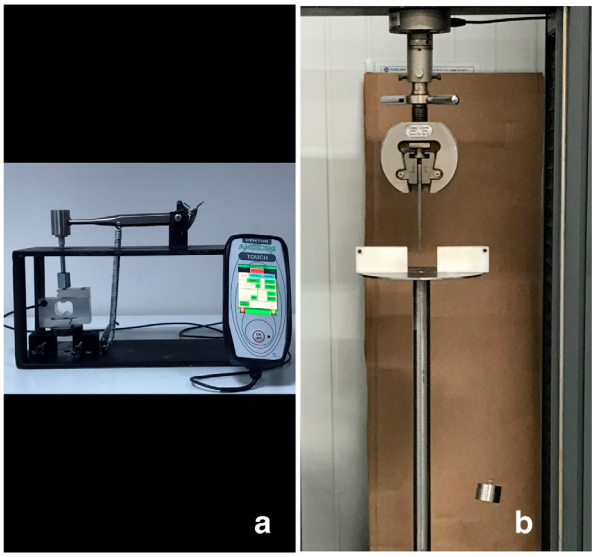

Figure 2: a) A hammer crank-based system and a load cell with a touchscreen (Centor Star Touch, Comten Inc., Florida, USA), b) Preparation of the test setup by adding 370 g weight of 5/0 polypropylene suture (Prolene, Ethicon Inc., Somerville, New Jersey) after placing a Cinelli osteotome into the WDW-350 Electronic Universal Testing Machine (TIME Group Inc., Beijing, China).

Supplemental Video 1: A hammer crank-based system always being dropped from the same height once the latch is released and hitting the osteotome forward.

All the osteotomes were made by the same manufacturer at the same size and weight and had original factory sharpness. Equal forces were applied to the osteotomes, and strokes were repeated until a full-thickness cut had been made in the artificial bone. The sharpness of all three osteotomes was measured at the baseline and after the 1st, 4th, 7th, and 10th complete osteotomies. These osteotomy sequences and measurements were designed based on those from Ransom et al. (5).

One of the three osteotomes was used in each of the following groups: the no-sharpening (NS) group, the Arkansas stone (AS) group, and the sandpaper (SP) group. In the AS and SP groups, the osteotomes were sharpened after the 1st, 4th, 7th, and 10th complete osteotomies, with three measurements then being repeated for each group (Figure 3).

Grit as a term refers to the number of particles per square inch (6). This study used coarser 500 grit followed by finer 1,000 grit for the both Arkansas stone and the sandpaper sharpening, applying the same technique to both (Figure 1a).

To measure the sharpness of the osteotomes, this study used the test setup Bloom et al. and Ransom et al. had created (4, 5). For this purpose, the double-guided Cinelli Osteotome was placed in a WDW-350 Electronic Universal Testing Machine (TIME Group Inc., Beijing, China), and then a monofilament 5/0 polypropylene suture (Prolene, Ethicon Inc., Somerville, New Jersey) was tied tightly (Figure 2b). This study fixed the suture material with a specially designed holder, and a 370-g weight was attached to the other side to create the necessary tension as described in Bloom et al.'s (and Ransom et al.'s measurement models (4, 5). Using the universal tester and holder, each osteotome was advanced downward into the suture at a constant speed (5 mm/min) until the suture was cut. The universal tester generates a force displacement curve. The force at the time of cutting is inversely proportional to the sharpness of the blade. In other words, the lower the force used to cut the suture, the sharper the blade. The force used to have the osteotome cut by applying pressure to the suture was measured and recorded in Newtons (N).

No sharpening (NS) group	Arkansas stone (AS) group		Sandpaper (SP) group	
Baseline measurements				
0,41	0,48		0,35	
0,50	0,65		0,38	
0,46	0,22		0,58	
1st osteotomy				
	Post-osteotomy	Post-sharpening	Post-osteotomy	Post-sharpening
0,51	0,59	3,39	1,19	1,97
0,39	0,17	2,80	1,45	1,66
0,50	0,10	1,37	0,38	1,77
4th osteotomy				
0,74	4,04	5,32	1,07	3,03
0,69	4,69	4,98	1,32	3,01
0,58	0,69	3,83	1,94	3,35
7th osteotomy				
1,32	3,64	1,68	3,24	5,07
0,79	3,50	4,08	2,63	5,60
0,76	1,46	2,24	3,13	6,80
10th osteotomy				
0,60	0,66	1,10	5,70	7,38
0,88	0,54	1,82	5,49	6,72
0,67	0,16	2,07	4,91	7,50

Figure 3: Graphic of the sharpness measurement of the groups at baseline and following the 1st, 4th, 7th, and 10th osteotomies and sharpening sessions.

Sharpening Technique

The study uses the hand-sharpening protocol described by Gryskiewicz et al. (3). In accordance with this protocol, forward-pressure pushes were performed 10 times on both sides of the osteotome at a 30-degree inclination. These were followed by 10 forward strokes at a 45-degree angle to both sides at less pressure, with one very gentle final forward stroke at a 60-degree angle. All sharpening was done by the same senior author (C.B.) using the same technique.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS, version 21.0; IBM Corp., Armonk, New York, USA) was used for the data analysis. Comparisons among the three groups were made using one-way analysis of variance (ANOVA), with the post-hoc Tukey honestly significant difference (HSD) test being performed for significant comparisons. The paired t-test was used to compare the measurements among the osteotomies. Lastly, the Pearson correlation test was used to show the relationship between the sharpness and the number of osteotomies in each group, with a $p<0.05$ being considered statistically significant.

RESULTS

No significant differences were found among the groups regarding the baseline measurements for all three Cinelli osteotomes ($p=0.986$). However, significant differences were observed in all of the comparisons among the groups after the 1st, 4th, 7th, and 10th osteotomies and the sharpening processes ($p<0.05$). After the 1st osteotomy and sharpening, the osteotomes in the AS group had become significantly blunted. After the 4th osteotomy sequence, the osteotomes in the AS (the dullest one) and SP groups were found to have become more significantly blunted (Table 1).

The AS group experienced a visible fracture after the 7th osteotomy, and the sharpness value decreased to the point that no difference appeared between the AS and NS groups in the last two measurements. Meanwhile, the SP group saw its sharpness continue to become increasingly blunted; this group received the worst score after the 10th osteotomy, significantly worse than the other osteotomes (Figure 3).

When evaluating the groups separately, the NS group could easily be seen to have been much more stable. When evaluating the paired comparisons within the groups, no significance was observed in the NS group ($p\geq0.05$). In the AS group, a strongly significant difference occurred in the comparisons between the base and 4th osteotomy and between the 1st and 4th osteotomies ($p=0.00$). In the SP group, on the other hand, the sharpness consistently became blunter, with strongly significant differences being observed in all paired comparisons except for between the 7th and 10th osteotomies. When comparing

Table 1: Comparison of sharpness scores (Newton) among groups inter-osteotomy and sharpening procedures

	No sharpening (NS) group	Arkansas stone (AS) group	Sandpaper (SP) group	P value[Y]
	(Mean ± *SD*)	(Mean ± *SD*)	(Mean ± *SD*)	
Base measurement	0.45 ± 0.04**a**	0.45 ± 0.21**a**	0.43 ± 0.12**a**	0.986
1st osteotomy	0.46 ±0.06**a**	2.52 ± 1.03**b**	1.80 ± 0.15a**b**	**0.016**
4th osteotomy	0.67 ± 0.08**a**	4.71 ± 0.78**b**	3.13 ± 0.19**c**	**0.001**
7th osteotomy	0.95 ± 0.31**a**	2.66 ± 1.25**a**	5.82 ± 0.88**b**	**0.002**
10th osteotomy	0.71 ± 0.14**a**	1.66 ± 0.50**a**	7.20 ± 0.42**b**	**0.001**

Y : One-Way ANOVA test , **a/b/c** letters show intergroup difference in each row (Post Hoc test-Tukey HSD test**),** statistically significant *p* values are emphasized in bold. *SD* = Standard deviation.

Table 2: Paired comparisons of base measurements and measurements after the 1st, 4th, 7th, and 10th osteotomy and sharpening for each group

	No sharpening (NS) group	Arkansas stone (AS) group	Sandpaper (SP) group
Base – 1st osteotomy	.887	.056	**.009**
Base – 4th osteotomy	.075	**.007**	**.000**
Base - 7th osteotomy	.135	.077	**.007**
Base - 10th osteotomy	**.**050	.076	**.001**
1st osteotomy - 4th osteotomy	.089	**.005**	**.013**
1st osteotomy - 7th osteotomy	.097	.890	**.019**
1st osteotomy - 10th osteotomy	.177	.427	**.001**
4th osteotomy - 7th osteotomy	.193	.131	**.022**
4th osteotomy - 10th osteotomy	.680	**.**051	**.002**
7th osteotomy - 10th osteotomy	.431	.257	.104

Paired t-test (statistically significant *p* values are emphasized in bold print.

the base measurements to those for the 10th osteotomy, no differences were observed for the NS or AS groups ($p \geq 0.05$), while a significant difference was found for the SP group ($p < 0.05$; Table 2, Figure 4).

The study also investigated correlations between the number of osteotomies and the measurements. The only highly positive significant correlation was observed in the SP group ($r = 0.990$, $p = 0.010$).

DISCUSSIONS

Maintaining surgical instruments is extremely important for surgical quality. The sharpness of an osteotome facilitates work on focused areas, which in turn results in fewer microfractures and prevents unwanted segmental fractures with large volumes

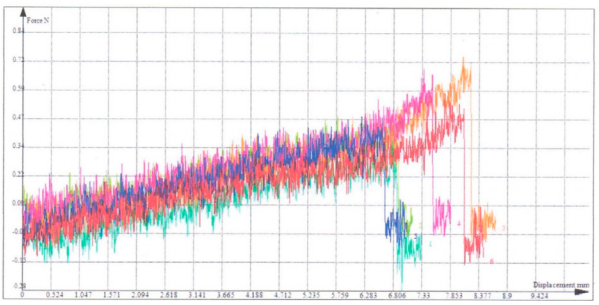

Figure 4: Box plots of sharpness measurements for the groups after the 10th osteotomy and sharpening session

by reducing any unnecessary excessive force on the hammer. In nasal surgery, osteotomes are generally used in hump reduction and lateral osteotomies. A sharp osteotome plays a very important role in achieving the desired result and avoiding complications such as irregularities or asymmetries (2, 4, 5, 8-10).

To date, no consensus has been reached regarding how to measure the sharpness of osteotomes or how often they should be sharpened or replaced after use. Surgeons themselves are the ones who usually decide to sharpen or buy new instruments by palpating with their fingers or sensing its sharpness during an operation (4, 5).

Some authors have tried a variety of methods for determining whether surgical instruments are sharp enough. For instance, Dr. S. Anthony Wolfe stated the best way to ascertain a tool's sharpness is by looking at the light reflectance along its working edge (1). Wolfe's opinion is that a less-sharp edge reflects more light due to the deterioration of the microcrystalline structure of the tool, whereas no light reflects on the sharp edge of a well-sharpened instrument. However, White et al.'s (10) recent article reported that their experimental osteotomy model found visual inspection to be unable to detect blunting of the sharp edge, even when the measured sharpness value had decreased by up to 50%.

More objective tests for measuring sharpness are also commercially available, including the Cutlery and Allied Trades Research Association (CATRA) sharpness tester. This involves a sharpness index that is based on the depths of the first three measurement cuts that are made by pushing the sharp side of a synthetic paper fixed in a station toward the blade while

facing up (11). McCarty et al. outlined a blade sharpness index (BSI) as an objective sharpness testing method that forces the osteotome into a soft wax substrate (12). This method also allows for measurement without damaging the fine edge. The current study has preferred using the reliable and reproducible objective method for sharpness as previously been defined by Bloom et al. and Ransom et al. (4, 5).

Many different techniques and sharpening materials are available for maintaining the sharpness of osteotomes. These can be divided into professional sharpening methods using powered instruments and sharpening done with hand tools. When looking at the materials that are used, coarse particulate stones such as aluminum oxide, carborundum, and Norton stones perform the sharpening process quickly but cause a striated appearance along the cutting edge. Arkansas, Neumar, and ceramic stones are examples of fine particle stones that provide sharp-edge softness. In addition, sandpaper can be used as a delicate, easy, and less-expensive sharpening method (13). The recommendations generally involve starting with coarse particle materials and finishing with fine particle sharpeners, which is why this study started sharpening at 500 grit and finished with 1,000 grit for both the SD and AS groups (14).

Manual sharpeners have been observed to possess better cutting edges than those made with powered tools (15, 16). Bloom et al. showed metal mass to decrease quicker with professional sharpening and stated that this situation could decrease the lifespan of the osteotome (4). However, neither professional sharpening nor hand sharpening was able to achieve a result close to the baseline values before the osteotomies.

One thing this study has definitively proven is that osteotomes become dull with use (4, 5). This study found sharpness to gradually decrease in the NS group, with a slight difference being observed between the baseline measurement and the 10th osteotomy/sharpening measurement (p=0.05). Sharpness values continued to deteriorate significantly in the SP group in spite of the sharpening, with a positive and strongly significant correlation between the number of osteotomies and the sharpness measurements (p=0.010, r=0.990). In the AS group, the measurements significantly decreased after the 1st and 4th osteotomies, even though the worst sharpness values among the groups differed significantly at the end of the 4th osteotomy (p<0.05). However, after the 7th and 10th osteotomies the measured change in sharpness decreased significantly, while the significant difference between the NS group's 7th and 10th measurements disappeared (p>0.05). Using a coarse particle sharpener before the osteotome had become dull appears to have resulted in much worse scores in the AS group. As a result of a cumulative effect due to repeated use, the AS group may have started with better scores.

Tebbett recommended sharpening osteotomes after each use (8). Based on the results obtained here, the current study believes that surgeons can use new osteotomes without sharpening them until they feel uncomfortable about their sharpness. Surgeons should also keep in mind the use of disposable osteotomes, as suggested by Bloom et al. (4). However, due to this not always being economically possible, this study believes that using an Arkansas stone in sharpening may provide better long-term results.

The limitation of this study is that, although the measurements were repeated three times, only one osteotome was used in each group. On the other hand, applying forces using a mechanism prevented any possible human-induced measurement variations and provided more objective information, which strengthened the study.

CONCLUSIONS

When considering the complications of a blunt-tipped osteotome, the need for more objective tests regarding the use of osteotomes may be important to note because surgeons cannot easily determine the sharpness of an osteotome, at least not until they use it. However, this study believes that using an osteotome without sharpening it until it becomes dull is better. These can then either be replaced with new ones or professionally sharpened. Sharpening after the first use may damage the cutting edge of the osteotome and blunt the cutting edge. In addition, choosing an Arkansas stone as the sharpening material might be a better choice compared to sandpaper with respect to sharpening.

Ethics Committee Approval: This study was approved by Samsun Training and Research Hospital Clinical Research Ethics Committee (Date: 26.09.2019, No: KAEK 2019/2/24).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- C.B.; Data Acquisition- M.E.S.; Data Analysis/Interpretation- C.B., N.F.T.; Drafting Manuscript- N.F.T.; Critical Revision of Manuscript- C.B., M.E.S.; Final Approval and Accountability- C.B.; Material or Technical Support- N.F.T., C.B.; Supervision- C.B.

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REFERENCES

1. Wolfe SA. On the maintenance and sharpening of instruments. Plast Reconstr Surg 2005;116(5):89-91.
2. Lee HM, Kang HJ, Choi JH, Chae SW, Lee SH, Hwang SJ. Rationale for osteo- tome selection in rhinoplasty. J Laryngol Otol 2002;116(12):1005-8.
3. Gryskiewicz JM, Gryskiewicz KM. Nasal osteotomies: a clinical comparison of the perforating methods versus the continuous technique. Plast Reconstr Surg 2004;113(5):1445-58.
4. Bloom JD, Ransom ER, Antunes MB, Becker DG. Quantifying the sharpness of osteotomes for dorsal hump reduction. Arch Facial Plast Surg 2011;13(2):103-8.

5. Ransom ER, Antunes MB, Bloom JD, Becker DG. Quantifying osteotome sharpness: comparing the major manufacturers. Otolaryngol Head Neck Surg 2012;146(5):707-11.
6. Rossi R,Smukler H. A scanning electron microscope study comparing the effectiveness of different types of sharpening stones and curets. J Periodontol 1995; 66(11):956-61.
7. Bottorf S. Sharpening Made Easy: A Primer on Sharpening Knives and Other Edged Tools. Knoxville, USA,In: Knife World Publications; 2002. 34.
8. Tebbets BJ. Primary Rhinoplasty –Redefining the Logic and Techniques. Philadelphia, In: Mosby-Elsevier, c2008. p. 211-24.
9. Skordaris G, Stergioudi F, Boumpakis A, Stergioudi D, Behrbohm H. A FEA-Based Methodology to Predict the Osteotome Wear Status during Nasal Bone Surgical Operations. Coatings 2019;9(12):855.
10. White DE, Bartley J, Whittington C, Garcia LMG, Chand K, Turangi C. Pilot investigation into osteotome hard surface coating and cutting-edge degradation. J Orthop Surg Res 2020;15(1):253.
11. Price, E. Design and validation of a device to measure the cutting edge profile of osteotomes. MEng, Institute of Technology, Sligo. 2005.
12. McCarthy CT, Hussey M, Gilchrist MD. On the sharpness of straight edge blades in cutting soft solids: part I – indentation experiments. Eng Fract Mech 2007;74(14):2205-24.
13. Kolle, Jefferson. "Getting an Edge with Waterstones, Oilstones, and Sandpaper". Finewoodworking. https://web.archive.org/web/20100621070933/http://www.finewoodworking.com/pages/w00003.asp. Publish Date:21.06.2010. Accessed January 23, 2021.
14. Acevedo RA, Cardozo AK, Sampaio JE. Scanning electron microscopic and profilometric study of different sharpening stones. Brazilian dental journal 2006;17(3):237-42.
15. Wilkins EM, Boyd LD. Clinical Practice of the Dental Hygienist. In: Linda D. Boyd, RDH, RD, EdD; Jane F. Halaris, ASDH, MA; Lisa F. Mallonee, MPH, RDH, RD, LD; Charlotte J. Wyche, BSDH, MS eds. Instrument Care and Sharpening. 13th ed, Jones & Bartlett Learning 2020:1997.
16. Antonini CJ, Brady JM, Levin MP, Garcia WL. Scanning electron microscope study of scalers. J Periodontol 1977;48(1):45-8.

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Comparison of High-Resolution Computed Tomography and Surgical Findings in Patients with Temporal Bone Cholesteatoma

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ABSTRACT

Objective: The present study aims to investigate the role of high-resolution computed tomography (HRCT) in temporal bone cholesteatoma.
Materials and Methods: Eighty-two patients with a pathological diagnosis of chronic otitis media with cholesteatoma were included in this retrospective study. All patients had a complete preoperative otorhinolaryngologic examination, audiological assessment, and HRCT. Preoperative radiological findings were evaluated together with the findings obtained during surgery.
Results: In HRCT, cholesteatoma was most common in pars flaccida (36.25%). The most common localization of cholesteatoma was holotympanic (36.25%). Erosion was most common in all ossicles (43.75%), but solitary erosion was most common in the incus (35%). The facial nerve canal was intact in 58 (72.5%) of the patients. The diagnostic sensitivities of HRCT in cholesteatoma cases were 97.6% for tissue mass, 97.6% for localization, 100% for malleus erosion, 84.8% for incus erosion, 100% for malleus and incus erosion, 40% for incus and stapes erosion, 94.6% for the erosion of all ossicles, and 100% for facial nerve canal erosion.
Conclusion: Preoperative HRCT evaluation in patients with cholesteatoma may be considered indispensable for the location of the disease and the detection of destructive structures.

Keywords: Cholesteatoma, Diagnostic imaging, Otitis Media, Surgery, Tomography

INTRODUCTION

Chronic otitis media (COM) is defined as inflammation and infection of the middle ear and mastoid cells lasting longer than 3 months, accompanied by perforation of the tympanic membrane, and recurrent or persistent otorrhea (1). Cholesteatoma is defined as a pathological cystic formation that contains keratin residues covered with squamous cell epithelium, spread within the pneumatized spaces in the middle ear and mastoid bone, and may cause bone erosion and related complications (2).

The presence of granulation tissue or cholesteatoma due to inflammation in chronic otitis media disease may lead to progressive destruction of structures in the temporal bone, especially the middle ear ossicles, and may lead to intracranial or extracranial complications, especially progressive hearing loss (1-4). Computed tomography (CT) and magnetic resonance imaging (MRI) methods are used in the preoperative evaluation of COM disease, in the investigation of the presence of complications, and in the determination of the presence of cholesteatoma (4, 5). High-Resolution Computed Tomography (HRCT) allows for determining the extent of the disease that cannot be evaluated by examination, evaluating the surgical landmarks, evaluating the risk of intraoperative complications, evaluating the condition of the temporal bone structures, and determining the complications related to the disease (5). Imaging methods can detect the suspicion of cholesteatoma, however, the definite diagnosis of cholesteatoma is made by pathological evaluation (5, 6).

Chronic otitis media treatment includes medical and surgical methods. Medical treatment includes antibiotics, anti-inflammatory drugs, and frequent aspiration (1-3). Surgical

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treatment is applied in cases that are resistant to medical treatment, have a cholesteatoma, and have complications (1-3). The primary aim of surgical treatment is to obtain a non-inflamed, dry, and well-ventilated middle ear cavity. The secondary aim is to restore hearing loss with an intact tympanic membrane and a repaired sound conduction mechanism (4).

Computed tomography (CT) and magnetic resonance imaging (MRI) methods are used in the preoperative evaluation of COM disease, in the investigation of the presence of complications, and in the determination of the presence of cholesteatoma (4, 5). High-Resolution Computed Tomography (HRCT) allows for determining the extent of the disease that cannot be evaluated by examination, evaluating the surgical landmarks, evaluating the risk of intraoperative complications, evaluating the condition of the temporal bone structures, and determining the complications related to the disease (5).

Tympanoplasty is the name given to the surgery performed to obtain a disease-free middle ear, repair the perforation of the tympanic membrane, and provide sound transmission with ossicular chain reconstruction (7). Mastoidectomy is a surgery performed to clear the inflammation spreading to the mastoid bone, to provide ventilation of the middle ear cavity, to treat COM complications, or to provide the necessary access route for advanced ear surgeries such as cochlear implants and facial nerve decompression (7, 8). Mastoidectomy procedures are divided into two classes, defined according to the extent of the pathology causing the surgery: procedures in which the posterior wall of the external auditory canal is preserved (intact canal (Canal Wall Up-CWU)), and procedures in which the posterior wall of the external auditory canal is downed (Canal Wall Down-CWD) (7, 8).

MATERIALS AND METHODS

This study was approved by the Istanbul University-Cerrahpaşa Clinical Research Ethics Committee (Date: 09.07.2021, No: 133594). Patients admitted to Cerrahpaşa Faculty of Medicine Hospital between June 2021 and June 2022 were included in this retrospective study. This study was conducted by the Declaration of Helsinki and informed consent was obtained from all patients.

Eighty-two patients whose surgical specimens were evaluated as cholesteatoma were included in the study. Patients whose surgery was revision surgery, who did not have an operation video in our archive, who did not have a detailed operation report in their file, whose preoperative radiological examinations were not performed in the radiology department of our hospital, whose preoperative radiology images were not registered in the system, who did not have a preoperative radiology report, and who did not have a postoperative pathology evaluation were excluded from the study.

Radiological evaluations of all patients were performed with HRCT with a section thickness of 1 mm. The presence of soft tissue in the middle ear, cholesteatoma types according to localization, ossicular destructions, and facial nerve canal erosion were evaluated. The operations were performed using a microscope and an endoscope. The surgical procedures performed were CWU and CWD, depending on the extent of the disease. Surgical evaluation of the study parameters was performed with the surgical epicrisis and videos. The correlation between preoperative CT images and surgical findings was investigated.

Statistical Analysis

Statistical analyses were performed using SPSS 23.0 software (IBM, USA). Demographic characteristics of the patients were defined, and sensitivity, specificity, and accuracy of computed tomography were determined.

RESULTS

The demographic characteristics of patients are given in Table 1. Eighty patients (97.6%) had at least one finding related to cholesteatoma in the radiology report (Figure 1, Figure 2). The parameters evaluated in HRCT are presented below.

Table 1: Demographic characteristics of patients

Parameters		Population (n=80)
Gender	**Male, n(%)**	44 (55)
	Female, n(%)	36 (45)
Age (years)	**Mean±SD (min-max)**	38.2±14.341 (8-60)

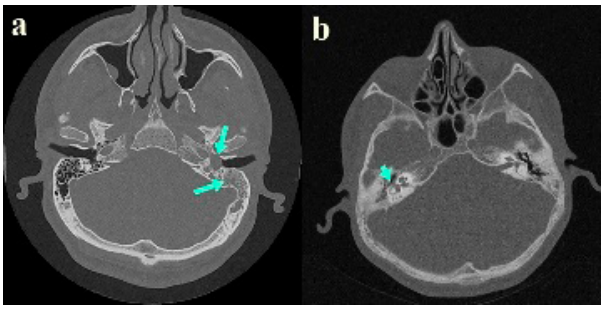

Figure 1a: The mass in soft tissue density in the middle ear and mastoid cavity
Figure 1b: Facial nerve canal defect

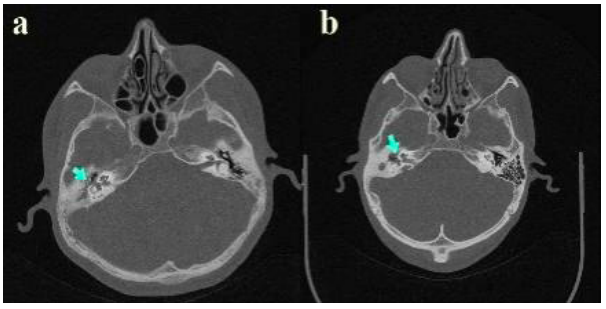

Figure 2a: Intact ossicles within the soft tissue
Figure 2b: The soft tissue accompanying destruction in all ossicles

Type of Cholesteatoma

The distribution of cholesteatoma types is presented in Table 2. Pars flaccida cholesteatoma was the most common type. However, pars tensa cholesteatoma was the least common type.

Table 2: Type of cholesteatoma in the computed tomography

Cholesteatoma type	Number of patients (n)	%
Pars tensa	23	28.75
Pars flaccida	29	36.25
Combined	28	35

Location of cholesteatoma

The locations of cholesteatoma are presented in Table 3. Epitympanic cholesteatoma was the most common, followed by holotympanic cholesteatoma.

Table 3: Locations of cholesteatoma in the computed tomography

Location		Number of patients (n)	%
Epitympanic	Attic	25	31.25
	Attico-antral	15	18.75
Mesotympanic		11	13.75
Holotympanic		29	36.25

Destruction of the ossicular chain

Table 4 shows the erosion of the ossicular chain. All ossicles were damaged most frequently in patients. When we examined the individual ossicles, the incus was the most frequently-eroded bone.

Table 4: Destruction of the ossicular chain in the computed tomography

Eroded ossicles	Number of patients (n)	%
Malleus only	4	5
Incus only	28	35
Malleus+Incus	3	3.75
Incus+Stapes	4	5
All ossicles	35	43.75

The integrity of the facial nerve canal

Table 5 presents the integrity of the facial nerve canal. In most of the patients, the facial nerve canal was intact on HRCT.

Table 5: Integrity of the facial nerve canal in the computed tomography

Facial Nerve Canal	Number of patients (n)	%
Intact	58	72.5
Eroded	22	27.5

Evaluation of computed tomography results

Table 6 shows the correlation between HRCT and intraoperative features. HRCT has the lowest sensitivity in the detection of incus + stapes erosions. The lowest specificity is for the detection of facial nerve canal defects.

Canal Wall-Down surgery was performed in 12 (14.63%) of 82 patients and CWU surgery was performed in 70 (85.37%) of them.

DISCUSSION

Patient history and otoscopic examination are essential for the diagnosis of cholesteatoma. High-resolution computed tomography is the most critical auxiliary examination in the preoperative evaluation in the presence or suspicion of cholesteatoma (9). In this study, preoperative HRCT findings and data obtained during surgery were compared in patients operated on for COM with cholesteatoma. In cases where incus and stapes erosions were together, the diagnostic sensitivity of HRCT was low (40%), and it was high in describing other investigated findings. The diagnostic specificity of HRCT is 100% for almost all parameters examined, whereas it is 96.6% due to false positives in the case of facial nerve canal erosion.

The main pathophysiological mechanism in the development of complications due to cholesteatoma in the middle ear is that the keratinized epithelium, which should not be in the middle ear, proliferates and expands towards the surrounding tissues and causes erosion in these surrounding tissues, both with the effect of compression and the effect of secreted enzymes

Table 6: Correlation between computed tomography and intraoperative features

Findings	Computed Tomography (CT)	Intraoperative Findings	False		Sensitivity of CT	Specificity of CT	Accuracy of CT
			Negative	Positive			
Tissue mass	80	82	2	0	97.6%	NA	97.6%
Location	80	82	2	0	97.6%	NA	100%
Malleus erosion	4	4	0	0	100%	100%	100%
Incus erosion	28	33	5	0	84.8%	100%	93.9%
Malleus+Incus	3	3	0	0	100%	100%	100%
Incus+stapes erosion	4	10	6	0	40%	100%	%92.7
Erosion of all ossicles	35	37	2	0	94.6%	100%	97.6%
Facial Nerve Canal erosion	22	20	0	2	100%	%96.8%	97.6%

NA: Not applicable

(10,11). The equivalent of this pathology in HRCT is the presence of soft tissue in the middle ear and the destruction of structures such as middle ear walls, ossicles, facial nerve canal, and semicircular canals (12). It is known that HRCT is superior to conventional CT in the diagnosis of cholesteatoma and its complications (13). The presence of cholesteatoma can be detected with high accuracy by HRCT (14). In the study by Bozan et al., 21 (91.3%) of 23 cholesteatoma cases, and in the study by Gomaa et al, 52 (92.8) of 56 cases were correctly diagnosed by HRCT (12, 15).

The most common findings related to cholesteatoma in HRCT are ossicular erosion, typical localization of the disease, and soft tissue mass in the middle ear (12). In previous studies, it has been shown that cholesteatoma is the most common type of combined cholesteatoma and pars flaccida cholesteatoma in the HRCT and the most common localization of cholesteatoma is the attic region (12, 15). When HRCT of cholesteatoma patients is evaluated for ossicular erosion, erosion is most common in all bones (no ossicles). However, the ossicle that is most frequently eroded alone is the incus (12). The result of the present study supports the literature.

A defective facial nerve canal is one of the most important causes of facial nerve paralysis, which is one of the intraoperative complications that can occur during chronic otitis media surgery (16). In the literature, the sensitivity of the diagnosis of eroded facial nerve canal in HRCT has been reported as 83.3% (12). In our study, the sensitivity of this diagnosis was found to be 100%. This may be due to the fact that the radiology department of our institute is a very experienced center in neuroradiology. Despite this high sensitivity in diagnosis, we still recommend using neuromonitoring to avoid the complication of facial paralysis.

An undamaged stapes due to COM is the most important parameter for hearing reconstruction (17, 18). The sensitivity of HRCT in the diagnosis of ossicular erosion is high. However, HRCT has low sensitivity to early stapes erosion (12-15). In our study, the sensitivity of the diagnosis of incus and stapes damage in HRCT was found to be 40%. This indicates that HRCT alone is insufficient for planning preoperative hearing reconstruction. Even if stapes damage is not mentioned in HRCT, this situation should be kept in mind, and materials such as total ossicular replacement prosthesis (TORP) should be available in case they can be used in surgery. Otherwise, this unexpected situation may require a second surgery for hearing reconstruction.

Some factors limit the value of this study. The first of these limitations is that our study is a retrospective study. The second limitation is that we did not evaluate all the structures that could be damaged by cholesteatoma, such as semicircular canals, middle ear, and mastoid cavity walls. The third limitation is that we did not have any patients who were misdiagnosed in HRCT, since we included patients with a definite diagnosis of cholesteatoma in our study. The final limitation is the number of patients in our study. Although our center is a tertiary center, the number of patients diagnosed with cholesteatoma during one year is 80. This can be explained by the inability of patients to visit the hospital due to the pandemic.

CONCLUSION

HRCT may be considered an indispensable test in all chronic otitis media cases, especially in cases accompanied by cholesteatoma, to avoid intraoperative complications, to plan hearing reconstruction, and to recognize and plan the repair of disease-related defects before the operation. Prospective studies with larger numbers of patients are needed to support the data we obtained.

Ethics Committee Approval: This study was approved by Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 09.07.2021, No: E-83045809-604.01.02-133594).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.Ç., S.U.; Data Acquisition- D.Ç.; Data Analysis/Interpretation- S.U.; Drafting Manuscript- D.Ç.; Critical Revision of Manuscript- D.Ç., S.U.; Final Approval and Accountability- D.Ç.; Material or Technical Support- D.Ç.; Supervision- S.U.

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REFERENCES

1. Brennan-Jones CG, Chong LY, Head K, Burton MJ, Schilder AG, Bhutta MF. Topical antibiotics with steroids for chronic suppurative otitis media. Cochrane Database Syst Rev 2020;8:CD013054.
2. Rutkowska J, Özgirgin N, Olszewska E. Cholesteatoma Definition and Classification: A Literature Review. J Int Adv Otol 2017;13(2):266-71.
3. Morris P. Chronic suppurative otitis media. BMJ Clin Evid 2012;2012:0507.
4. Peng T, Ramaswamy AT, Kim AH. Common Otologic Surgical Procedures: Clinical Decision-Making Pearls and the Role of Imaging. Neuroimaging Clin N Am 2019;29(1):183-96.
5. Banerjee A, Flood LM, Yates P, Clifford K. Computed tomography in suppurative ear disease: Does it influence management? J Laryngol Otol 2003;117:454-8.
6. Casazza G, Carlson ML, Shelton C, Gurgel RK. The Medially-Invasive Cholesteatoma: An Aggressive Subtype of a Common Pathology. Ann Otol Rhinol Laryngol 2021;130(1):38-46.
7. Merkus P, Kemp P, Ziylan F, Yung M. Classifications of mastoid and middle ear surgery: A scoping review. J Int Adv Otol 2018;14:227-32.
8. Jones JW, Archbold R, Hillman TA, Chen DA. The Role of Mastoidectomy in Draining Ventilation Tubes. Ear Nose Throat J 2020;99(1_suppl):35-8.
9. Watts S, Flood LM, Clifford K. A systematic approach to interpretation of computed tomography scans prior to surgery of middle ear cholesteatoma. J Laryngol Otol 2000;114(4):248-53.

10. Castle JT. Cholesteatoma Pearls: Practical Points and Update. Head Neck Pathol 2018;12(3):419-29.
11. Gilberto N, Custódio S, Colaço T, Santos R, Sousa P, Escada P. Middle ear congenital cholesteatoma: systematic review, meta-analysis and insights on its pathogenesis. Eur Arch Otorhinolaryngol 2020;277(4):987-98.
12. Gomaa MA, Abdel Karim AR, Abdel Ghany HS, Elhiny AA, Sadek AA. Evaluation of temporal bone cholesteatoma and the correlation between high resolution computed tomography and surgical finding. Clin Med Insights Ear Nose Throat 2013;6:21-8.
13. Sethom A, Akkari K, Dridi I, Tmimi S, Mardassi A, Benzarti S, et al. Apport de la tomodensitométrie dans le bilan pré opératoire de l'otite moyenne chronique cholestéatomateuse. A propos de 60 cas [Preoperative CT Scan in middle ear cholesteatoma]. Tunis Med 2011;89(3):248-53.
14. Manik S, Dabholkar Y, Bhalekar S, Velankar H, Chordia N, Saberwal A. Sensitivity and specificity of high-resolution computed tomography (HRCT) of temporal bone in diagnosing cholesteatoma and ıts correlation with ıntraoperative findings. Indian J Otolaryngol Head Neck Surg 2021;73(1):25-9.
15. Bozan N, Fidan B, Tiren Ö, Arslan A, Kundi P, Özkan H, et al. Kronik Süpüratif Otitis Media Hastalarında Radyolojik ve Cerrahi Bulguların Karşılaştırılması [Comparison of Radiological and Surgical Findings in Patients with Chronic suppurative Otitis Media] Van Tıp Derg 2017;24(4):293-7.
16. Kamalden TMIT, Yusof ANM, Misron K. A review of delayed facial nerve paresis as complication following total endoscopic ear surgery. J Int Adv Otol 2021;17(6):570-3.
17. Eryılmaz A, Uyar M, Oğuz O, İriz A, Boynueğri S, Acar A, et al. Hearing results according to ossiculoplasty techniques in chronic otitis media. Praxis of ORL 2014;2(1):11-7.
18. Demir D, Güven M, Yılmaz M, Çelik B, Kara A. Hearing Results According To Ossiculoplasty Techniques In Chronic Otitis Media. Kbb-Forum 2018;17(4):117-22.

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Effects of Acitretin Treatment on Hearing in Patients with Psoriasis Vulgaris

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ABSTRACT

Objective: In this study, we aimed to compare the hearing thresholds and outer hair cell functions of patients with psoriasis vulgaris (PV) with healthy individuals and to investigate the ototoxic effects of acitretin treatment (AT) in patients with PV.
Materials and Methods: This study included 23 patients with PV who required treatment with acitretin as well as 23 healthy individuals. Conventional and extended high-frequency pure-tone audiometry and transient-evoked otoacoustic emission tests were performed at regular intervals during the 24 weeks of acitretin treatment.
Results: During the acitretin treatment for the PV group, the hearing thresholds of 4,000 Hz (right ear, p=0.004) presented a significant difference that did not have a worsening effect. The signal-to-noise ratios of TEOAE did not show a significant difference. At 24 weeks of AT, the changes in the hearing thresholds (4,000 Hz) and TEOAE signal-to-noise ratios did not indicate any worsening owing to acitretin. According to the ASHA criteria, there was no significant evidence of ototoxicity related to acitretin. According to the TUNE ototoxicity grading system, it was seen that at 24 weeks of AT, all the patients with psoriasis were scored as grade 0 (no hearing loss).
Conclusion: This study showed that acitretin does not have an ototoxic effect when it is used to treat PV in the recommended treatment doses.

Keywords: Acitretin, high-frequency hearing, ototoxicity, psoriasis vulgaris

INTRODUCTION

Psoriasis vulgaris (PV) is a T-lymphocyte mediated chronic inflammatory disease that is characterized by the focal formation of inflamed, swollen plaques, which is caused by excessive growth of skin epithelial cells and leads to the continuous shedding of scales. It affects approximately two to three percent of adults (1). PV, which has been considered cutaneous for a long time, is now considered a systemic inflammatory disorder that shares pathogenic pathways with many other chronic and progressive diseases (2).

Retinoids (acitretin, isotretinoin, alitretinoin, and bexarotene) are a group of drugs that are used to treat multiple dermatological diseases. Acitretin is a second-generation oral aromatic retinoid and has been effective in treating severe keratinizing skin lesions, such as PV and ichthyosis since the early 1980s (3). Some studies have mentioned that the metabolism of acitretin could cause dose-dependent adverse effects (4-8), such as sensorimotor neuropathy and some ototoxic effects; however, this is unclear (9, 10).

In the literature, there are studies that mention the ototoxic side effects of acitretin. Hearing loss has been reported with tinnitus and bilateral sudden hearing loss during the first week of using acitretin, but the symptoms disappeared after the decrement of acitretin dose (11). In a group of 12 patients with

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hydradenitis suppurativa who were treated with acitretin, one patient had tinnitus in the fourth month of treatment, and the complaint disappeared with dose reduction (12). In another study, the side effects of the retinoid group (oral isotretinoin and acitretin) on hearing were evaluated with audiometric tests and did not present any significant changes to the hearing thresholds. In the isotretinoin group, the 500 Hz air-conduction hearing thresholds declined significantly in the third month of treatment (13).

The ototoxicity assessment has two purposes: to detect the otologic effect that is caused by the drug regimen as early as possible and adjust the dose of the drug accordingly and to plan the patient's auditory rehabilitation to support the verbal communication capacity of the patient when ototoxicity occurs permanently (1, 2, 14). Although there are many studies on the ototoxic effects of isotretinoin, a member of the retinoid group, the presence of relatively few studies on the ototoxic effects of acitretin led to the planning of this study. In this study, we aimed to investigate the ototoxic effects of acitretin treatment in patients with PV and to compare their hearing thresholds and outer hair cell functions with healthy individuals.

MATERIALS AND METHODS

This prospective interdisciplinary longitudinal study was performed after getting ethical approval from the local clinical research ethics committee (Date: 27.06.2018, no: 2018/0197). Written informed consent was obtained from all the patients.

This study included 23 patients with PV who required treatment with acitretin along with 23 healthy individuals. The inclusion criteria were as follows: older than 18 years, the presence of moderate to severe PV (plaque-type psoriasis) for longer than six months, and no history of prior acitretin use. The exclusion criteria were determined as follows: younger than 18 years, pregnant, lactating, the presence of systemic or local infections, history of head or ear trauma, barotrauma, ototoxic drug usage, history of otologic surgery, patients with psoriatic arthritis, history of ear diseases (such as otosclerosis, Meniere's disease, or suppurative labyrinthitis), and a flat tympanogram. In addition, if the patient had a history of previous treatment, including phototherapy, immunosuppressive, and/or immunomodulating drugs and biological agents within the last 12 weeks, they were excluded from the study. If the hearing evaluations were not completed, the patients were excluded from the analysis. The control group in this study consisted of 23 healthy individuals. The healthy individuals were selected from volunteers who had normal hearing thresholds and no history of dermatologic and/or otologic problems.

Acitretin therapy and clinical assessments

Acitretin at a dose of 0.25–0.5 mg/kg per day was orally administered to patients with PV. The basic biochemical measurements were performed at baseline and after three months of acitretin treatment These included: the complete blood count; liver and kidney function tests; and triglyceride, total cholesterol, and low-density lipoprotein. The clinical improvement was measured by the Psoriasis Area and Severity Index (PASI). Accordingly, acitretin treatment (AT) was started at low doses (0.25–0.30 mg/kg/day), with the patients being evaluated monthly. The dose was gradually increased according to the patients' ability to tolerate the mucocutaneous side effects of the drug, such as dryness and cheilitis, and the severity of the disease. In patients who did not develop side effects and a had more severe disease, the dose was increased every month to reach 0.5 mg/kg/day.

Audiological measurements

All the participants underwent a detailed otorhinolaryngological examination. Before the audiological evaluation, a detailed medical history was taken from all the participants. Audiological tests were performed in the PV group before treatment as a baseline as well as in the second, fourth, sixth, eighth, 12th, and 24th week of AT. In the control group, all audiological assessments were performed once. The audiological results of the controls were compared with those of the PV group before AT.

An acoustic immitancemetry test was performed to evaluate the integrity of the external ear canal, tympanic membrane, flexibility of the middle ear, and the acoustic reflex arc using the Interacoustics AT235h clinical tympanometer (Interacoustics, Assens, Denmark). The pure-tone air-conduction thresholds were measured at the decibel hearing level (dB HL) at 250-8,000 Hz. In addition, the bone-conduction hearing thresholds were evaluated at 500-4,000 Hz. The degrees of hearing loss were calculated as the average of four frequencies (500–4000 Hz) (Pure tone average-PTA) (15). The high-frequency hearing thresholds were evaluated at 9.0-14.0 kHz. All audiometric measurements were performed with a calibrated Astera 2 clinical audiometer (Madsen-Otometrics, Denmark). The TDH 39 supra-aural headphone (Telephonics, Farmingdala, NY, USA) was used for determining the air conduction. The Radio-ear B-71 bone vibrator was used for the bone-conduction threshold. The high-frequency hearing thresholds were determined using the Sennheiser HAD 200 circum-aural headphones (Sennheiser Electronic GmbH & Co. KG, USA). The transient-evoked otoacoustic emissions (TEOAEs) were recorded and analyzed using the Madsen Capella Oto-acoustic Emissions System Model: 8-03-460 (Otometrics/ Natus Medical ApS, Denmark). TEOAEs were obtained using rectangular clicks at an intensity of 80±2 dB sound pressure level (SPL). The signal to noise ratios were analyzed at 1,000, 1,500, 2,000, 3,000, and 4000 Hz. Six dB peak-equivalent SPL (peSPL) SNR for at least three frequencies were accepted as normal TEOAEs.

High-frequency hearing was evaluated with high-frequency audiometry test in both groups, the patients with psoriasis and the control group. All audiological tests were performed in a double-walled, sound-isolated audiometric booth by two audiologists.

The ototoxicity decision was made according to the American Language Speech Hearing Association (ASHA) criteria (1994)

and the TUNE grading system (2014). The ASHA criteria have been developed to identify ototoxicity as early as possible by comparing the deterioration to the baseline pre-drug tests (16). According to the ASHA criteria, the presence of one of the following three conditions is sufficient to decide on ototoxicity: (a) a decline of the air-conduction hearing threshold at any test frequency ≥ 20 dB, (b) a decline of the hearing threshold of ≥ 10 dB at any two consecutive frequencies, and/or (c) a loss of response at any consecutive three frequencies that were previously detected.

The TUNE grading system uses air conduction measurements to evaluate speech intelligibility (17). According to the TUNE grading system: grade 0 indicates no hearing loss, grade 1a corresponds to 10 dB or more threshold shift at high frequencies (pure tone average of 8-10-12.5 kHz) or subjective complaints, grade 1b corresponds to 10 dB or more threshold shift at conventional frequencies (pure tone average of 1-2-4 kHz), grade 2a corresponds to 20 dB or more threshold shift at high frequencies (pure tone average of 8-10-12.5 kHz), grade 2b corresponds to 20 dB or more threshold shift at conventional frequencies (pure tone average of 1-2-4 kHz), grade 3 corresponds to 35 dB or more hearing level at conventional frequencies pure tone average of 1-2-4 kHz, and grade 4 corresponds to 70 dB or more hearing level at conventional frequencies (pure tone average of 1-2-4 kHz).

Statistical Analyses

A sample size was calculated using G* Power version 3.1.9.2 based on the ability of mean difference between two dependent means (matched pairs) for the post hoc test. The power of the study was found to be 93% according to the total sample size of 51 participants, with a confidence level of 95% (p<.05) and an effect size of 0.5. The sample size of our study was decreased by 10% to address the possibility that nonparametric statistics might have to be used because of non-normality of the dependent and independent variables, giving an overall sample size of 46 participants (23 with PV and 23 controls). Descriptive data were provided as means and standard deviations for numeric variables and as percentages for categorical variables. The Shapiro-Wilk normality test was used to assess the normality of the distribution for each finding, and it was decided that using a non-parametric test would be appropriate for modeling the data. The chi-squared test was used to compare the nominal and ordinal data. To test the differences between the repeated measurements, the Friedman's two-way analysis of variance by ranks test and Kendall's coefficient of concordance calculations were used, which are non-parametric alternatives of the repeated measures analysis of variance test. The independent samples of the Mann-Whitney U test was used to identify the differences between the PV and control groups. A p value of <0.05 was considered statistically significant.

RESULTS

The demographic data of the PV group are presented in Table 1. The study and control groups were matched for gender. There was no significant difference between the groups in terms of mean ages (p=0.664). The mean duration of the disease was 7.86±9.2 years. All the participants had normal acoustic reflexes. The distributions of the tympanogram types between the groups were similar (p>0.05) (Table 1).

Table 1. Demographics of the psoriasis vulgaris and the control groups

		PV group	Control group
N		23	23
Age (years)		34–67 (52.4±9.5)	30–64 (51.1±8.7)
Gender	**Male (n, %)**	10, 43.5	10, 43.5
	Female (n, %)	13, 56.5	13, 56.5
Duration of disease (years)		7.9±9.2	-
Tympanograms			
Type A		19 (82.6%)	20 (86.9%)
Type As		4 (17.4%)	3 (13.1%)
Acoustic reflexes Yes/No		23/0	23/0

PV: Psoriasis vulgaris

The pure-tone hearing thresholds and the TEOAE signal-to-noise ratios of the PV group before acitretin treatment and the control group are presented in Table 2. Accordingly, the air-conduction hearing thresholds at 2,000 (left ear, p=0.017), 3,000 (bilaterally, p<0.001), and 4,000 Hz (bilaterally, p<0.001) were significantly worse in the PV group than in the control group. Furthermore, the right and left ear four-frequency PTA (bilaterally p<0.001) values were significantly worse in the PV group. However, in both the PV and control groups, the PTA values were within the audiological normal hearing limits (18). The high frequency audiometry findings were similar between the groups except 14,000Hz of the left ear (p=0.036). The TEOAE signal-to-noise ratios of the PV group were also significantly lower at 3,000 (bilaterally, p<0.05) and 4,000 Hz (bilaterally, p<0.05) than the control group (Table 2).

In the PV group, after 24 weeks of AT, the air-conduction hearing thresholds of conventional pure-tone and extended high-frequency audiometry were significantly different at 4,000 Hz right ear (Tables 3 and 4). During the AT hearing thresholds of 4,000 Hz, (right ear, p=0.004) presented a significant difference, however it did not present a worsening effect and was below the 10 dB audiological error level (10 dB). The signal-to-noise ratios of TEOAE did not show any significant difference (Table 5).

At 24 weeks of AT, the changes in the hearing thresholds (4,000 Hz) and TEOAE signal-to-noise ratios did not indicate any worsening owing to acitretin. The findings of patients with PV did not present a declining 10 dB hearing threshold at two or more consecutive frequencies nor an over 20 dB decline for one frequency. According to the ASHA criteria, there was no significant evidence of ototoxicity related to acitretin.

According to the TUNE grading system, when PTAs (both

Table 2. Hearing thresholds and TEOAE signal to noise ratios of the psoriasis vulgaris and control groups before acitretin treatment

		PV group Mean±SD	Control group Mean±SD	*p* values	Effect size (Hedges' g)
Pure-tone Audiometry (dBHL)					
PTA	Right	16.07±5.85	9.06±3.03	**< .001**	1.504
	Left	15.65±6.05	8.62±4.47	**< .001**	1.321
250 Hz	Right	11.91±4.60	9.75±3.79	.094	0.512
	Left	11.42±6.91	9.75±6.97	.371	0.299
500 Hz	Right	12.62 ±7.84	8.5±4.89	.068	0.630
	Left	10.95±7.35	9.25±4.94	.329	0.271
1000 Hz	Right	13.57±7.44	10.25±3.43	.279	0.573
	Left	11.91±8.29	9.5±4.83	.48	0.355
2000 Hz	Right	11.91±9.01	8.25±5.19	.183	0.497
	Left	13.09±8.28	7.5±5.73	**.017**	0.785
3000 Hz	Right	19.04±7.84	8.75±5.34	**< .001**	1.534
	Left	19.88±7.96	7.87±5.57	**< .001**	1.748
4000 Hz	Right	26.19±10.82	9.25±4.93	**< .001**	2.014
	Left	26.66±12.87	8.25±7.82	**< .001**	1.728
6000 Hz	Right	16.66±9.66	16±14.74	.461	0.052
	Left	19.04±10.07	14.25±12.38	.088	0.424
8000 Hz	Right	18.33±12.68	16.5±14.78	.645	0.132
	Left	20.71± 8.41	18.00±14.90	.324	0.223
High Frequency Audiometry (dBHL)					
9 kHz	Right	24.5±13.26	18.5±19.41	.114	0.360
	Left	30.01±16.14	25.52±24.14	.351	0.218
10 kHz	Right	39±17.29	26±29.63	.081	0.535
	Left	36.25±20.7	26.32±27.38	.158	0.409
11.2 kHz	Right	45.75±18.44	33±32.13	.277	0.486
	Left	43.75±17.68	28.94±30.84	.134	0.589
12.5 kHz	Right	54.64±16.46	33.52±28.05	.059	0.918
	Left	53.92±14.43	33.75±30.08	.052	0.855
14 kHz	Right	56.87 ±5.3	36.42±29.38	.238	0.968
	Left	55±10.00	33.46±27.71	**.036**	1.034
Transient-evoked otoacoustic emissions (dBpeSPL)					
1 kHz	Right	10.41±2.96	10.91±2.62	.773	0.178
	Left	10.53±2.74	11.09±2.31	.751	0.221
1.5 kHz	Right	11.38 ±3.73	11.17±4.1	.84	0.053
	Left	11.48±3.59	12.05±3.6	.665	0.158
2 kHz	Right	9.74±4.36	10.41 ±4.68	.729	0.148
	Left	10.24±3.87	11.16 ±4.2	.506	0.227
3 kHz	Right	8.61±3.01	11.29±4.29	**.049**	0.723
	Left	8.89±2.89	11.21±3.75	**.037**	0.693
4 kHz	Right	7.72±3.25	9.91±3.63	**.043**	0.635
	Left	8.23±2.92	10.22±3.62	**.043**	0.605

PV: Psoriasis vulgaris, dBHL: Decibel hearing level, dBSPL: Decibel sound pressure level, PTA: 500–4000 Hz pure-tone average

Table 3: Pure-tone hearing thresholds of the psoriasis vulgaris group before and during acitretin treatment

	Hearing Thresholds (dBHL)							
Right Ear	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**	**6000 Hz**	**8000 Hz**
Before AT	11.91±4.60	12.62±7.84	13.57±7.44	11.91±9.01	19.04±7.84	26.19±10.82	16.66±9.66	18.33±12.68
Second week of AT	13.81±8.2	11.19±8.64	12.85±8.30	11.42±8.96	18.92±9.5	26.42±13.79	17.61±11.68	22.14±16.16
Fourth week of AT	11.42±7.76	10.23±7.98	11.66±8.26	10.47±8.64	17.02±9	23.57±13.4	16.91±10.66	20.71±16.61
Sixth week of AT	10.47±9.34	10.95±8.89	11.66±7.12	11.19±9.21	17.02±9.44	22.85±12.99	17.38±10.07	18.57±15.9
Eighth week of AT	11.91±8.13	10±8.36	12.85±9.02	11.66±9.26	18.09±8.97	24.52±12.33	18.81±12.33	19.76±16.84
12th week of AT	12.61±9.82	10.23±8.72	11.91±8.87	10.95±8.45	18.69±8.46	26.42±12.56	19.05±11.35	20.1±15.57
24th week of AT	10.75±10.67	11±8.52	11.25±8.09	10.5±9.02	18.75±9.44	27±13.41	18.75±10.98	18.25±15.75
Friedman's two-way analysis of variance by ranks	0.096	0.173	0.536	0.593	0.077	**0.004**	0.114	0.442
Kendall's coefficient of concordance	0.009	0.075	0.042	0.038	0.095	**0.157**	0.085	0.049
Effect Size (partial eta squared)	0.911	0.788	0.805	0.693	0.915	**0.929**	0.808	0.709
Left Ear	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**	**6000 Hz**	**8000 Hz**
Before AT	11.42±6.91	10.95±7.35	11.91±8.29	13.09±8.28	19.88±7.96	26.66±12.87	19.04±10.07	20.71±8.41
Second week of AT	10.95±8.3	9.76±7.66	12.38±8.61	10.71±8.11	19.28±7.37	27.85±12.41	21.91±14.35	23.81±18.96
Fourth week of AT	9.28±7.62	9.52±7.05	11.42±7.61	11.66±8.11	19.41±8.69	27.14±13.09	19.04±13.47	21.42±17.68
Sixth week of AT	9.76±8.72	9.76±8.28	11.91±7.32	10.95±7.84	18.92±8.49	26.91±13.17	20.47±12.33	24.05±19.41
Eighth week of AT	11.91±8.13	10±8.36	12.85±7.51	11.66±8.26	19.64±8.63	27.61±13	20.71±13.34	24.28±19.76
12th week of AT	10.71±8.25	10±8.51	12.14±7.34	11.19±8.2	20.11±9.43	29.04±14.54	20.47±13.77	25.47±20.11
24th week of AT	9.75±8.95	10.25±8.02	12.5±6.58	10.75±8.62	20.37±9.84	30±14.23	21.5±13.86	25.25±19.7
Friedman's two-way analysis of variance by ranks	0.506	0.715	0.343	0.193	0.864	0.407	0.53	0.162
Kendall's coefficient of concordance	0.044	0.031	0.056	0.072	0.021	0.051	0.043	0.077
Effect Size (partial eta squared)	0.868	0.745	0.868	0.759	0.932	0.881	0.829	0.882

AT: Acitretin treatment, dBHL: Decibel hearing level

Table 4: High-frequency hearing thresholds of the psoriasis vulgaris group before and during acitretin treatment

	Hearing Thresholds (dBHL)				
Right Ear	**9000 Hz**	**10000 Hz**	**11200 Hz**	**12500 Hz**	**14000 Hz**
Before AT	24.5±13.26	39±17.29	45.75±18.44	54.64±16.46	56.87±5.3
Second week of AT	25±12.77	39±18.68	45.51±18.77	54.06±16.75	56±6.51
Fourth week of AT	23.75±12.65	38.5±18.07	46.75±17.18	55±17.08	55±7.07
Sixth week of AT	24±14.56	38.75±19.92	45.75±17.71	53.33±16.65	55±7.07
Eighth week of AT	24.75±12.41	39.75±18.31	46±16.98	53.12±15.37	53.33±7.63
12th week of AT	25±11.92	39±19.37	46.75±18.37	54±16.61	53.33±7.63
24th week of AT	24.47±12.34	39.21±19.23	45.52±16.49	52.5±16.49	50±7.07
Friedman's Two-Way Analysis of Variance by Ranks	0.831	0.612	0.871	0.515	0.423
Kendall's Coefficient of Concordance	0.025	0.039	0.022	0.079	0.5
Effect Size (partial eta squared)	0.855	0.891	0.896	0.945	0.990
Left Ear	**9000 Hz**	**10000 Hz**	**11200 Hz**	**12500 Hz**	**14000 Hz**
Before AT	30.00±16.14	36.25±20.7	43.75±17.68	53.92±14.43	55±10.00
Second week of AT	30.25±16.73	38.25±19.75	43±17.27	54.64±14.21	50±7.07
Fourth week of AT	31.5±17.92	38.75±19.25	45.75±17.34	53.75±14.16	52±8.36
Sixth week of AT	28.25±17.18	35±19.6	43.25±18.93	50.83±14.27	48.75±6.29
Eighth week of AT	28.75±17	36.75±20.20	43±17.87	53.33±13.04	51.66±2.88
12th week of AT	27.63±15.39	36.05±19.61	42.63±18.05	62.63±20.3	51.66±2.88
24th week of AT	27.89±17.02	35.52±18.84	43.15±16.93	50.45±13.12	50±7.07
Friedman's Two-Way Analysis of Variance by Ranks	0.425	0.215	0.761	0.592	0.423
Kendall's Coefficient of Concordance	0.052	0.073	0.03	0.086	0.5
Effect Size (partial eta squared)	0.786	0.845	0.904	0.979	0.992

AT: Acitretin treatment, dBHL: Decibel Hearing Level

Table 5: Transient-evoked otoacoustic emissions in the psoriasis vulgaris group before and during acitretin treatment

	TEOAE Signal Noise Ratios (dBpeSPL)				
Right Ear	**1000 Hz**	**1500 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**
Before AT	10.41±2.96	11.38±3.73	9.74±4.36	8.61±3.01	7.72±3.25
Second week of AT	10.35±2.87	11.11±3.64	9.61±4.31	8.73±2.68	8.07±3.39
Fourth week of AT	11.1±3.01	12±3.73	10.08±4.22	8.97±3.17	7.83±3.33
Sixth week of AT	10.43±3.06	11.25±3.53	9.77±4.3	9.04±2.81	8.17±3.42
Eighth week of AT	11.02±3.17	12.01±3.71	10.51±4.29	9.45±3.37	8.31±3.67
12th week of AT	11.01±3.31	12.12±3.76	10.74±4.41	9.66±3.59	8.67±3.98
24th week of AT	10.23±3.35	11.84±3.58	10.15±4.46	8.92±3.31	7.82±3.29
Friedman's two-way analysis of variance by ranks	0.224	0.148	0.05	0.379	0.496
Kendall's coefficient of concordance	0.072	0.083	0.116	0.056	0.047
Effect Size (partial eta squared)	.932	.944	.88	.94	.869
Left Ear	**1000 Hz**	**1500 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**
Before AT	10.53±2.74	11.48±3.59	10.24±3.87	8.89±2.89	8.23±2.92
Second week of AT	10.41±2.69	11.55±3.47	10.47±3.88	9.02±2.81	7.99±3.43
Fourth week of AT	11.06±2.57	12.01±3.38	11.06±3.64	8.78±2.77	7.94±3.26
Sixth week of AT	10.77±2.53	11.75±3.34	10.54±3.88	9.55±2.98	8.35±3.37
Eighth week of AT	11.11±2.72	11.58±3.67	10.59±3.95	8.65±2.96	8.41±3.6
12th week of AT	11.58±2.81	12.1±3.46	11.38±3.88	9.18±3.32	8.78±3.91
24th week of AT	10.88±3.47	12.02±3.47	10.71±3.92	9.05±3.23	7.98±3.22
Friedman's two-way analysis of variance by ranks	0.089	0.462	0.779	0.184	0.577
Kendall's coefficient of concordance	0.096	0.05	0.028	0.077	0.042
Effect Size (partial eta squared)	.961	.951	.92	.938	.907

AT: Acitretin treatment, TEOAE: Transient-evoked otoacoustic emission, dBpeSPL: Decibel peak equivalent sound pressure level

Table 6: Results of the TUNE ototoxicity grading system in the psoriasis vulgaris group before and after acitretin treatment

	Pre-treatment	Post-treatment
HFR	34.04±12.34	34.04±13.47
HFL	34.76±12.03	34.24±14.68
CFR	17.22±6.46	16.25±8.09
CFL	17.22±6.54	17.75±7.95

HFR: Right ear pure tone average of high frequencies (8-10-12.5 kHz), HFL: Left ear pure tone average of high frequencies (8-10-12.5 kHz), CFR: Right ear pure tone average of conventional frequencies (1-2-4 kHz), CFL: Left ear pure tone average of conventional frequencies (1-2-4 kHz).

conventional and high frequencies) were calculated, it was seen that at 24 weeks of AT, all the patients with psoriasis were scored as grade 0 (no hearing loss) (Table 6).

DISCUSSION

Ototoxicity is one of the most important topics in the field of audiology because of its almost irreversible damage to the inner ear. It requires an examination of the side effects of drug therapy, such as hearing loss, tinnitus, hyperacusis, aural fullness, or balance problems (19). Several ototoxicity classification systems have been published to allow a simple, reliable, and valid interpretation of the audiometric results (20). In this study, the ASHA criteria and TUNE grading system were used for the ototoxicity decision making. The ASHA criteria can be applied to the air-conduction hearing thresholds at both conventional or high frequencies and sensitive to ototoxicity and minimize variability with the use of adjacent test frequencies. A baseline assessment and repeat testing is recommended to confirm that the changes in the threshold are related to ototoxicity (16). The TUNE grading system is a newly developed system for ototoxicity in adults. This system evaluates both the frequencies related to speech intelligibility and higher frequencies. The main difference in our study was the use of two different ototoxicity classification or grading systems. In other studies, there was not an acceptable ototoxicity classification protocol to evaluate the ototoxicity owing to acitretin or isotretinoin. Statistically significant changes in hearing thresholds should be interpreted using an ototoxicity classification system.

For comprehensive ototoxicity monitoring, acoustic immitancemetry, transient-evoked, and/or distortion product oto-acoustic emissions were suggested to combine with the conventional and high-frequency pure-tone audiometry (20).

The TEOAEs are more sensitive to ototoxic changes than the pure-tone hearing threshold; however, the most sensitive test for ototoxic changes is high-frequency audiometry (14). In this study, the TEOAE tests were combined with the conventional and high-frequency audiometry tests for ototoxicity monitorization.

Acitretin, etretinate, isotretinoin, and tretinoin are aromatic retinoid analogues of vitamin A. Acitretin toxicity has generally been described as dose-dependent and has been reported to cause transaminitis, pseudotumor cerebri, hyperostosis, and hyperlipidemia (21). Etretinate, a metabolite of acitretin, has also been reported to cause peripheral neuropathy (11).

Studies on the effects of acitretin on hearing are few (11-13), and the mechanism of ototoxicity has not been defined yet. The effect of oral acitretin intake on hearing was reported for the first time in a 31-year-old patient using acitretin for psoriasis. Tinnitus and hearing loss were described in the patient one week after starting acitretin. The averages of 500–2,000 Hz were 47 dBHL in the right ear and 33 dBHL in the left ear. Tinnitus was more severe in the right ear. As soon as otological complaints began, acitretin was discontinued, and prednisolone at a dose of 1mg/kg/day was initated. In the audiological evaluation of the patient two years later, it was determined that the tinnitus disappeared, and the mean of 500–2,000 Hz was obtained as 35 dBHL on the right and 30 dBHL on the left. In this study, the daily dose of orally administered acitretin was not specified. No baseline evaluation was made in this case report, and only conventional frequencies were evaluated with pure tone audiometry tests after the patient's complaints started, with high frequency audiometry and otoacoustic emission tests not being performed (11). In the second study reporting hearing impairment with the use of acitretin, four-year follow-up findings of 12 patients with hidradenitis suppurativa were presented. These patients were treated with acitretin at a dose of 0.59 mg/kg/day for nine to 12 months. Bilateral tinnitus was observed in one patient four months after the onset of acitretin, but hearing loss was not described. When the drug was discontinued, the complaint disappeared. When acitretin was restarted three weeks later, tinnitus, headaches, and concentration impairment reappeared, resulting in the patient stopping acitretin completely (12). In this study, no findings regarding hearing assessment were given. Karaosmanoglu et al. reported the average hearing thresholds of 30 patients with PV at 250–10,000 Hz frequencies at baseline at the first and third months during 0.5–0.75 mg/kg/day oral acitretin use (13). Hearing thresholds in the acitretin group did not change significantly after treatment. The audiological findings presented in this study are those obtained after three months of follow-up. In that study, considering that otologic complaints emerged after using acitretin for four months, the adequacy of a three-month follow-up period is controversial. Otoacoustic emission assessments were not performed (13). Important points that distinguish our study from others include the six-month follow-up period, the evaluation of frequencies above 10,000 Hz, and the otoacoustic emission findings.

Isotretinoin, like acitretin, is a member of the retinoid group and has similar action and side-effect mechanisms to acitretin (13). However, its ototoxicity has been more studied than that of acitretin. In the literature, clinical studies and case reports suggest that isotretinoin affects hearing (22-27). Akdağ et al. have reported a case with permanent bilateral sensorineural hearing loss after isotretinoin treatment (22). A 15-year-old male who was treated with isotretinoin displayed bilateral mild to moderate sensorineural hearing loss on the fifth day of treatment, which did not improve even after ceasing isotretinoin. The mechanism of ototoxicity-related inner ear damages was explained by the decreased microcirculation and oxidative stress related apoptosis (22). However, a clear definition of the ototoxic mechanism of acitretin has not been made, and longitudinal studies with different dose applications are required.

Rosende et al. have reported a 15-year-old boy who displayed hypoacusia and tinnitus during the six weeks of isotretinoin treatment (23). After withdrawing isotretinoin, he improved. In another study, Akdağ et al. have stated that the 1–6 kHz air-conduction hearing thresholds got significantly worse after isotretinoin treatment, whereas the otoacoustic emissions did not decline (24). Uğur et al. have reported a clinical study consisting of the audiological results of 25 patients who were treated with isotretinoin (25). After treatment, the conventional and high-frequency hearing thresholds were better than the pre-treatment thresholds. Otoacoustic emission amplitudes did not present a significant change after treatment. Karabulut et al. evaluated 38 patients with conventional and high-frequency pure-tone audiometry and found in the third week of isotretinoin treatment, the hearing thresholds were better than the pre-treatment thresholds (26). There are also experimental studies that report that retinoic acid stimulates the *in vitro* regeneration of auditory hair cells in ototoxic-poisoned rat organs of Corti (27, 28). In this study, after 24 weeks of AT, the audiologic findings of patients with PV did not present a 10 dB hearing threshold decline at two or more consecutive frequencies or over a 20 dB decline for one frequency. According to the ASHA criteria, there was no significant evidence of ototoxicity related to acitretin. Similarly, according to the TUNE grading system, it was seen that at 24 weeks of AT, all the patients with psoriasis were scored as grade 0 (no hearing loss).

PV is considered an autoimmune and dermatological disease. It was reported that the vascular or autoimmune effects of PV on the inner ear may increase the chance of sensorineural hearing loss (29). Vir et al. compared the patients with PV and the healthy control group in terms of cochlear function and hearing evaluation (30). They found statistically significant differences between the two groups regarding the pure-tone thresholds at high frequencies and distortion product otoacoustic emission (DPOAE) responses at all frequencies. In their study, they explained that these significant differences were caused by the damage to the outer hair cells of the cochlea in patients with PV, which resulted in high-frequency hearing loss. Yen et al. reported that the risk of sudden sensorineural hearing

loss in patients with psoriasis was 1.51 times higher than in healthy individuals (31). Possible causes of this finding are the systemic effects (microvascular or cellular) of psoriasis on the cochlea. In their study, Borgia et al. have evaluated the hearing function of patients with PV and compared it with the healthy controls (32). The comparison of the audiometric tests between the groups revealed pronounced hypoacusis in patients with PV than in the control group with a clear prevalence of sensorineural hearing loss. Furthermore, SNHL increased in patients with PV proportionally to their age, which was at a higher rate than in healthy individuals and could be linked to metabolic syndrome (32). In two different studies, the pure-tone audiometry and DPOAE findings of patients with PV were compared with healthy individuals, and no significant differences were observed between the groups (33-34). In this study, the pre-treatment two (left ear), three, and 4,000 Hz hearing thresholds of the pure-tone audiometry test and three and 4,000 Hz TEOAE signal-to-noise ratios of the PV group were significantly worse than those of the healthy controls. Although the hearing thresholds were within normal limits, except for 4,000 Hz, the significant difference between the PV and control group may be related to a subclinical autoimmune involvement. Therefore, an audiological follow-up of PV patients is important.

This study had some limitations. As the study population was small, the dose-dependent effects of acitretin were not evaluated. In addition, the patients were only followed for 24 weeks because the sale of acitretin in Turkey was stopped temporarily at that time. Another limitation was that the otoacoustic-emission assessment was made with the TEOAE test instead of DPOAE, owing to a technical failure of the DPOAE probe.

In conclusion, six months of AT has no significant ototoxic effects on patients with PV. As ototoxicity causes irreversible damage to the inner ear, it is important to collaborate between the dermatology, ear-nose-throat, and audiology departments to analyze the risk of ototoxicity with treatment methods as early as possible.

Ethics Committee Approval: This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (Date: 27.06.2018, No: 2018/0197).

Informed Consent: Written informed consent was obtained.

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REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133(2):377-85.
2. Pariser DM, Bagel J, Gelfand JM, Korman NJ, Ritchlin CT, Strober BE, et al. National Psoriasis Foundation. National Psoriasis Foundation clinical consensus on disease severity. Arch Dermatol 2007;143(2):239-42.
3. Pilkington T, Brogden RN. Acitretin. A review of its pharmacology and therapeutic use. Drugs 1992;43(4):597-627.
4. Lee CS, Li K. A review of acitretin for the treatment of psoriasis. Expert Opin Drug Saf 2009;8(6):769-79.
5. Ortiz NE, Nijhawan RI, Weinberg JM. Acitretin. Dermatol Ther 2013;26(5):390-9.
6. Magis NL, Blummel JJ, Kerkhof PC, Gerritsen RM. The treatment of psoriasis with etretinate and acitretin: a follow up of actual use. Eur J Dermatol 2000;10(7):517-21.
7. Orfanos CE. Treatment of psoriasis with retinoids: present status. Cutis 1999;64(5):347-53.
8. Kullavanijaya P, Kulthanan K. Clinical efficacy and side effects of acitretin on the disorders of keratinization: a one-year study. J Dermatol 1993;20(8):501-6.
9. Tsambaos D, Sakkis T, Chroni E, Koniavitou K, Monastirli A, Pasmatzi E, et al. Peripheral sensory neuropathy associated with short-term oral acitretin therapy. Skin Pharmacol Appl Skin Physiol 2003;16(1):46-9.
10. Chroni E, Monastirli A, Pasmatzi E, Sakkis T, Georgiou S, Paschalis C, et al. Sensorimotor polyneuropathy after a three-month oral acitretin therapy. Clin Neuropharmacol 2002;25(6):310-2.
11. Mahasitthiwat V. A woman with sudden bilateral sensorineural hearing loss after treatment psoriasis with acitretin. J Med Assoc Thai 2005;88(Suppl 1):S79-81.
12. Boer J, Nazary M. Long-term results of acitretin therapy for hidradenitis suppurativa. Is acne inversa also a misnomer? Br J Dermatol 2011;164(1):170-5.
13. Karaosmanoğlu N, Akkoç A, Akkoca Ö, Ekşioğlu HM. The effects of oral retinoids on hearing status: A prospective clinical study. J Med Sci 2019;39:245-50.
14. Durrant J, Campbell K, Fausti S. American Academy of Audiology Position Statement and Practical Guidelines, Ototoxicity monitoring. J Am Acad of Aud 2009;1-25. URL: audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf
15. American National Standards Institute. (2004a). Methods for manual pure-tone threshold audiometry (ANSI S3.21-2004). New York https://webstore.ansi.org/standards/asa/ansiasas3212004r2009
16. American Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. ASHA 1994;36:11-19. https://www.asha.org/policy/gl1994-00003/
17. Theunissen EA, Dreschler WA, Latenstein MN, Rasch CR, van der Baan S, de Boer JP, et al. A new grading system for ototoxicity in adults. Ann Otol Rhinol Laryngol 2014;123(10):711-8.
18. Clark JG. Uses and abuses of hearing loss classification. ASHA 1981;23:493-500.

19. Lord SG. Monitoring Protocols for Cochlear Toxicity. Semin Hear 2019;40(2):122-43.
20. Crundwell G, Gomersall P, Baguley DM. Ototoxicity (cochleotoxicity) classifications: A review. Int J Audiol 2016;55(2):65-74.
21. Heath MS, Sahni DR, Curry ZA, Feldman SR. Pharmacokinetics of tazarotene and acitretin in psoriasis. Expert Opin Drug Metab Toxicol 2018;14:919-27.
22. Akdağ M, Akkurt ZM, Özkurt FE. Irreversible hearing loss due to the use of oral isotretinoin. J Basic Appl Sci Res 2013;3:288-91.
23. Rosende L, Verea-Hernando MM, de Andrés A, Piñeyro-Molina F, Barja J, Castro-Castro S, et al. Hypoacusia in a patient treated by isotretinoin. Case Rep Med 2011;2011:789143. doi: 10.1155/2011/789143.
24. Akdag M, Akkurt ZM, Gul A, Ucmak D, Yılmaz B, Sengul E, et al. The effects of oral isotretinoin (13-Cis retinoic acid) on the inner ear: a prospective clinical study. Clin Invest Med 2014;37(2):E102-7.
25. Ugur KS, Erpolat S, Kurtaran H, Ark N, Sarifakioglu E, Gunduz M. The effects of oral isotretinoin (13-Cis Retinoic Acid) on the inner ear: A clinical study. Int Adv Otol 2012;8(3):339-44.
26. Karabulut H, Karadag AS, Acar B, Dagli M, Karabulut I, Ozmen E, et al. The effect of oral isotretinoin (13-cis retinoic acid) on hearing systems in patients with acne vulgaris: a prospective study. Int J Dermatol 2011;50(9):1139-43.
27. Lefebvre PP, Malgrange B, Staecker H, Moonen G, Van de Water TR. Retinoic acid stimulates regeneration of mammalian auditory hair cells. Science 1993;260(5108):692-5.
28. Alan MA, Eryılmaz MA, Kaymaz F, Suzer A, Arıcıgil M. Isotretinoin's action against cisplatin-induced ototoxicity in rats. Pak J Pharm Sci 2018;31(6 (Supplementary):2579-84.
29. Sun YS, Fang WH, Kao TW, Yang HF, Peng TC, Wu LW, et al. Components of Metabolic Syndrome as Risk Factors for Hearing Threshold Shifts. PLoS One 2015;10(8):e0134388. doi: 10.1371/journal.pone.0134388.
30. Vir D, Sharma P, Mahajan R, Dogra S, Bakshi J, Panda NK. Investigation of high-frequency hearing loss and outer hair cell function of the cochlea in patients with psoriasis: a case-control study. Clin Exp Dermatol 2019;44(5):520-3.
31. Yen YC, Lin YS, Weng SF, Lai FJ. Risk of sudden sensorineural hearing loss in patients with psoriasis: a retrospective cohort study. Am J Clin Dermatol 2015;16(3):213-20.
32. Borgia F, Ciodaro F, Guarneri F, Bartolotta A, Papaianni V, Guarneri C, et al. Auditory System Involvement in Psoriasis. Acta Derm Venereol 2018;98(7):655-9.
33. Karabulut H, Karadag AS, Dagli M, Acar B, Babademez M, Şahin Y, et al. Investigation of hearing and outer hair cell function of cochlea in patients with psoriasis. J Int Adv Otol 2010;6(2):239-44.
34. Ertugrul G, Ertugrul S, Soylemez E. Evaluation of audiovestibular system in psoriasis patients without joint involvement. Dermatol Ther 2020;33(3):e13396. doi: 10.1111/dth.13396.

RESEARCH ARTICLE
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Virtual Reality Glasses (Cardboard VR): A New Tool for The Assessment of Nystagmus

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ABSTRACT

Objective: Virtual reality (VR) glasses are tools that provide a more realistic perception of the image viewed from mobile phones. The aim of this study was to assess nystagmus with Cardboard VR, the most widely used and simplest form of VR glasses, and to compare the findings with those obtained via conventional Frenzel goggles.

Materials and Methods: A total of 97 patients were included in the study. Balance tests were performed at one-hour intervals using Cardboard VR and Frenzel goggles. Direction, frequency, and duration of nystagmus were recorded during the examinations. Following the examinations, patients using both glasses were asked to rate the general comfort and holding quality of the glasses on a visual analogue scale (VAS).

Results: No significant difference was found between the two glasses in terms of the direction of nystagmus (p>.05). There was no significant difference between the two glasses (Cardboard VR vs Frenzel goggles) in terms of frequency (0.73±0.29 beats/sec and 0.86±0.39 beats/sec, respectively) (p>.05). There was no significant difference between the two glasses in terms of the duration of observation (18.58±5.54 sec and 20.54±6.40 sec, respectively)(p>.05). The VAS score of the Carton VR was found to be significantly higher than that of the Frenzel goggles (8.69±1.02 and 5.24±1.31, respectively) (p=0.001).

Conclusion: Cardboard VR is an easy-to-use, easily accessible, inexpensive, and effective tool that can be used to assess nystagmus under polyclinic and emergency conditions.

Keywords: Dizziness, positional vertigo, vertigo, peripheral, virtual reality

INTRODUCTION

Vertigo is a symptom that causes a person to feel as if they or their surroundings are moving even if they are not. There are two main pathologies in the etiology of vertigo: central or peripheral vestibular pathology. Assessment of nystagmus plays a major role in both peripheral (inner ear or vestibular nerve) and central (pons or cerebellum) vestibular pathologies (1). Nystagmus is involuntary, rhythmic, back and forth eye movements with slow and fast phases and corrective saccades. Assessment of nystagmus provides a significant distinction both in otolaryngology practices and in neurology and emergency departments. Today, there are many instruments used to assess nystagmus in patients presenting with dizziness. These can be listed as follows from simple to complex: Frenzel goggles (F glasses), Fresnel-based device (M glasses), ophthalmoscope, video Frenzel goggles, infrared CCD Camera (IR-CCD), and electronystagmography (ENG).

The development of computer technologies and their impact on daily life is increasing every day. Virtual reality glasses have been used for visual field examination since 1998. They are currently used to increase the reality of the image on mobile phones. For this purpose, many different types of VR glasses have been developed. There are studies investigating the use of these glasses in ophthalmology and microsurgery (2, 3).

The aim of this study is to compare the efficacy of Cardboard VR, an easily accessible, practical and inexpensive type of VR glasses, in the evaluation of nystagmus with classical Frenzel goggles.

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MATERIAL AND METHOD

Study Design

Prior to the study, permission was obtained from the local research ethics committee of our university. A total of 97 patients, who were admitted to our otorhinolaryngology clinic with the complaint of dizziness and probably had a history of benign paroxysmal positional vertigo (BPPV), were included in the study. The reason for including only BPPV patients in the study was to optimize the study as much as possible. After the patients were informed about the study, verbal and written informed consents were obtained.

Patients who did not want to participate in the study, those who had non-BPPV peripheral and central pathology in their history, and patients whose eye movements were difficult to assess due to mental retardation, claustrophobia and so on, were excluded from the study.

The glasses were used at one-hour intervals. The order of application was changed for each patient. For instance, conventional Frenzel goggles were applied first for the first patient and Cardboard VR was applied first for the second patient. The reason for one-hour intervals without any corrective maneuver was to ensure the objective assessment of nystagmus. All examinations were performed in the same examination room under artificial light and without exposing the patients to daylight. The aim was to provide similar examination conditions. The Dix-Hallpike maneuver was performed for all patients.

Frenzel Goggles and Cardboard VR

The classic simple Frenzel goggles (DEHAG, Rosdorf, Germany) were used in the study. Frenzel goggles are an instrument with a weight of approximately 500 g and dimensions of approximately 20 × 13 × 7 cm. They have two lenses of +19 to +20 diopters and also a handle for the person who will apply the test to hold the instrument. The Cardboard VR (VR 3D Box Cardboard, Google Cardboard 3D Virtual Reality Glasses) used in the study were obtained via internet shopping. The cover on which the phone was placed was removed and the device was made ready for use (Figure 1). The Cardboard VR weigh 50 gr and have dimensions of 15 x 8 x 6 cm. They have two lenses of +19 to +20 diopters. The person who will perform the application does not need to hold the instrument; there is an elastic head band for fixing the device on the patient's head.

Evaluation Parameters

Visibility of nystagmus: The presence of nystagmus was evaluated using glasses in patients with a history of BPPV.

Direction of Nystagmus: The direction of nystagmus was determined.

Frequency and duration of nystagmus: The time from the occurrence of the nystagmus to the time it stopped and the number of beats during this time were evaluated using a stopwatch.

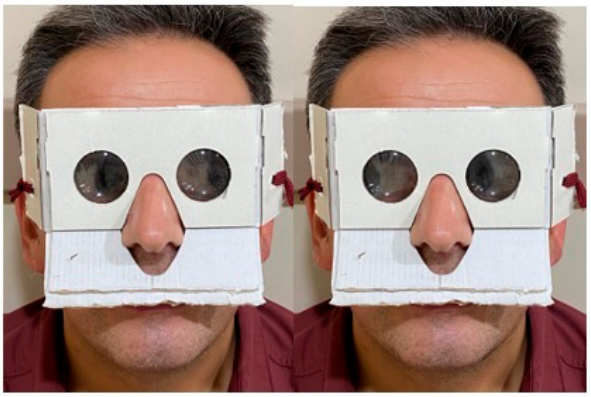

Figure 1: Cardboard VR

Ease-of-use of glasses: Patients were asked to score the ease of use of the instrument on a visual analogue scale (VAS) from 0 to 10 (0: very bad, 10: very good).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 24.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). All quantitative variables were estimated using measurements of central location (i.e. mean and median) and measurements of dispersion (i.e. standard deviation [SD]). Data normality was assessed using the Kolmogorov-Smirnov test of normality. Student's t-test was used to compare the quantitative data of the groups, whereas, Chi-square test was used to compare the qualitative data. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 97 patients were included in the study. Of the patients, 56 were female and 41 were male patients. The mean age was 45.36±9.75 years. Nystagmus was observed in 53 and 46 participants in the Frenzel goggles examination and Cardboard VR examination, respectively. There was no significant difference between the methods (p=0. 315).

Assessment of the nystagmus direction revealed horizontal rotatory nystagmus in all patients. Of the 53 patients who were found to have nystagmus in the Frenzel goggles examination, nystagmus was on the right side in 23 patients and on the left side in 30 patients. Of the 46 patients who were found to have nystagmus in the Carton VR examination, 20 patients had nystagmus on the right side, whereas, 26 had nystagmus on the left side. There was no significant difference between the two glasses in terms of nystagmus direction (p=0.993).

The duration of observation of nystagmus was 18.58±5.54 sec in the Cardboard VR examination and 20.54±6.40 sec in the Frenzel goggles examination. There was no significant difference in terms of the duration of observation (p=0.109) (Figure 2).

The frequency in the cardboard VR examination was 0.73±0.29 beats/sec, while it was 0.86±0.39 beats/sec in the Frenzel goggles examination. There was no significant difference

between the two glasses in terms of frequency (p=0.074) (Figure 3). Those who applied the test evaluated both goggles in terms of general comfort and holding quality with VAS. The mean VAS score was 5.24±1.31 and 8.69±1.02 in the Frenzel goggles examination and the Cardboard VR examination, respectively. There was a statistically significant difference between the two instruments in terms of general comfort and holding quality (p=0.001) (Figure 4).

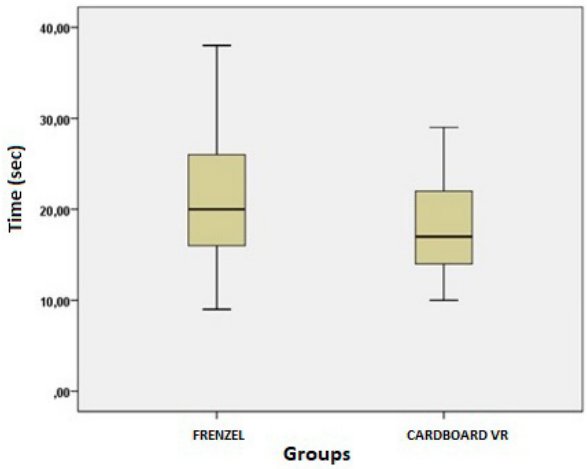

Figure 2: Nystagmus duration of the groups

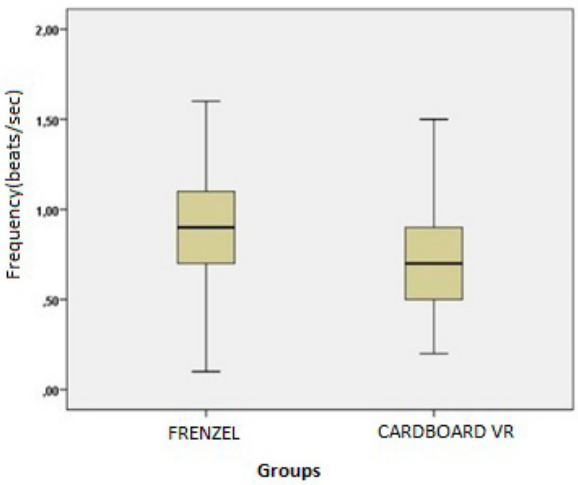

Figure 3: Nystagmus frequencies of the groups

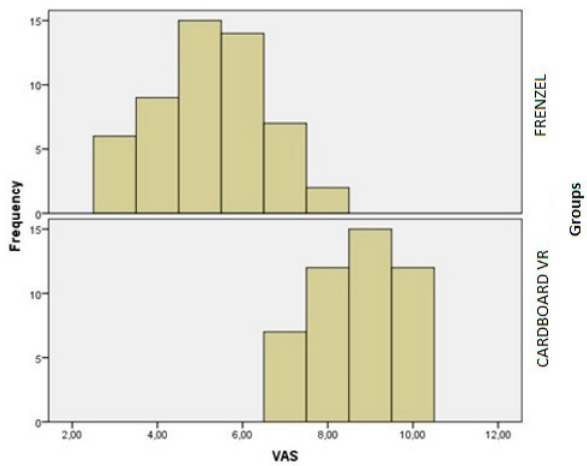

Figure 4: Visual analog scale values of the groups

DISCUSSION

Distinguishing the central and peripheral vertigo can significantly change the approach to the patient in both emergency and polyclinic settings. Assessing the nystagmus is the most important factor that changes this approach. Its assessment in emergency or polyclinic settings at first admission plays a decisive role in diagnosis. Changes that may occur in the medication or symptoms may mask the accurate diagnosis. Many advanced techniques (ENG, IR-CCD camera, video Frenzel) have been developed to assess nystagmus. However, such techniques take time and are not available in many emergency and polyclinic settings. Therefore, conventional Frenzel goggles are used most frequently in the assessment of nystagmus in clinical practice. However, they have some disadvantages: they are about 500 g in weight and 20x13x7 cm in size, they require electrical support, and a holder is needed to fix the instrument to the patient's eye, which limits the person who performs the examination (4). The present study found that Cardboard VR glasses are as effective as the Frenzel goggles to show the visibility of the nystagmus direction, and the speed and frequency of the nystagmus.

We frequently encounter VR glasses in our daily lives with the developing technology. They are available in many different formats, but the most accessible and least costly ones are cardboard VR glasses. They can be used as Frenzel goggles when the mobile phone holder part located on the frontside is removed from the instrument. In the evaluation of the two lenses via autorefractor, diopter degrees were found to be +19 to +20. The two instruments were compared after determining that these values were similar to the conventional Frenzel goggles and that these glasses could prevent fixation, the most important feature of these glasses.

Nystagmus was observed in 53 (54.63%) of 97 participants in the Frenzel goggles examination, whereas, nystagmus was observed in 46 patients (47.42%) in the Cardboard VR examination. There was no significant difference between the two glasses in terms of the visibility of the nystagmus direction. Different results have been reported in the studies comparing the visibility of nystagmus with Frenzel goggles and other methods. Ben-David et al. and Strauss and Meyer zum Gottesberge have reported that there was no significant difference between ENG and Frenzel goggles in terms of the visibility of nystagmus (5-6). West et al. have reported that the visibility rate of nystagmus via conventional Frenzel goggles is 10% and the light in the examination room significantly affects visibility (1). We believe that the low visibility rate in this study is due to the inclusion of patients who were admitted to the outpatient clinic with the complaint of general dizziness and had no significant history of dizziness. In a study by Baba et

al., 100 patients with vertigo were evaluated and nystagmus was detected in 33 patients via conventional Frenzel goggles (7). We believe that the reason for the high nystagmus rates in our study is due to the inclusion of patients in the acute phase and patients with a history of BPPV.

In the study by Baba et al., horizontal nystagmus was detected in 91% of patients whose nystagmus was detected via Frenzel goggles (7). In the present study, horizontal nystagmus was detected in all patients with nystagmus in both the Frenzel goggles examination and the Cardboard VR examination. There was no significant difference between the groups in terms of the direction of nystagmus. High rates of nystagmus in our study can be attributed to the fact that the participants had a possible BPPV diagnosis in their history.

Since it was aimed to assess the basic and practical nystagmus, the speed and duration of nystagmus in Cardboard VR and Frenzel goggles were evaluated with the naked eye by the person who applied the test. During the assessment, another person recorded the values using a stopwatch. No significant difference was observed between the duration and frequency of nystagmus in our study. This shows that the Cardboard VR glasses are as effective as the Frenzel goggles to show the speed and frequency of the nystagmus.

Strupp et al. developed M glasses, Fresnel-based glasses, to overcome the limitations of the conventional Frenzel goggles (4). As a result of the comparison of M glasses and Frenzel goggles, M glasses were found to be equivalent to Frenzel goggles in terms of the assessment of nystagmus. The M glasses consist of two lenses and a steel frame that connects them to each other. The advantages of M glasses compared to Frenzel goggles are being cheaper (M glasses = $ 100, Frenzel Goggles = $ 484), lighter and easier to use. The study on M glasses was published four years ago, but their use has not yet become widespread. Cardboard VR glasses have many common features with M glasses (easy to use, lightweight, and easily accessible). Therefore, these features are their advantages compared to Frenzel goggles. Furthermore, we compared the Cardboard VR with Frenzel goggles in terms of general comfort and holding quality and, as a result, the ease of use of the Cardboard VR was found to be significantly higher than the Frenzel goggles. Studies using VR glasses in different medical fields have been conducted in recent years. In a recent study by Choque-Velasquez et al., the authors reported that VR glasses can be used for educational purposes in the microsurgical area of neurosurgery (3). In a recent study by Tsapakis et al., VR glasses were shown to have a high correlation with Humphrey perimetry in visual field examination and to be suitable for clinical use (2). This is the first study in the literature showing that Cardboard VR have similar features to conventional Frenzel goggles in the assessment of nystagmus. The fact that eye movements can be evaluated with VR glasses suggests that this technology can be developed and used more effectively and widely in clinical use.

CONCLUSION

In conclusion, Cardboard VR have been found to be an easily accessible, light, inexpensive, and easy-to-use tool that can be used as an alternative to conventional Frenzel goggles in the assessment of nystagmus. We believe that their use may be useful in the examination of patients presenting with the complaint of vertigo.

Ethics Committee Approval: This study was approved by Bezmialem Vakif University Clinical Researches Ethics Committee (Date: 20.02.2019, No: 4/15).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- R.D., N.D.; Data Acquisition- R.D., N.D.; Data Analysis/Interpretation- R.D., N.D.; Drafting Manuscript- R.D., N.D.; Critical Revision of Manuscript- R.D., N.D.; Final Approval and Accountability- R.D., N.D.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. West PD, Sheppard ZA, King EV. Comparison of techniques for identification of peripheral vestibular Nystagmus. J Laryngol Otol 2012;126(12):1209-15.
2. Tsapakis S, Papaconstantinou D, Diagourtas A, Droutsas K, Andreanos K, Moschos MM, et al. Visual field examination method using virtual reality glasses compared with the Humphrey perimeter. Clin Ophthalmol 2017;11:1431-43.
3. Choque-Velasquez J, Colasanti R, Collan J, Kinnunen R, Rezai Jahromi B, Hernesniemi J. Virtual Reality Glasses and «Eye-Hands Blind Technique» for Microsurgical Training in Neurosurgery. World Neurosurg 2018;112:126-30.
4. Strupp M, Fischer C, Hanß L, Bayer O. The takeaway Frenzel goggles: a Fresnel-based device. Neurology 2014;83(14):1241-5.
5. Ben-David Y, Hafner H, Fradis M, Krasnitz G, Podoshin L. Do Frenzel glasses have a place in the modern electronystagmography laboratory? Am J Otol 1996;17(1):89-92.
6. Strauss P, Meyer zum Gottesberge A. Caloric nystagmus: ENG in comparison with observation by Frenzel's glasses. Adv Otorhinolaryngol 1979;25:134-7.
7. Baba S, Fukumoto A, Aoyagi M, Koizumi Y, Ikezono T, Yagi T. A comparative study on the observation of spontaneous nystagmus with Frenzel glasses and an infrared CCD camera. J Nippon Med Sch 2004;71(1):25-9.

RESEARCH ARTICLE
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Determining Eustachian Tube Function in Mucosal Ear Disease Using Cost-Effective, Consistent, Constant, Convenient Tests: A Hospital Based Study

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ABSTRACT

Objective: Using a range of methods, the aim of this study was to measure the patency of the eustachian tube for its effectiveness in all cases of mucosal ear disease. The eustachian tube plays a pivotal role connecting the middle ear with the nasopharynx. It preserves the equilibrium between the middle ear and the outer air and protects the ear from various nasopharyngeal pressure changes, mounting secretions and microorganisms. Healthy eustachian tube functions and patency are prerequisites for effective graft uptake and successful tympanoplasty. The most common reason behind failure of graft uptake is abnormal function of the eustachian tube, where mucosal ear disease is present in the main pathology.
Materials and Methods: 100 patients in the ENT OPD of the Subbaiah Institute of Medical Sciences, Shivomogga, were selected and screened and their tubal function was evaluated and equated with a few tests.
Results: The results were tabulated based on 5 tests: Valsalva maneuver, siegalisation test, ear drops test, nasopharyngoscopy and tympanometry to which all selected patients were subjected. The outcomes were tabulated accordingly.
Conclusion: Of all the tests carried out in this study, Toynbee was the only test which was accurate regarding the function of the eustachian tube as an opening and closing mechanism for the regulation of air pressure in the middle ear.

Keywords: Eustachian tube, mucosal ear disease, tympanometry, toynbee maneuver

INTRODUCTION

The eustachian tube (ET) forms a vital bridge connecting the middle ear (ME) with the nasopharynx. It maintains the equilibrium between ME and the outer air and protects it against variations in nasopharyngeal pressure as well as ascending secretions and microorganisms. This triad makes the tube in question a complex organ. Any midline infections of nose and throat are the prime cause of ME infections which have to be dealt with first.

Mucosal ear disease is one of the most common ear conditions encountered in any hospital set up of Otorhinolaryngology practice with abnormal ET function being its main etiology. Though there are many prerequisites for a successful graft uptake in tympanoplasty, the most effective of them all is good preoperative tubal function.

With the aid of good diagnostic procedures, it has now become easy, cost effective, consistent and convenient to find out the cause behind the failure of tympanoplasty i.e ET dysfunction.

This study aims to evaluate eustachian tube patency in all cases of mucosal ear disease, to examine the effectiveness of different methods used for assessing eustachian tube patency, and lastly to assess the most accurate method of measuring eustachian tube function.

MATERIALS AND METHODS

A cross sectional study of 100 out-patients was conducted at Subbaiah Institute of Medical Sciences, Shivamogga, over one year. The patients were screened for ear discharge and deafness. After a thorough history and detailed clinical

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examination, several tests were conducted to determine ET function. These tests included Valsalva maneuver, siegalisation test, ear drops method, nasopharyngoscopy and tympanometry with Toynbee maneuver. The criteria specified the inclusion of patients with mucosal ear disease. Excluded were traumatic cases, postoperative cases, cases of tubercular otitis media & eosinophilic otitis media and squamosal ear disease. The study was conducted after obtaining institutional ethical clearance and written /informed consent from the patients. The procedure (tests) that were conducted on all the patients mentioned above were performed according to universally standard, acceptable and approved protocols.

RESULTS

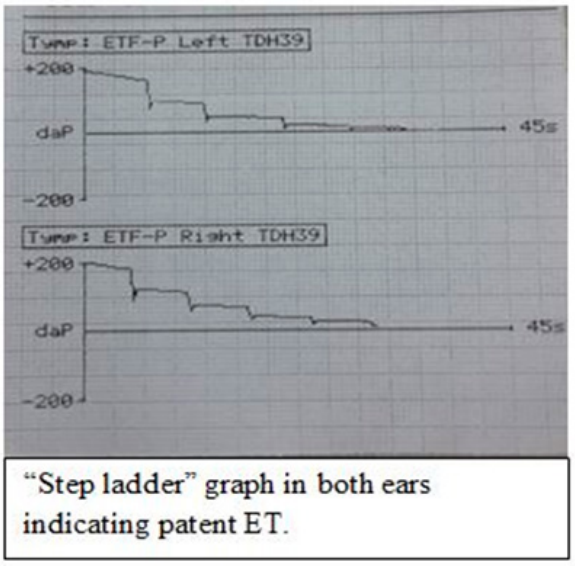
After conducting the Valsalva maneuver on the patients included in the study it was found that in 84 patients an air leak was present indicating ET patent, while in 16 patients no air leak was found indicating a blocked ET. As for the results of the pneumatic otoscopy, in 86 patients there was active mobility of tympanic membrane in the drum with small to moderate perforation indicating patent ET, while in the remaining 14 patients, the tympanic membrane did not move. This was due either to ET block or to inability to assess mobility due to large perforation. In the ear drops method test, in 87 patients, a bitter sensation was felt in the throat within a few minutes indicating patent ET and good mucociliary clearance of ET, but the remaining 13 patients did not feel the presence of the drops in the throat due to a block in the ET or diminished mucociliary mechanism of the ET. In the tympanometry test, in 75 patients, pressure could not be built up indicating patent ET while in the remaining 25 patients, a pressure build-up was seen suggesting a blocked ET. These patients then underwent Toynbee's maneuver. In Toynbee's test, 16 patients showed "step-ladder" graph (Graph A) suggesting normal ET function while 9 patients showed "flat" graph (Graph B) indicating temporary ET block due to various ENT conditions as mentioned below in Figure 1.

In the nasopharyngoscopy test, 80 patients showed a normal active ET opening indicating good ET function. In 12 patients, there was inflammation around the ET opening due to allergic rhinitis and chronic sinusitis and in the remaining 8 patients, the ET opening was not seen due to adenoid hypertrophy, cleft palate, or soft tissue in the nasopharynx all causing obstruction at the nasopharyngeal end of the tube indicating poor ET function. These results are depicted in tabulation form in Table 1 and diagrammatically in Figure 2. The demographic data and clinical characteristics of the patients are summarized in Table 1.

DISCUSSION

Valsalva is a technique for ME pressure equalization and is a highly sensitive and specific test. It also indicates patency of ET (8). It is both easy and convenient and does not need expensive equipment. It evaluates ET function accurately and is fit for a basic level hospital (20). Its efficiency when performed alone for the assessment of the ET opening and closing function is

A



B

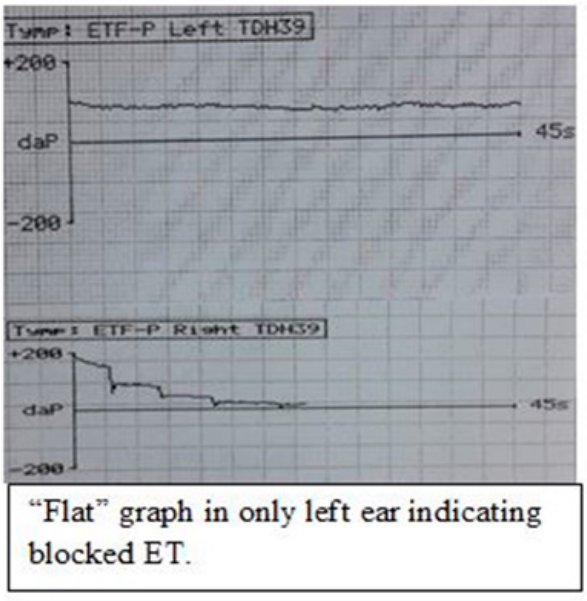


Figure 1: Graph A shows patent ET in the form of "Step ladder" graph while Graph B shows blocked ET in the form of "Flat" graph

of less prognostic value though it yields good success when combined with Toynbee due to common physiology (24). As per Dhingra, failure of this test does not prove tube block because only 65% of subjects can successfully perform this test. This test always gives good results when performed both pre- and post-operatively in cases of mucosal disease following surgery in order to assess tubal function irrespective of graft material and surgery performed. Pre-operatively, the results of this test on the assessment of tubal function were 30% (22). This test is a reliable tool among all the tests for ET function which evaluate the pressure opening and closing functions of ET both qualitatively and quantitatively (1). In

Table 1: Summary of all tests among all the patients

Gender distribution	**52 -** males **48 -** females
Age-wise distribution	1 to 10 years **- 7,** 11 to 20 years **- 20,** 21 to 30 years **- 23,** 31 to 40 years **- 32,** 41 to 50 years **- 18.**
Size of perforation	**86:** small to moderate perforation, **14:** large perforation.
Valsalva maneuver	**84:** air leak present indicating ET patent, **16:** no air leak due to blocked ET. **(biased and dependent on patient's response).**
Pneumatic otoscopy	**86-** active mobility of TM with small - moderate perforation indicating patent ET. **14 -** TM did not move either due to ET block or inability to assess mobility due to large perforation. **(does not hold good for large central perforation as appreciation of mobility of TM is difficult).**
Ear drops test	**87-** felt bitter sensation in throat within few minutes indicating patent ET and good mucociliary clearance of ET**.** **13-** did not feel presence of drops in throat due to block in ET or diminished mucociliary mechanism of ET. **Duration of result varies depending on size and site of perforation.**
Tympanometry test	**75-** pressure could not be built up indicating patent ET. **25-** pressure build-up was seen suggesting blocked ET. These patients then underwent Toynbee's maneuver.
Toynbee maneuver	**16-** "step-ladder" graph (Graph A) suggesting normal ET function (64%) **9-** "flat" graph (Graph B) indicating temporary ET block due to: allergic rhinitis (1 case), enlarged adenoids (5 cases), cleft palate (2 cases), nasopharyngeal mass (1 case) (36%)
Nasopharyngoscopy	**80 -** normal active ET opening indicating good ET function. **12 -** inflammation around ET opening due to allergic rhinitis & chronic sinusitis. **8 -** ET opening not seen due to adenoid hypertrophy, cleft palate, soft tissue in nasopharynx all causing obstruction at nasopharyngeal end of tube indicating poor ET function.

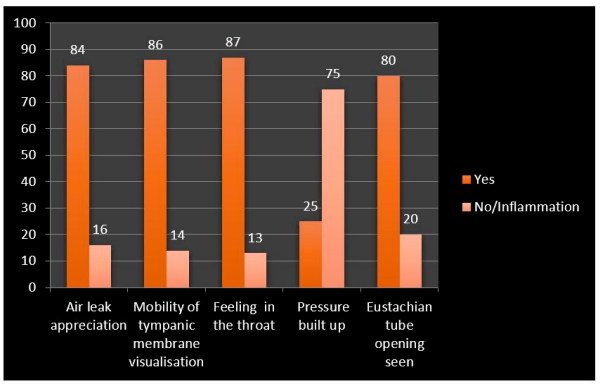


Figure 2: Diagrammatic representation of the entire study, where all 5 tests conducted in this study are represented in the form of Clustered column representation

children with cleft palate, the ability to alter ME pressure is disrupted. As a result, they have high prevalence of developing ME disease. So, one of the reasons for functional obstruction of ET is anatomical abnormality (1, 37). As cases of mucosal ear disease are common in the institute where this research was conducted, 100 patients were clinically evaluated to look for tubal patency. Here, 84 % showed good results in terms of air leak appreciation. The results were better compared to a study done by Uzun et al. Also, the result showing 2 cases of cleft palate correlates with the study quoted by Doyle et al.

Otitis media (OM) and otitis media with effusion (OME) are common childhood disorders. Tube dysfunction plays an important role in OM. Pneumatic otoscopy is used to evaluate tubal function in cases with otitis media (21). A normal appearance of TM does not mean a normal functioning tube, but normal TM mobility on siegalization indicates good patency of tube. In any ME disease, the presence of high negative ME pressure or both are determined by pneumatic otoscopy giving presumptive evidence of ET dysfunction (19). Here, 86% showed movement of TM with small to moderate perforation indicating good tubal patency. The remaining members of the sample group had a large central perforation; thus mobility of TM could not be assessed.

An ear drops test is done to look for patency of ET. It is one of the simplest, cost effective and valuable diagnostic tools to assess the mucociliary function of the tube and hence assess tubal patency (3-5, 13). The ear drops test in 100 patients showed that 84 patients could feel a bitter sensation in their throat as they had a dry ear. Three patients had a delayed response, and the rest could not feel the drops in the throat. As regards the 84 patients, the travel of the drop was fast, but the remaining patients had various conditions which prevented them from feeling the drop, such as a blocked tube, inability to make a response, or a delayed response. Depending on the condition of ME mucosa, patients with a dry ear felt a bitter sensation in their throat comparatively earlier than those with a wet ear. In keeping with the study conducted by Shreyas et al., nearly 87.5% patients had a good ET function with an inactive ear that correlates well with this study.

As mentioned by Uzun et al., Jesic et al., Benne et al., tympanometry is used to assess ET function (22-24). In a good tubal function the ME pressure is between 0 to -250mm H2O when swallowing whereas a condensed tubal opening is seen when the ME pressure is below the optimal level of 0 to

-200mm H2O. These levels are evaluated by tympanometry. Impedance audiometry is a reliable tool to evaluate the pressure opening and closing functions of ET both qualitatively and quantitatively. During this study, the pressure in the case of 75 patients could not be built up indicating patent ET, while in 25 patients, a build-up of pressure was seen suggesting blocked ET. These patients then underwent Toynbee's maneuver, the results of which were very similar to the above-mentioned studies. Tympanometry is a readily available procedure that may be useful in patients to prevent chronic ME disease. It is also a very practical and easy test (21). Frequent recurrence of ME infection is due to anatomic and craniofacial abnormalities, enlarged adenoids, previous episodes of acute otitis media, allergic rhinitis, and chronic sinusitis, all of which contribute to ET dysfunction. Diagnostic evaluation by tympanometry plays a pivotal role that has proved to be more efficient than other air equalization methods in assessing the course and prognosis of OM and also in evaluating tubal function (14). Tympanometry is based on acoustic immittance that measures positive and negative air pressure variations produced in external acoustic meatus that lead to changes in physical properties in the ME and TM. Immittance tests are also used to study the ventilatory function of ET and hence this pressure equalization swallow test is accurate to assess tube dysfunction (10). Modern impedance audiometer enables the physiological function of the ET to be ascertained, not only in intact TM but also in the presence of perforation. Its advantages are that it is quick, non-invasive, accurate and inexpensive. Another advantage is that patient compliance not required. The results of tympanometric assessment in the study was 80% (3). ET function is related to the duration, type and location of TM perforation in chronic suppurative otitis media. Impedance audiometry is a simple, invasion-free method to evaluate ET function. There is a strong association between the tube function and graft uptake and the Toynbee test proves whether the tube is patent or not. This suggests that the ET plays a major role in the success of tympanoplasty (2). When the 100 patients in our study who had a perforated tympanic membrane were subjected to tympanometry the results showed that in 75 of them pressure could not be built up, thus indicating patent ET. In the remaining 25, pressure was built up which suggested a blocked ET. Toynbee's test was then done in these 25 patients and among them 16 showed a "step-ladder" type of graph suggesting normal ET function while the remaining 9 showed, a "flat" graph indicating a temporary ET block due to allergic rhinitis, cleft palate, enlarged adenoids and nasopharyngeal mass. This study also shows good results (75%) which are very similar to the study by Shreyas et al.

Normal endoscopic results indicate good tubal function, while an abnormal result indicates organic tubal obstruction which is correctable. Any inflammation around the tube due to the presence of recurrent episodes of OM, URI, chronic sinusitis, enlarged adenoids, cleft palate and nasopharyngeal mass all make the opening of tube blocked and non-visualizable. Hence, nasopharyngoscope has been a diagnostic tool here (22). The morphological changes of pharyngeal ostium of the ET play an important role both in the beginning stage and in the development of OM. Hence, nasopharyngoscope is a very useful tool in diagnosis and treatment of OM as it is an accurate, non-invasive test (17). ET dysfunction plays an important role in the development, persistence and recurrence of OME and chronic OM. To identify the characteristics of the dynamic function of the pharyngeal orifice of the tube in children, a transnasal endoscopic examination of the nasopharyngeal opening of the tube is conducted using a nasopharyngoscope (16). Nasopharyngoscope is an indispensable and diagnostic tool in localizing and treating hidden lesions responsible for obstruction (7). Here, similar results were seen in 80 patients where the tube opening was normal and visualized suggesting a good ET function. But in 20 patients, inflammatory changes were noted around tube opening. Of these, 12 had allergic rhinitis and chronic sinusitis. In the remaining 8, the tubal opening was not visualized due to the presence of enlarged adenoids, cleft palate and nasopharyngeal mass indicating poor tube function.

ET function is related to the duration, type and location of TM perforation in CSOM (4-5, 20). Cleft palate has a high prevalence of chronic OM due to the limited ability of the tensor veli palatini muscle to dilate the tube actively on swallowing, which is the cause of the functional obstruction of ET (23). Impairment in the active opening function of the tube was found both in children with OME (71.8%) and adults with chronic OM (51.8%). This impairment was due to the functional obstruction of the tube. However, organic obstruction was noted in 45.6% of adults with chronic OM and 28.2% of children with OME. Though functional obstruction of the tube was found to be the cause of ME diseases, organic obstruction is also related to pathogenesis of OME (24).

One of the main causes of tubal dysfunction is enlarged adenoids which is the reason behind recurrent OME. So, in such children, adenoidectomy is the surgical mode of intervention. Causative factors responsible for tube dysfunction in adults are rhinosinusitis, obstructive sleep apnea, craniofacial deformity, difficulty in deglutition, all of which can affect the overall quality of life. Hence treating the central cause is very important in order for ME infections to be healed (21, 22). The tubal mucociliary transport is important for the elimination of inflammation products from the ME and hence enabling the restoration of normal ME pressure. The association between the degree of mucosal defect and the time of mucociliary transport was evidenced in both types of chronic suppurative inflammation of ME (19, 23).

Enlarged adenoids and allergic rhinitis in the nose and nasopharynx cause ET dysfunction by blocking osteomeatal complex leading to chronic OM. This altered communicatory function of the tube plus ME with nasopharynx, nasal cavity, PNS has led to decreased elasticity of TM, hearing impairment and variations in ME pressure. Tubal function can be affected directly by histamine released in nasal mucosa or indirectly by nasal obstruction due to viral URI that may promote secondary bacterial infections by altered bacterial adherence, modulating host immune and inflammatory responses and impairing ET function (6, 11-12, 15, 18). ME infections are

commonly seen in 28-38% of pre-school children due to disorders of mucin production resulting from ME bacterial infection and ET dysfunction. This affects ME pressure, and damages the mucosal and mastoid system, as well as the ME ossicles. In cases of nasopharyngeal mass, tube dysfunction is characterized by high opening pressure and high active resistance (9).

CONCLUSIONS

Toynbee's test shows that ET is both patent and functioning. In 64% of patients a "step ladder" graph is seen, and 36% patients show a "flat type" of graph inferring a blocked tube at the time of the test. 89% patients had a patent eustachian tube in this study. All the above tests indicate the patency of the ET, but it is only Toynbee's test which gives an accurate idea of ET function, namely, that it is the opening and closing mechanism for the equalization of pressure in the ME. The purpose of this study was to draw attention to the amalgamation of old school methods and new ideas to assess both the patency and function of the ET, which is the topmost priority for successful graft uptake in tympanoplasty as well as maintaining acceptable and adequate ventilation of the middle ear and mastoid air cell system.

Ethics Committee Approval: This study was approved by Government of India Directorate General of Health Services Central Drugs Standard Control Organization Ethics Committee Registration Division (Date: 16.03.2020, No: EC/19/000405).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Doyle WJ, Swarts JD, Banks J, Casselbrant ML, Mandel EM, Alper CM. Sensitivity and specificity of Eustachian tube function tests in adults. JAMA Otolaryngol Head Neck Surg 2013;139(7):719-27.
2. Kanagamuthu P, Padmanabhan K, Venkataramanujam NC, Sambandan AP. Evaluation of Eustachian tube function in chronic suppurative otitis media (tubotympanic type) with reference to its treatment outcome. Indian J Otol 2013;18(4):179-83.
3. Shreyas SJ, Mohan J, Saurabh A, Dnyaneshwar A. Tympanometry, a prognostic indicator of myringoplasty with assessment of eustachian tube function. International Journal of Otolaryngology and Head & Neck Surgery 2012;1(3):105-8.
4. Nishant K, Madkikar N, Kishve S, Chilke D, Shinde KJ. Using Middle Ear Risk Index and ET Function as Parameters for Predicting the Outcome of Tympanoplasty. Indian J Otolaryngol Head Neck Surg 2012;64(1):13-6.
5. Nishant K, Devashri C, Puttewar MP. Clinical profile of tubotympanic CSOM and its management with special reference to site and size of tympanic membrane perforation, eustachian tube function and three flap tympanoplasty. Indian J Otolaryngol Head Neck Surg 2012;64(1):5-12.
6. Ghasem A, Sepideh A, Ashkan D. Eustachian Tube Function in Repeated Upper Respiratory Tract Infections. Australian Journal of Basic and Applied Sciences 2011;5(11):943-5.
7. Marseglia GL, Caimmi D, Pagella F, Matti E, Labó E, Licari A, et al. Adenoids during childhood: the facts. Int J Immunopathol Pharmacol 2011;24(4):1-5.
8. Hidir Y, Ulus S, Karahatay S, Satar B. A comparative study on efficiency of middle ear pressure equalization techniques in healthy volunteers. Auris Nasus Larynx 2011;38(4):450-5.
9. Hurst DS. The role of allergy in otitis media with effusion. Otolaryngol Clin North Am 2011;44(3):637-54.
10. Renata RM, Jackeline YF, Daniela G. Eustachian tube function in adults with intact tympanic membrane. Braz J Otorhinolaryngol São Paulo 2010;76(3):340-46.
11. Pollini F, Capristo C, Boner AL. Upper respiratory tract infections and atopy. Int J Immunopathol Pharmacol. 2010;23(1 Suppl):32-7.
12. Pelikan Z. Audiometric changes in chronic secretory otitis media due to nasal allergy. Otol Neurotol 2009;30(7):868-75.
13. Prasad KC, Hegde MC, Prasad SC, Meyappan H. Assessment of Eustachian tube function in tympanoplasty. Otolaryngol Head Neck Surg 2009;140(6):889-93.
14. Pelikan Z. Role of nasal allergy in chronic secretory otitis media. Curr Allergy Asthma Rep 2009;9(2):107-13.
15. Hong CK, Park DC, Kim SW, Chang CI, Cha S, Yeo SG. Effect of paranasal sinusitis on the development of otitis media with effusion: influence of Eustachian tube function and adenoid immunity. Int J Pediatr Otorhinolaryngol 2008;72(11):1609-18.
16. Skotnicka B, Hassmann-Poznańska E. Video endoscopic analysis of Eustachian tube functions in children with middle ear pathology. Otolaryngol Pol 2007; 61(3):301-6.
17. Yuan Y, Li G, Zhou W, Xu Y. Study of morphological alterations in pharyngeal ostium of Eustachian tube and its surrounding tissue and its association with SOM. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2007;21(22):1024-5.
18. Yeo SG, Park DC, Eun YG, Cha CI. The role of allergic rhinitis in the development of otitis media with effusion: effect on Eustachian tube function. Am J Otolaryngol 2007;28(3):148-52.
19. Seibert JW, Danner CJ. Eustachian tube function and the middle ear. Otolaryngol Clin North Am 2006;39(6):1221-35.
20. Xiao S, Tan D, Liao M, Yang L, Tu X. Evaluation of Eustachian tube functions with impedance audiometry in chronic suppurative otitis media .Lin Chuang Er Bi Yan Hou Ke Za Zhi 2006;20(7):306-8.
21. Lazo-Sáenz JG, Galván-Aguilera AA, Martínez-Ordaz VA, Velasco-Rodríguez VM, Nieves-Rentería A, Rincón-Castañeda C. Eustachian tube dysfunction in allergic rhinitis. Otolaryngol Head Neck Surg 2005;132(4):626-9.
22. Uzun C, Cayé TP, Andersen J, Tos M. Eustachian tube patency and function in tympanoplasty with cartilage palisades or fascia after cholesteatoma surgery. Otol Neurotol 2004;25(6):864-72.
23. Jesić S, Nesić V. Mucociliary transport in the Eustachian tube in chronic suppurative otitis media. Srp Arh Celok Lek 2004; 132(5-6):148-51.
24. Bunne M, Falk B, Magnuson B, Hellström S. Variability of Eustachian tube function: comparison of ears with retraction disease and normal middle ears. Laryngoscope 2000;110(8):1389-95.

RESEARCH ARTICLE
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The Restorative Effects of Three Commonly Used Materials on Hearing Thresholds in Patients with Austin-Kartush Type A Ossicular Defects

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ABSTRACT

Objective: This study aims to compare the effect on the hearing results of three different materials used in ossiculoplasty for patients with chronic otitis media (COM) and Austin-Kartush type A defect.

Materials and Methods: This retrospective study includes 79 patients with the Austin-Kartush type A defect due to COM. The ossiculoplasty had been performed with a glass ionomer cement (GIC), titanium partial ossicular replacement prosthesis (PORP), or incus interposition between 2011-2021. Age, gender, operation side, hearing thresholds, computed tomography images, intraoperative findings, and middle ear risk index (MERI) were obtained from medical records. Air-conduction (AC) and bone-conduction (BC) thresholds were calculated by averaging the threshold values for 500, 1,000, 2,000 and 3,000 Hz, and air-bone gap (ABG) values were calculated by subtracting the BC thresholds from the AC thresholds, preoperatively and postoperatively. Hearing gains were obtained by subtracting ABG values in the first postoperative year from the preoperative ABG values.

Results: This study included 32 male and 47 female patients. The GIC group had 28 patients, the incus interposition group had 28, and the PORP group had 23. No statistically significant difference occurred among the groups regarding MERI scores (p = 0.699). The mean preoperative ABG levels were 37.46±9.23dB in the GIC group, 38.96±11.35dB in the incus interposition group, and 37.34±10.16dB in the PORP group, while the mean postoperative ABG levels were 24.42±11.20dB in the GIC group, 23.25±10.09dB in the incus interposition group, and 22.82±13.59dB in the PORP group (p = 0.814). The ABG gains were 13.75±11.66dB in the GIC group, 15.71±11.55dB in the incus interposition group, and 14.52±9.98dB in the PORP group (p = 0.803).

Conclusion: The incus long process defect or lack of the incus due to COM may be repaired with GIC, incus interposition, or titanium PORP, all with similar ABG gains.

Keywords: Chronic otitis media, ossiculoplasty, Austin-Kartush type A defect, glass ionomer cement, incus interposition, partial ossicular replacement prosthesis

INTRODUCTION

The ossicular chain is located in the middle ear and transmits sound energy from the tympanic membrane to the oval window. Chronic otitis media (COM) can cause ossicular chain defects that are commonly seen in the incus long process (1). Various prostheses and materials have been developed for restoring ossicular defects, and the characteristics of successful ossiculoplasty methods include low extrusion rates, biocompatibility, cost-effectiveness, no transmission of contagious diseases, long-term stability, and the effective biomechanical transmission of sound. Ossiculoplasty in the absence of incus or incus long process defects can be performed with an incus remnant, bone, cartilage, glass ionomer cement (GIC), or partial ossicular replacement prosthesis (PORP) (2-3).

The aim of this study is to compare effects on the hearing results of three different materials (GIC, incus remnant, and PORP) used for ossicular reconstruction in patients with COM-based Austin-Kartush type A ossicular defects.

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MATERIALS AND METHODS

This study was approved by ethics review board of our tertiary hospital (Date: May 11, 2022, No: 2022/313). A total of 106 consecutive patients with defect of the incus or incus long process (Austin-Kartush type A) because of COM were reviewed retrospectively. These patients had each undergone an operation using the canal wall up mastoidectomy between 2011-2021. The exclusion criteria of this study were the presence of tympanosclerosis (13 patients), a graft failure (2 patients), PORP extrusion (2 patients), fixation of the malleus or the stapes (3 patients), and prior history of otologic interventions (7 patients). This study examined the remaining 79 patients. Inclusion criteria were comprised of patients having small retraction pockets, cholesteatomas limited to the mesotympanum and not reaching beyond the antrum, tympanic membrane perforation, and conductive or mixed type hearing loss.

The study obtained information about age, gender, operation side, hearing thresholds, computed tomography images, intraoperative findings, and middle ear risk index (MERI) from the patients' medical records.

Audiological Evaluation

Postoperative audiometric evaluations were performed in the third, sixth, and twelfth months after surgery. Air-conduction (AC) and bone-conduction (BC) thresholds were calculated by averaging at the threshold values for the frequencies of 500, 1000, 2000, and 3,000 Hz, with the air-bone gap (ABG) values being calculated by subtracting the BC thresholds from the AC thresholds, preoperatively and postoperatively (4). Hearing gains were obtained by subtracting the ABG values in the first postoperative year from the preoperative ABG values.

Preoperative and postoperative ABG scores were categorized as grade I (0-10 dB), grade II (11-20 dB), grade III (21-30 dB), and grade IV (> 30 dB) (4). Postoperatively, ABG scores of 20 dB or less were regarded as a successful ossiculoplasty.

Surgical Procedures and Groups

All surgeries were performed using an operating microscope under general anesthesia. The edges of the tympanic membrane perforation were refreshed and the tympanomeatal flap was elevated. Retraction pockets with or without cholesteatoma were removed, if present. The middle ear and ossicular chain were observed under the microscope. Upon detecting the incus or its long process defect, the mobility of the malleus and stapes was checked gently by tapping.

In the presence of a useless incus destroyed by cholesteatoma or surrounded by cholesteatoma, the incudomalleolar joint was disarticulated and the incus was removed from the middle ear. If a useful incus was present, it was used for restoring the ossicular integrity based on the size of the defect in the incus long process. The autograft incus was used for ossicular reconstruction when present and useful.

For an incus long process defect smaller than one-third the length of the incus long process, ossicular reconstruction was performed by re-bridging, using a piece of GIC (AquaCem, Dentsply, Konstanz, Germany). The mucosa covering the incus long process remnant and stapes capitulum was first peeled back. After preparing a dry medium around the ossicles, a piece of GIC was placed between the stapes capitulum and the incus long process remnant (GIC group).

For a defect greater than two-thirds the length of the incus long process, the incus was removed entirely (5). The incus was reshaped with a small cutting-burr, and an acetabulum for the stapes capitulum was created. A small groove was created to fit the malleus handle. The ossicular chain continuity was maintained by interposing the sculptured incus between the stapes capitulum and the malleus handle (incus interposition group).

For the incus that was not available, largely destroyed, or surrounded by the cholesteatoma matrix, ossicular reconstruction was performed using the titanium PORP (Dmetrixcell, divine medicure technology, GJ, India; PORP group). PORP length was adjusted appropriately for the distance between the stapes capitulum and the tympanic membrane, and the PORP was placed onto the stapes capitulum. A small piece of cartilage was placed between the headplate of the titanium PORP and the tympanic membrane to prevent extrusion.

A cartilage-perichondrium composite graft from the tragus was used in all patients to repair the tympanic membrane perforation. Patients were regularly examined, and audiograms were obtained in the third, sixth, and twelfth month after operation. The graft was considered a failure if the tympanic membrane perforated within the first year after operation.

Statistical Analysis

Statistical analysis was performed using SPSS (version 24.0; IBM, SPSS Inc.), with the data being shown as mean ± standard deviation for continuous variables and number of cases for categorical variables. Normal distribution of the data was checked using the Shapiro-Wilk test. The χ^2 test was employed for comparing differences between groups in terms of gender. One-way analysis of variance (ANOVA) was employed to compare the mean age, preoperative ABG, preoperative MERI, postoperative change in ABG (C-ABG), and postoperative frequency-specific C-ABG values among the groups. Multivariate linear regression was performed to assess the relative effect of the independent variables (surgery type and MERI values) on the postoperative C-ABG values, with p values < 0.05 being regarded as statistically significant.

RESULTS

This study included a total of 79 patients (32 males and 47 females). The GIC group had 28 patients, the incus interposition group had 28 patients, and the PORP group had 23 patients. There were eight males and 20 females in the GIC group, 11 males and 17 females in the incus interposition group, and 13 males and 10 females in the PORP group. The mean age of all patients was 34.75±14.76 years (Range=9-68 years). Forty patients had the operation in their right ear and 39 in their

left ear. When evaluating the gender distributions among all three groups, there was no statistically significant difference (p=0.127). The mean age was similar among all groups (p=0.933). Table 1 shows the demographic characteristics for all the patients.

The mean MERI score for all patients was 4.74±1.42. The mean MERI scores for each group were 4.57±1.25 for the GIC group, 4.89±1.47 for the incus interposition group, and 4.78±1.59 for the PORP group. No statistically significant difference occurred among the groups regarding MERI scores (p=0.699).

The mean preoperative and postoperative ABG values for all patients were 37.96±10.19 dB and 23.54±11.45 dB, respectively, with a mean ABG gain of 14.67±11.05 dB. The mean preoperative ABG levels were 37.46±9.23dB for the GIC group, 38.96±11.35 dB for the incus interposition group, and 37.34±10.16 dB for the PORP group (p=0.814), while the mean postoperative ABG levels were 24.42±11.20 dB, 23.25±10.09 dB, and 22.82±13.59dB in the respective GIC, incus interposition, and PORP groups (Table 2). The ABG gains were 13.75±11.66 dB in the GIC group, 15.71±11.55dB in the incus interposition, and 14.52±9.98dB in the PORP group (p=0.803).

The mean ABG gain at each frequency by group were as follows: 17.92 dB at 500 Hz, 13.10 dB at 1,000 Hz, 13.32dB at 2,000 Hz, and 7.67 dB at 3,000 Hz in the GIC group; 17.85 dB at 500 Hz, 15.82 dB at 1,000 Hz, 16.64 dB at 2,000 Hz and 12.53 dB at 3,000 Hz in the incus interposition group; and 18.73 dB at 500 Hz, 17.21 dB at 1,000 Hz, 12.17 dB at 2,000 Hz, and 9.91 dB at 3,000 Hz in the PORP group. When considering the ABG gains for 500 Hz, 1,000 Hz, 2,000 Hz and 3,000 Hz, no statistically significant difference was found among the groups, which had respective p values of 0.977, 0.567, 0.377 and 0.363 for the 500, 1,000, 2,000, and 3,000 Hz.

Upon performing the multivariate linear regression, neither surgery type (p=0.755) nor preoperative MERI index (p=0.614) exhibited any statistically significant effect on postoperative change in ABG levels (Table 3). The mean follow-up period was 35 months in the GIC group, 36 months in the incus interposition group, and 27 months in the PORP group, with a 33-month mean for all patients (Range=12-88 months).

DISCUSSION

Debates on ossiculoplasty materials are still ongoing in the otological practice, with no optimal material having yet been defined. This study reviewed the ABG gain scores for ossiculoplasty techniques performed with three different materials (i.e., GIC, the incus and titanium PORP) in regard to Austin-Kartush type A defects. All three patient groups had comparable hearing gains.

Serviceable hearing requires normal hearing pathways from the auricula to the central auditory cortex. Patients with chronic otitis media may suffer from tympanic membrane perforation, ossicular erosion or fixation, tympanosclerosis, and infectious events that may result in various degrees of hearing loss. Tympanic membrane perforations and erosion of the incus long process are quite commonly encountered, and many different materials are currently being used to rebuild the integrity of the ossicular chain. The features of these introduced materials should include being bioinert, cost-effective, easy to use, resistant to recurrent infections, low extrusion, and time saving. In addition, optimal methods for ossicular reconstruction are those that

Table 2: Preoperative and postoperative ABG scores according to ossiculoplasty types

	GIC (n=28)	II (n=28)	PORP (n=23)	Total (n=79)
Preoperative ABG				
Grade I (0-10 dB)	0	0	0	0
Grade II (11-20 dB)	1	0	0	1 (1.2%)
Grade III (21-30 dB)	4	4	7	15 (18.9%)
Grade IV (>30 dB)	23	24	16	63 (79.7%)
Postoperative ABG				
Grade I (0-10 dB)	2	1	4	7 (8.8%)
Grade II (11-20 dB)	10	14	9	33 (41.8%)
Grade III (21-30 dB)	9	6	5	20 (25.3%)
Grade IV (>30 dB)	7	7	5	19 (24%)

ABG: air-bone gap, GIC: glass ionomer cement, II: incus interposition, PORP: partial ossicular replacement prothesis

Table 1: Demographic features and the mean middle ear risk index scores of the patients based on ossiculoplasty type

	GIC (n=28)	II (n=28)	PORP (n=23)	Total (n=79)	p value
Age (year, SD)	35.53±13.93	34.60±14.97	34.0±16.07	34.75±14.76	(p=0.933)
Gender					(p=0.127)
Male	8	11	13	32	
Female	20	17	10	47	
Side					
Right	11	19	10	40	
Left	17	9	13	39	
MERI (SD)	4.57±1.25	4.89±1.47	4.78±1.59	4.74±1.42	(p=0.699)

GIC: glass ionomer cement, II: incus interposition, PORP: partial ossicular replacement prothesis, MERI: middle ear risk index

Table 3: Multivariate linear regression of c-ABG

Model	Unstandardized Coefficients		Standardized Coefficients	t	p	95.0% Confidence Interval for β	
	β	Standard Error	β			Lower Bound	Upper Bound
Constant	15.851	5.194		3.052	0.003	5.505	26.196
Surgery type	.492	1.572	.036	.313	.755	-2.640	3.624
MERI index	-.449	.888	-.058	-.506	.614	-2.218	1.319

Dependent variable: c-ABG: change-air-bone gap

best mimic the ossicular chain anatomically and physiologically. Prostheses are used for implementing any function in the human body and they consist of the artificially developed materials. Therefore, POPRs replace the incus in order to restore hearing. Ossicular reconstruction can also be performed with tissue grafts (called autografts, homografts, and allografts). Autografts involve grafts of the cartilage (tragal or conchal), cortical bone, or ossicle (the incus remnant or malleus head), and these autografts have biocompatible properties, no additional cost, low extrusion rates, and low likelihood of contagious disease transmission. The drawbacks of autografts are graft migration or resorption as a result of recurrent infections, as well as the autograft incus possibly containing microscopic cholesteatoma (6). Allografts that are fabricated as an ossicular reconstruction prosthesis are biocompatible and they have an additional cost. They are ready to use, but adjusting the length, tension, and position of the prosthesis requires experience. Another subject to consider is prosthesis extrusion that can be avoided by placing a small piece of cartilage between the prosthesis and the tympanic membrane (7).

Glass ionomer cement has powder and liquid components. When these two components are mixed in an *in vitro* medium, an exothermic reaction happens. The mixture hardens within a few minutes and can be used easily once it becomes semisolid. It should not be used before becoming semisolid, because thermal injury may occur as a result. In addition, the liquid phase may be less viscous and end up damaging the surrounding structures. In neurotological practice, GIC has been demonstrated to lead to aluminum encephalopathy and irreversible neuronal blockage (8). Therefore, attention should be paid to the presence of labyrinthine fistula, perilymphatic fistula, or gusher and dehiscence in the fallopian canal when using GIC. Using GIC may provide a more anatomical reconstruction compared to other methods and GIC is MRI compatible material as well. GIC use, with low cost, has also been demonstrated to enable rather successful hearing results when used to repair defects in the incus long process (3, 5, 9). ABG gains are higher when using GIC (17.0±11.96 dB) compared to incus interposition (11.0±13.02 dB) (5). Conversely, some studies have reported similar postoperative hearing gains to have been obtained in patients regardless of whether GIC or incus interposition has been used for the ossiculoplasty (3, 10). With regard to defects in the incus long process, Dere et al. (10) reported that ABG declined from 27 dB preoperatively to 20.7 dB postoperatively when using GIC. Successful ABG closure rates (i.e., 10 dB or greater gain in ABG) occurred in 78.6% of GIC patients and 43.0% of incus interposition patients (5). Postoperative ABG was 20 dB or less in 42.8% of the GIC patients in the current study.

Incus interposition may be one of the options among ossicular reconstruction techniques, but the incus can occasionally be completely absent or useless. A malleus and incus surrounded by cholesteatoma may exhibit histologically microscopic cholesteatoma on their surfaces (31.6%) and no intra-ossicular cholesteatoma, which may render the incus remnant unreliable for ossicular reconstruction (11). Additionally, examining the incus with an operating microscope with regard to cholesteatoma is unreliable (12). An acetabulum correspondence to the stapes capitulum and a groove correspondence to the malleus handle can be formed so that the reshaped incus becomes more stable. While shaping the incus, however, care should be taken to avoid thermally damaging it. For additional stabilization, the incus may furthermore be attached to the malleus handle and stapes capitulum with a small amount of GIC. Additionally, short- and long-term postoperative ABG results in patients with the incus interposition are comparable (13). Magnetic resonance imaging also does not constitute any problem in patients who ossicular reconstruction has been performed with the incus remnant.

O'Reilly et al. suggested a postoperative ABG of 20 dB or less in 66.4% of patients who'd undergone an incus interposition, with a MERI score of 3.78±1.79 (6). At the 12th postoperative month, 53.5% of the current study's patients had an ABG of 20 dB or less in the incus interposition group.

Partial ossicular replacement prostheses are fabricated from diverse materials containing titanium, hydroxyapatite, and Plastipore. Extrusion constitutes an important problem for an ossicular prothesis in direct contact with the tympanic membrane. A small piece of cartilage placed on the headplate of the titanium PORP can be enough to prevent extrusion. PORPs with adjustable length also allow one to adjust a proper-prosthesis length for the distance between the stapes capitulum and tympanic membrane (14). The weight of the prosthesis can impair sound transmission, with heavier prostheses having lower sensitivities for higher frequencies in this regard. Moreover, higher tensions in prosthesis placement may cause resonance frequency shifts toward higher frequencies (15). Titanium in the middle ear of rabbits has been histologically indicated to be coated by normal middle ear mucosa without signs of inflammation (e.g., no accumulation of macrophage or giant cells) (16). Martin and Harner [17] demonstrated an ABG ≤ 20dB to be seen in 68% of patients who've used a PORP , and

ossiculoplasty with bone cement and PORP in incus defects has been shown to provide similar hearing gains regarding ABG (18). Postoperative ABG in the current study was 20 dB or less in 56.5% of the patients in the PORP group.

CONCLUSION

Defects in the incus long process or the lack of the incus due to COM may be repaired with GIC, incus interposition, or titanium PORP, with each showing similar ABG gains. Small defects of the incus long process (smaller than one-third of the incus long process) may be amenable to ossiculoplasty with GIC, while ossiculoplasty may be performed using incus interposition or titanium PORP for large defects exceeding two-thirds the length of the incus long process).

Ethics Committee Approval: This study was approved by Mersin University Clinical Research Ethics Committee (Date: 11.05.2022, No: 2022/313).

Informed Consent: Written informed consent was obtained.

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REFERENCES

1. McGee M, Hough JVD. Ossiculoplasty. Otolaryngol Clin North Am 1999;32(3):471-88.
2. Chole RA, Skarada DJ. Middle ear reconstructive techniques. Otolaryngol Clin North Am 1999;32(3):489-503.
3. Ozer E, Bayazit YA, Kanlikama M, Mumbuc S, Ozen Z. Incudostapedial rebridging ossiculoplasty with bone cement. Otol Neurotol 2002;23(5):643-6.
4. Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc. Otolaryngol Head Neck Surg 1995;113(3):186-7.
5. Guler I, Kum RO. Management of Incus Defects in Children: Comparison of incus transposition versus glass ionomer cement. Ear Nose Throat J 2021;100(2):97-102.
6. O'Reilly RC, Cass SP, Hirsch BE, Kamerer DB, Bernat RA, Poznanovic SP. Ossiculoplasty using incus interposition: hearing results and analysis of the middle ear risk index. Otol Neurotol. 2005;26(5):853-8.
7. Smyth GD. Five-year report on partial ossicular replacement prostheses and total ossicular replacement prostheses. Otolaryngol Head Neck Surg 1982;90(3 Pt 1):343-6.
8. Brook IM, Hatton PV. Glass-ionomers: bioactive implant materials. Biomaterials 1998;19(6):565-71.
9. Yazıcı H, Uzunkulaoğlu H, Emir HK, Kızılkaya Z, Doğan S, Samim E. Comparison of incus interpositioning technique versus glass ionomer cement application in type 2 tympanoplasty**.** Eur Arch Otorhinolaryngol 2013;270(5):1593-6.
10. Dere H, Ozdogan F, Ozcan KM, Selcuk A, Ozcan I, Gokturk G. Comparison of glass ionomer cement and incus interposition in reconstruction of incus long process defects. Eur Arch Otorhinolaryngol 2011;268(11):1565-8.
11. Rupa V, Krishnaswami H, Job A. Autograft ossicle selection in cholesteatomatous ear disease: histopathological considerations. J Laryngol Otol 1997;111(9):807-9.
12. Dornhoffer JL, Colvin GB, North P. Evidence of residual disease in ossicles of patients undergoing cholesteatoma removal. Acta Otolaryngol 1999;11(1)9:89-92.
13. Siddiq MA, East DM. Long-term hearing results of incus transposition. Clin Otolaryngol Allied Sci 2004;29(2):115-8.
14. Krueger WWO, Feghali JG, Shelton C, Green JD, Beatty CW, Wilson DF et al. Preliminary ossiculoplasty results using the Kurz titanium prostheses. Otol Neurotol 2002;23(6):836-9.
15. Meister H, Walger M, Mickenhagen A, von Wedel H, Stennert E. Standardized measurements of the sound transmission of middle ear implants using a mechanical middle ear model. Eur Arch Otorhinolaryngol 1999;256(3):122-7.
16. Schwager K. Titanium as a biomaterial for ossicular replacement: results after implantation in the middle ear of the rabbit. Eur Arch Otorhinolaryngol 1998;255(8):396-401.
17. Martin AD, Harner SG. Ossicular reconstruction with titanium prosthesis. Laryngoscope 2004;114(1):61-4.
18. Baylancicek S, Iseri M, Topdağ DÖ, Ustundag E, Ozturk M, Polat S et al. Ossicular reconstruction for incus long-process defects: bone cement or partial ossicular replacement prosthesis. Otolaryngol Head Neck Surg 2014;151(3):468-72.

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Investigation of Ototoxicity of Intratympanic 5-fluorouracil in Rats

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ABSTRACT

Objective: Although 5-fluorouracil is beneficial in treating cholesteatoma in people, it is unknown if this drug harms the inner ear. We are planning to contribute to the literature by investigating the effects of the intratympanic administration of 5-fluorouracil solution form to the middle ear on the inner ear in rats.
Materials and Methods: The study was conducted on 11 Wistar albino male rats: a positive control group was treated with amikacin, a study group was treated with 5-FU, and a negative control group received no treatment. One week after intratympanic drug administration, the rats were sacrificed, and ototoxicity was histopathologically examined by light microscopy and TUNEL (**T**erminal deoxynucleotidyl transferase-mediated d**U**TP **N**ick **E**nd **L**abeling) method.
Results: There was a significant difference between the two groups treated with amikacin and 5-fluorouracil in terms of apoptosis ($p<0.05$). The difference in stria vascularis thicknesses was significant between the amikacin group and the 5-fluorouracil group and the negative control group ($p<0.05$).
Conclusion: The intratympanic administration of 5-fluorouracil to rats did not have any ototoxic effects, according to the results of the histological analysis that looked at apoptosis.

Keywords: 5-fluorouracil, ototoxicity, intratympanic injection, animal model

INTRODUCTION

Cholesteatoma is a histopathologically benign but clinically aggressive and destructive tumor of the middle ear. Today, surgery is the known treatment of cholesteatoma (1). The surgical technique of choice is open or closed mastoidectomy depending on the location and extent of the cholesteatoma. Both surgical techniques pose a risk of morbidity. Moreover, a second surgery may be required with both techniques as residual and recurrent cholesteatoma may develop depending on the course of the disease (2). The residue and recurrence rates of cholesteatoma were shown to be greater in individuals treated with the closed approach compared to those treated with the open technique, particularly when performed by less skilled surgeons (3). To effectively combat the condition, a therapeutic approach that lowers the postoperative recurrence of cholesteatoma will be very helpful. Studies show that topical application of 5-fluorouracil (5-FU), a chemotherapeutic agent, is effective in the treatment of cholesteatoma (4, 5). In addition to disrupting DNA and RNA synthesis, 5-FU causes cell cycle arrest and apoptosis by increasing the expression of p53, a tumor suppressor gene. Considering the theories regarding cholesteatoma development, it can be understood that it is effective in the treatment of cholesteatoma (6). Recent studies have shown that the systemic absorption of topically applied 5-FU is <2%, with no evidence of any vestibular and cochlear damage in humans even with systemic use (7). Ototoxicity has been investigated by applying the cream form of 5-FU to the external auditory canal of guinea pigs, and it has been found that application to the external auditory canal is safe in terms of damage to the inner ear (8). However, there is no data on the toxicity of the intratympanic 5-FU solution form in

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the literature. It is crucial to understand whether or not 5-FU given intratympanically is ototoxic before using it to treat cholesteatomas both intraoperatively and postoperatively. The original value of the study is that it aimed to investigate the potential ototoxic effects of intratympanic administration of 5-FU solution form to the middle ear in rats.

MATERIALS AND METHODS

Rats

The approval for the study was obtained from the Ethics Committee for Animal Experimentation (Date: 21.05.2019, no: 77.637.435). In line with the Guide for the Care and Use of Laboratory Animals, animal rights were protected in our study. In this investigation, a total of 11 healthy male rats weighing between 300 and 400 grams (0.66 and 0.88 pounds) were employed. The rats were kept in cages in the same room, with 12 hours of light and 12 hours of darkness, and an average temperature of 21°C. They had access to food and water. Care was taken to keep the background noise level below 50 dB. The study was conducted in the Laboratory of Experimental Animals in accordance with the principles of Helsinki, and a histopathological examination was performed in the Laboratory of Histology and Embryology.

Anesthesia and Drug Administration

General anesthesia was provided with a mixture of 10 mg/kg xylazine HCl and 100 mg/kg ketamine HCl. The rats were first divided into 2 groups: 25 mg amikacin/rat (Amikacin sulfate, 500 mg/2 ml vial, Zentiva) was administered to 4 rats in the amikacin group as a positive control. In the 5-FU group, 5 mg 5-FU/rat (Fluorouracil, 1000mg/20 ml vial, Kocak) was administered to 7 rats. Both drugs were administered via intratympanic injection at a dose of 0.10 ml to the inferior quadrant of the right eardrum using a 27-gauge needle. The same anesthetic dose was intracardially injected into the amikacin and 5-FU groups one week after the drug administration, and then the rats were sacrificed, and their cochlea was dissected (Figure 1). The left cochleas of 3 rats in the 5-FU group, which was not given any drug, were included in the study as the third group (negative control).

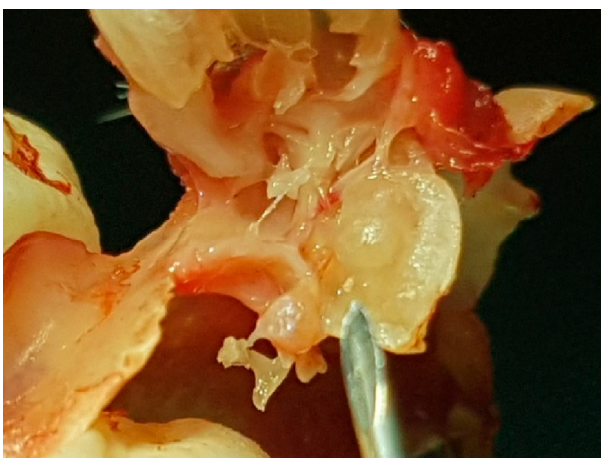

Figure 1: The rat cochlea

Histopathological Examination

Rat cochleas were fixed in a 10% formalin solution for 24 hours. After 2 weeks of decalcification in 0.1M EDTA (ethylene diamine tetra-acetic acid) solution, the tissues were rapidly dehydrated with a series of increasing concentrations of alcohol. The routine paraffin follow-up procedure was completed after the dehydrated tissues were embedded in paraffin and made transparent with xylene. From paraffin blocks, five micron-thick sections were sliced, deparaffinized, rehydrated, stained with H&S (Hematoxylin-Eosin), and examined using an Olympus BX-40 light microscope. TUNEL (Terminal deoxynucleotidyl transferase-mediated dUTP Nick End Labeling) staining was performed to determine apoptotic cell death.

With Hematoxylin-Eosin (H&S) staining, cochlear edema, cytoplasmic changes, stria vascularis thickness, and signs of inflammation as well as edema, cytoplasmic changes, lipid accumulation, vacuolization, signs of inflammation in the spiral limbus, and edema, nucleus pycnosis, increased acidophilia, satellite cell changes, and signs of inflammation in the spiral ganglion were evaluated and graded as 0- No histopathological change, 1-Minimal change, 2-Moderate change, 3-Severe change. Semi-quantitative histopathological examination was performed according to the number of degenerated cells; 0: No histopathological change, 1-5: Minimal change, 6-10: Moderate change, >10: Severe change. Apoptotic cells in the stria vascularis, spiral limbus, and spiral ganglion were counted and graded at 40x magnification as **0**: No apoptotic cells, **1**: 1-5 apoptotic cells, **2**: 6-10 apoptotic cells, and **3**: more than 10 apoptotic cells.

Statistical Analysis

Using power analysis, the sample size for each group was determined. The study used a minimum of 7 experimental animals due to a power of 80%, an effect size of d=1.40, and a significance level of 0.05. IBM SPSS Statistics v15.0 software was used for statistical analysis. Since the number of experimental animals was <30 in the study, nonparametric tests were used. The Chi-square test was used for the comparison of categorical data, and Fisher's exact test was applied when the frequency determined in the 4-cell evaluation was <5. Kruskal wallis test and Mann-Whitney U test were used for intergroup evaluation of stria vascularis thickness. Bonferroni corrections were performed for multiple comparisons. The significance level was established as α=0.05.

RESULTS

Evaluation of histological changes: The spiral ganglion and spiral limbus were the most severely affected structures, and the overall cochlear structure was impaired in the Amikacin group, according to the analysis of H&S-stained preparations. There was no significant difference between the 5-FU group and the amikacin group in terms of edema and cytoplasmic changes in the stria vascularis ($p>0.05$), and no statistical evaluation was made since no inflammation was observed in both group (Table 1). Stria vascularis thickness (µm) was compared in pairs between the amikacin group, the 5-FU group, and the negative control group; the 5-FU group (median 17.30; min-max 15.03-

21.57) had a lower stria vascularis thickness than the amikacin group (median 22.56; min-max 18.85-26.04) and a higher stria vascularis thickness than the negative control group (median 13.31; min-max 12.83-13.70), with a statistically significant difference between the groups ($p<0.05$) (Table 1).

The difference in lipid accumulation and vacuolization seen in the spiral limbus between the 5-FU group and the amikacin group was not statistically significant ($p>0.05$), according to the semi-quantitative histopathological grading presented in Table.1. While spiral limbus edema was minimal in the 5-FU group, it was minimal (25%) and moderate (75%) in the amikacin group. The 5-FU group had minimal cytoplasmic changes (86%) and no change (14%), while the entire amikacin group had moderate changes. While no spiral limbus inflammation was observed in the entire 5-FU group, the amikacin group had moderate (50%), minimal (25%) spiral limbus inflammation, and no change (25%), with statistically less spiral limbus inflammation in the 5-FU group ($p<0.05$).

Spiral ganglion edema was minimal (57%) and moderate (43%) in the 5-FU group, while it was moderate (50%) and severe (50%) in the amikacin group, with statistically less spiral ganglion edema in the 5-FU group ($p<0.05$). There was no statistically significant difference between the 5-FU and amikacin groups in terms of nucleus pycnosis and acidophilia increases in the spiral ganglion ($p>0.05$) (Tablo.1). Satellite changes in the spiral ganglion were moderate (25%) and severe (75%) in the amikacin group, while no change was observed in the 5-FU group ($p<0.05$). While the signs of spiral ganglion inflammation were minimal (75%) and moderate (25%) in the amikacin group, no sign of spiral ganglion inflammation was noted in the 5-FU group ($p<0.05$) (Figure 2,3,4).

Evaluation of apoptotic cells: The comparison of the amikacin group with the 5-FU group showed a lower number of apoptotic cells in the stria vascularis, spiral limbus, and spiral ganglion in the 5-FU group, with a statistically significant difference ($p<0.05$) (Figure 5). In addition, there was no statistically significant difference in the apoptosis grading of the stria vascularis, spiral limbus, and spiral ganglion in the 5-FU group compared to the negative control group ($p>0.05$) (Table 2).

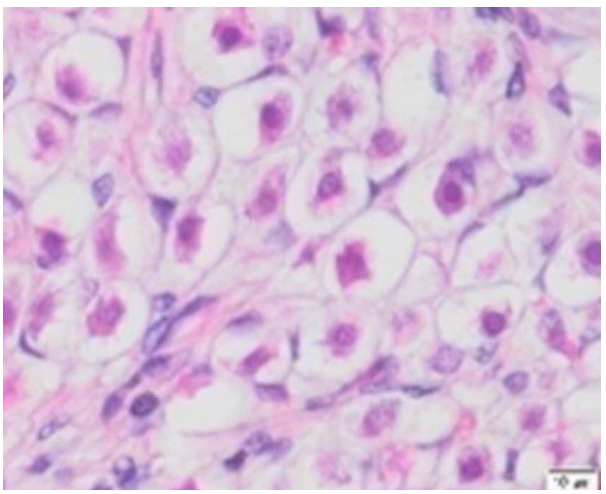

Figure 2: Hematoxylin-Eosinstaining (x400, bar= 10 µm). Spiral ganglion-The 5-FU group

Table 1: Grading of histopathological changes in the groups

		The Amikacin group				The 5-Fluorouracil group						The Negative group			
	Rat no:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**3**
Stria vaskularis	Edema	2	1	3	0	0	1	1	0	2	1	1	1	0	0
	Cytoplasmic Changes	2	1	3	0	0	0	0	0	0	0	0	1	0	0
	Signs of inflammation	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Thickness (µm)	21.20	18.85	26.04	23.93	16.12	17.30	1623	15.03	21.57	19.02	20.23	13.31	13.70	12.83
Spiral limbus	Edema	2	2	2	1	1	1	1	1	1	1	1	0	0	0
	Cytoplasmic changes	2	2	2	2	1	0	1	1	1	1	1	0	0	0
	Lipid accumulation	0	1	0	0	1	0	1	1	0	0	0	0	0	0
	Vacuolization	2	1	0	0	0	0	0	0	0	0	0	0	0	0
	Signs of inflammation	0	2	1	2	0	0	0	0	0	0	0	0	0	0
Spiral ganglion	Edema	2	2	3	3	1	2	1	1	1	2	2	0	1	0
	Nucleus pycnosis	1	0	0	2	1	1	0	1	0	1	1	0	1	0
	Increased Acidophili	3	1	1	3	0	2	1	1	1	1	1	0	1	0
	Satellite cell changes	2	3	3	3	0	0	0	0	0	0	0	0	1	0
	Signs of inflammation	1	2	1	1	0	0	0	0	0	0	0	0	0	0

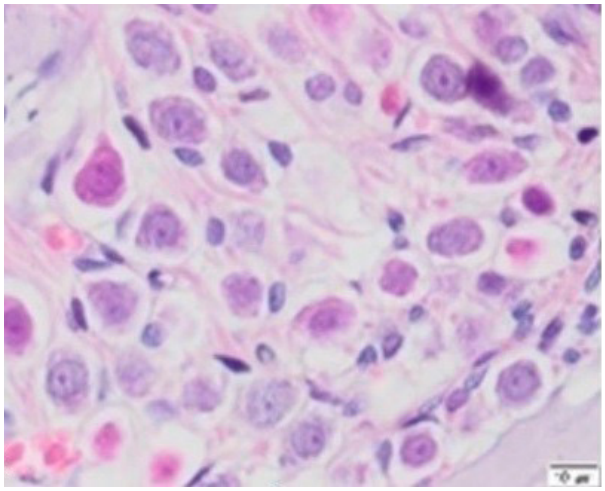

Figure 3: Hematoxylin-Eosinstaining (x400, bar= 10 µm). Spiral ganglion – The Negatif group

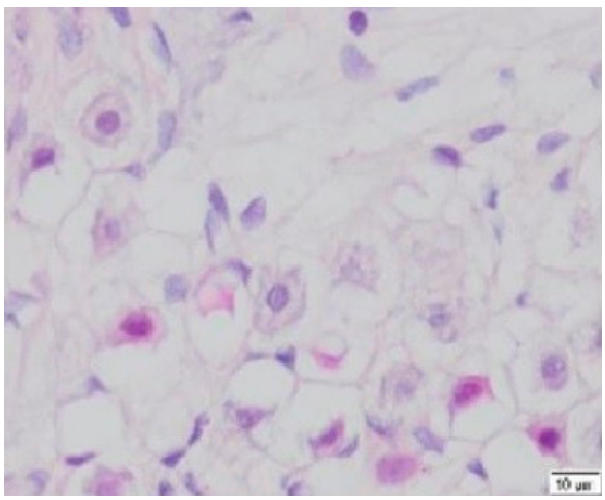

Figure 4: Hematoxylin-Eosinstaining (x400, bar= 10 µm). Spiral ganglion – The Amikasin group

(In amikacin group compared to the other two groups, there is an increase in pycnosis and edema in the nucleus and a deterioration in satellite cell distribution around the ganglion cell.)

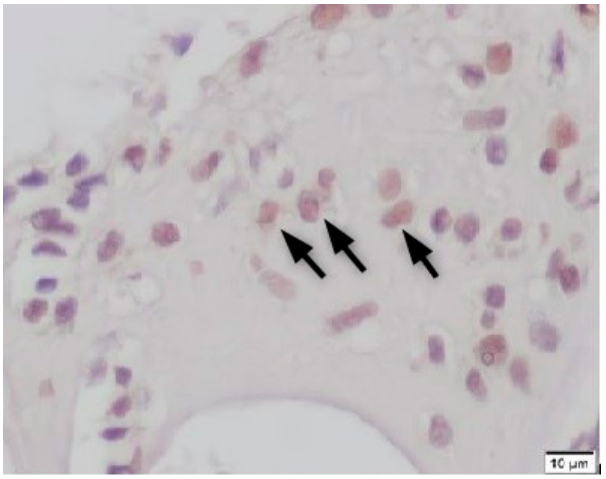

Figure 5: TUNEL method (bar= 10 µm). Spiral limbus – The Amikasin group

(Black arrows -TUNEL positiveBrown apoptotic cells with nucleus pushed aside)

DISCUSSION

Our study demonstrated no ototoxic effect of intratympanic administration in 5-FU to rats in the histopathological examination performed by evaluating apoptosis. While there is no universally accepted medical treatment for cholesteatoma, surgery is the known treatment. Studies on both humans and animals have demonstrated the effectiveness of topical 5-FU in the management of cholesteatoma (4, 8, 9). Considering that residual and recurrent cholesteatoma may develop depending on the surgical technique, the location and extent of the cholesteatoma, and the surgeon's experience, we think that intratympanic 5-FU may be a complementary treatment (2).

Our study aimed to investigate the middle ear, where cholesteatoma is most common. The intratympanic technique, which is currently used for the treatment of many diseases and is very practical and applicable, was chosen to access the middle ear. Ototoxicity was considered to be a limiting factor for intratympanic 5-FU administration. Therefore, rat cochlea

Table 2: Distribution of apoptosis in the groups

	Apoptotic cell number	The Amikacin group (n=4)	The 5-Fluorouracil group (n=7)	The Negative group (n=3)
Stria Vascularis p=0.009	**0**	-	1 (14.3%)	2 (66.7%)
	1-5	1 (25%)	6 (85.7%)	1 (33.3%)
	6-10	3 (75%)	-	-
	>10	-	-	-
Spiral Limbus P=0.020	**0**	-	-	1 (33.3%)
	1-5	-	4 (57.1%)	2 (66.7%)
	6-10	1 (25%)	3 (42.9%)	-
	>10	3 (75%)	-	-
Spiral Ganglion P=0.004	**0**	-	-	-
	1-5	-	2 (28.6%)	3 (100%)
	6-10	-	4 (57.1%)	-
	>10	4 (100%)	1 (14.3%)	-

was examined to investigate drug ototoxicity, considering intratympanic pharmacokinetics (10). 5-FU is a water-soluble chemotherapeutic agent. We believe that this feature may affect both its passage through the round window as well as its absorption by the middle ear mucosa and its residence time in the tissue. Additionally, the drug's molecular weight may have an impact on ototoxicity. Studies have shown that one of the excipients in the cream form of 5-FU, propylene glycol, lowers the endocochlear potential and induces ototoxicity. However, it is unclear whether the ototoxicity brought on by the cream form is caused by an increase in molecular weight or by propylene glycol (11, 12).

In their study on guinea pigs, Iwanaga et al. applied the cream form of 5-FU only to the external auditory canal of the first group and to the external auditory canal and the middle ear of the second group with myringotomy (5). They did not find any change in the stria vascularis thickness by light microscopy in both groups, concluding that 5-FU did not cause degeneration in the inner ear. The results of our study showed that stria vascular thickness was higher in the 5-FU group than in the negative control group and lower than in the amikacin group ($p<0.05$). However, considering apoptosis, 5-FU was similarly found to not cause degeneration in the inner ear. Iwanaga et al. connected the study's findings that the cream form of the drug might result in ototoxicity by increasing molecular weight to the group receiving drugs with myringotomy's poor electrophysiological measurements (5).

Chemotherapeutic agents usually cause ototoxicity via apoptosis (13). Examination by the TUNEL method gives an idea about apoptotic cell detection and ototoxicity. Electrophysiological tests could not be used in our study due to technical deficiencies. However, we think that more comprehensive results can be obtained by supporting histopathological findings with electrophysiological tests (7). In addition, we think that it would be useful to examine ototoxicity biochemically (14).

In our study, 5-FU was administered at a dose of 7.5-10 mg/rat, considering the maximum bulla volume of the rat. In intratympanic administration of 5-FU, it can be thought that middle ear volume limits the maximum administrable dose of the drug. However, we believe that 5-FU, which is known to have no ototoxic effect even in systemic administration, can be administered via intratympanic injection at repeated doses to increase its efficacy.

In ototoxicity, symptoms may arise immediately after drug administration or may develop within days or weeks (15). In our study, ototoxicity was assessed one week following 5-FU and amikacin administration. We think that prolonging the research duration and giving the medicine in multiple doses will lead to more accurate results for ototoxicity. Considering the side effects of 5-FU, the most serious complication observed with the cream form is chronic ulceration of the skin. Smith reported chronic ulceration in humans with the application of topical 5-FU cream to patients undergoing open surgery (4). There is no information on whether the 5-FU solution form causes pain or ulceration in the middle ear mucosa after intratympanic administration.

The histopathological examination performed by evaluating apoptosis revealed no ototoxic effect of the intratympanic administration of 5-fluorouracil in rats. The current findings imply that topical 5-FU application may be preferred as an adjunct to surgical treatment for early-stage cholesteatomas to prevent residual and recurrent cholesteatomas or to stop the progression of cholesteatoma in patients who cannot undergo the procedure because of underlying diseases. However, there is a need for controlled randomized studies supported by the electrophysiological technique to examine the efficacy of intratympanic 5-FU in both experimentally induced cholesteatoma and cholesteatoma patients.

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Ethics Committee Approval: This study was approved by the Laboratory Animals Local Ethics Committee of Manisa Celal Bayar University (Date: 21.05.2022, No: 77.637.435).

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REFERENCES

1. Olszewska E, Chodynicki S, Chyczewski L. Apoptosis in the pathogenesis of cholesteatoma in adults. Eur Arch Otorhinolaryngol 2006; 263:409-13.
2. Sheehy JL, Brackmann DE, Graham MD. Cholesteatoma Surgery: Residual and Recurrent Disease. Ann Otol Rhinol Laryngol 1977;86(4):451-62
3. Tomlin J, Chang D, McCutcheon B, and Harris J. Surgical technique and recurrence in cholesteatoma: a meta-analysis. Audiol Neurotol 2013;18(3):135-42.
4. Smith MF. The topikal use of 5-fluorouracil in the ear in the management of cholesteatoma and excessive mucous secretion. Laryngoscope 1985;95(10):1202-3.
5. Iwanaga T, Tanaka F, Tsukasaki N, Terakado M, Kaieda S, Takasaki K, et al. Does topical application of 5-fluorouracil ointment influence inner ear function? Otolaryngol Head Neck Surg 2006:134;961-5.
6. Ceilley RI. Mechanisms of action of topical 5-fluorouracil: Review and implications for the treatment of dermatological disorders. J Dermatolog Treat 2010;23(2):83-9.

7. Erlanger M, Martz G, Ott F, Storck H, Rieder J, Kessler S. Cutaneous absorption and urinary excretion of 5-fluorouracil ointment applicated in an ointment to healthy and diseased human skin. Dermatologica 1970;140 (suppl I):7-14.
8. Takahashi H, Funabiki K, Hasebe S, Yamamoto TF, Kaieda S, Iwanaga T, et al. Clinical efficacy of 5-fluorouracil (5-FU) topical cream for treatment of cholesteatoma. Auris Nasus Larynx 2005:32(4);353-7.
9. Sala DT. Topical applications of 5-fluorouracil in the medical treatment of cholesteatoma of the middle ear. Ear Nose Throat J 1994;73(6):412-4.
10. Salt AN, Plontke SK. Principles of local drug delivery to the inner ear. Audiol Neurootol 2009;14:350-60.
11. Morizono T, Paparella MM, Juhn SK. Ototoxicity of propylene glycol in experimental animals. Am J Otolaryngol 1980;1(5):393-9.
12. Wright CG, Bird LL, Meyerhoff WL. Effect of 5-fluorouracil in cholesteatoma development in an animal model. Am J Otolaryngol 1991;12(3):133-8.
13. Elmore S. Apoptosis: A Review of Programmed Cell Death. Toxicol Pathol 2007;35(4):495-516.
14. Salcan İ, Dilber M, Bayram R, Süleyman E, Yazıcı GN, Çoban A, Süleyman H. Effect of Rutin on Gentamicin-Induced Ototoxicity in Rats: A Biochemical and Histopathological Examination. ENT-Updates 2021;11(1):8-13.
15. Ganesan P, Schmiedge J, Manchaiah V, Swapna S, Dhandayutham S, Kothandaraman P P. Ototoxicity: A Challenge in Diagnosis and Treatment. J Audiol Otol 2018;22(2):59-68.

RESEARCH ARTICLE
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Comparison of Video Head Impulse Test Results of Pediatric Patients with Dizziness with Healthy Volunteers

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ABSTRACT

Objective: The Video Head Impulse Test (V-HIT) is a non-invasive diagnostic test that evaluates the functions of the semicircular canals separately. This test records eye movements in response to head movements, and the vestibulo-ocular reflex gain (VOR-G) is calculated. V-HIT is frequently used in diagnosing adult patients and has been increasingly used in children in recent years. Indeed, V-HIT measurements may be useful in the diagnosis, especially in pediatric patients where vestibular pathologies are difficult to evaluate. In this study, V-HIT findings of pediatric patients with dizziness were examined, and the results were compared with healthy volunteers.
Methods: Thirteen pediatric patients who applied to our clinic with dizziness and nine healthy children were included in the study. The necessary evaluations and radiological imaging were performed, and children diagnosed with any pathology were excluded. Each patient underwent GN Otometrics ICS Impulse V-HIT examination, and the results were recorded. The Video Head Impulse Test (v-HIT) results of children with vertigo were compared with those of healthy volunteers and analyzed.
Results: The mean age of the patients included in the study was 10.5±3.5 years (range: 5-16). Five of these children were boys, and 8 were girls. In the control group, there were five girls and four boys, and their mean age was 9.3±3.9 years (range: 5-16). None of the children had any additional disease. When the groups were compared, the left anterior canal and left lateral canal VOR-Gs were significantly different between the patients and healthy volunteers (p=0.027 and p=0.007, respectively). No statistically significant difference was observed between the groups in terms of the right anterior canal, right lateral canal, left posterior canal, and right posterior canal VOR-G measurements (p=0.928, p=0.738, p=0.588, and p=0.780,).
Conclusion: V-HIT, a non-invasive method for evaluating the etiology of vertigo in children, can be easily applied even in very young children. The use of glasses suitable for children will facilitate the procedure.

Keywords: Video head impulse test, Video Head Impulse Test, dizziness in children, vertigo

INTRODUCTION

Childhood dizziness has a prevalence of 8% to 15%, and its etiology is usually different from that in adults. It is not easy for a child to describe dizziness, and physical examination is also challenging in children. Therefore, it is more challenging to diagnose pediatric cases than adults, and vestibular tests come to the fore in evaluating vertigo and dizziness in this patient group (1).

The main vestibular tests used for the evaluation of children are video electronystagmography (VENG), cervical vestibular-evoked myogenic potential (cVEMP), ocular vestibular-evoked myogenic potential (oVEMP), caloric test, rotatory chair, and video head impulse test (V-HIT), the use of which has increased in recent years (2).

V-HIT is a relatively new technique used in the diagnosis of dizziness. This technique can measure the functions of six semicircular canals (SCC) separately (3). Eye movements in

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response to head movement are recorded by a camera installed on eyeglasses that can record high-speed motion. This is called vestibulocular reflex gain (VOR-G) (3, 4).

Compared to VENG, cVEMP, oVEMP, and caloric test used in diagnosing dizziness, V-HIT, which is simpler to apply in children, provides information about all SSCs, unlike the former that mainly give information about lateral SCC. Since V-HIT is a non-invasive test, its applicability is higher in the pediatric age group (5).

Children put on glasses with a camera placed on the right side and are asked to look at a fixed point. During this procedure, VOR-G is recorded while head movements are made by following a sequence. The V-HIT test is frequently used in adults, and many studies have been conducted on normal V-HIT values in this patient group. However, studies on the pediatric patient population are lacking (5-8).

In this study, we aimed to evaluate the applicability of the V-HIT test in the pediatric patient group and V-HIT findings in pediatric patients with dizziness.

MATERIALS AND METHODS

This study was conducted on both healthy volunteers and patients who applied to the Otolaryngology Clinic of a private tertiary care hospital for dizziness between 2019 and 2022.

Ethical Board Approval

This study was approved by Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee (ATADEK) (Date: 25.03.2022, No: 2022-06/11).

Study Design and Participants

In this study, two groups of pediatric populations were evaluated with V-HIT. Medical records of pediatric patients with dizziness were reviewed retrospectively, and healthy volunteer children with parental consent were invited to the study for the V-HIT test as the control group.

The patients included in the study were evaluated with the diagnostic criteria of chronic idiopathic dizziness. Patients with normal neurological and ENT examinations in addition to a non-vertiginous imbalance condition were evaluated to see if they met the criteria. Patients were included in the study if 3 of the following 5 conditions were present: dizziness with the feeling of swaying; light-headedness; subjective unsteadiness during standing and/or walking; something wrong in the head; a feeling of a disturbance of balance. As a time criterion, patients whose dizziness had been present at least 8 days per month for the previous 3 months were included.

The children with dizziness underwent routine otolaryngology and head and neck examinations, and audiological evaluations were also conducted. These children were also evaluated by a pediatric neurologist, and contrast-enhanced inner ear and cranial MRIs were taken. Neurological and vestibular examinations of the children in the patient group were normal. Children detected with hearing loss in pure tone audiometry and children with any pathology detected in cranial and ear MRI were excluded from the study. Nine children in the control group had no symptoms, and their vestibular examinations were normal. V-HIT was applied to all children, and the results were recorded.

Sixteen pediatric patients were evaluated for inclusion in the study. One patient was excluded from the study because of labyrinth inflammation in the MR imaging, and two patients were excluded because they could not comply with the test. After those patients were excluded, the study continued with 22 participants, including 13 children who were evaluated retrospectively in the patient group and 9 children in the control group.

Statistical Anylasis

SPSS 24.0 was used for statistical analysis. The “Shapiro-Wilk test” was used for the distribution and normality of the data, and the “Independent Samples t Test” was used to compare the VOR-G mean values of both groups, and the significance level was determined as $p<0.05$.

Video Head Impulse Test

Tests were performed in a well-lit test room using the V-HIT Otometrics ICS Impulse (A/S Taastrup, Denmark) instrument. Before the test, participants and parents were informed. First, the subject was asked to keep their head still, and calibration was performed with the help of laser lights displayed around an object placed 1m away. Then, the participant was asked to follow a sinusoidally moving target with head movements, and thus the calibration control was performed. Following the completion of the calibration, the subject was asked to lock their gaze on a target object and to keep it fixed on the object even if the operator moved the subject’s head. All tests were conducted by a single operator. During the test, the operator made random movements of the patient’s head 10-20 degrees in all three planes. To test the vertical channels, the subject’s head was made to move 30 degrees to the right or the left. The same settings were used for each test (8). The device processes all the data and outputs the information separately for each SSC as a graphic output (Figure 1).

RESULTS

Of the 22 children included in the study, 13 were girls, and 9 were boys. The mean age of the children included in the study was 10±3.6 years. In the patient group, 5 of the children were boys, 8 of them were girls, and their mean age was 10.4±3.5 years. The mean age of the children in the control group was 9.3±3.9 years, and 4 of the children in this group were boys, and 5 were girls. None of the children had any additional disease (Table 1). The mean VOR-G values in the patient group were as follows: left anterior canal mean VOR-G value: 0.75±0.07 (0.64-0.92); right anterior canal mean VOR-G value: 0.85±0.15 (0.65-1.12); left lateral canal mean VOR-G value: 0.77±0.09 (0.56-0.88); right lateral canal mean VOR-G value; 0.96±0.14 (0.75-1.34); left posterior canal mean VOR-G value: 0.86±0.16

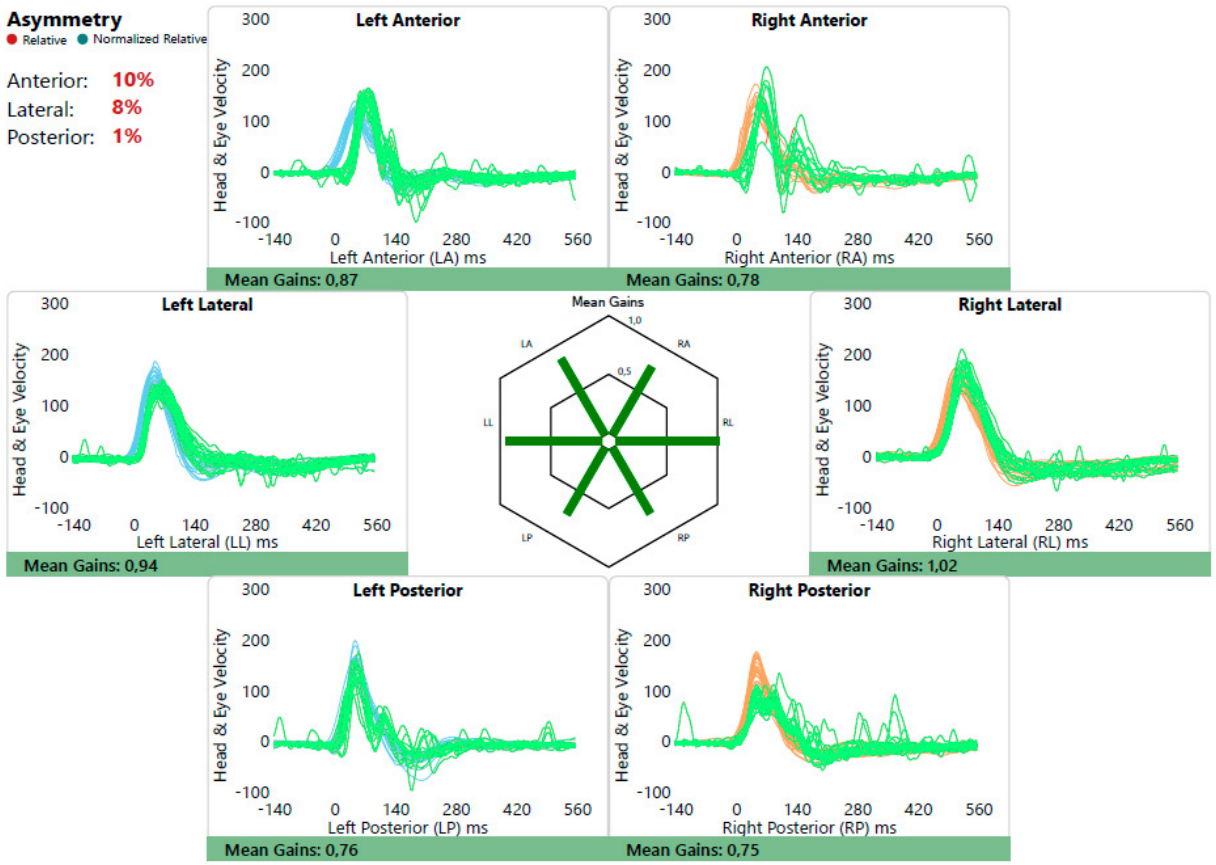

Figure 1: Graphical representation of the vestibulocular reflex gains of the six semicircular canals.

Table 1: Demographic informations

		Study group	Control group	Both
Age		10.5±3.5 (5-16)	9.3±3.9 (5-16)	10±3.6 (5-16)
Gender	**Male**	5	4	9
	Female	8	5	13
Number		13	9	22

(0.65-1.13); right posterior canal mean VOR-G value: 0.85±0.16 (0.7-1.24). Similarly, the VOR-G values obtained from the children in the control group were as follows: mean VOR-G of the left anterior canal: 0.84±0.11 (0.68-1); mean VOR-G of the right anterior canal: 0.84±0.13 (0.68-1.1); mean VOR-G of the left lateral canal: 0.89±0.1 (0.69-0.98); mean VOR-G of the right lateral canal: 0.94±0.17 (0.79-1.22); left posterior canal mean VOR-G: 0.90±0.18 (0.76-1.3); mean VOR-G of the right posterior canal: 0.86±0.15 (0.69-1.2). Left anterior canal and left lateral canal VOR-G values were significantly different between the groups (p=0.027 and p=0.007). No statistically significant difference was observed between the groups in terms of the mean VOR-G values of the right anterior canal, right lateral canal, left posterior canal, and right posterior canal (p=0.928, p=0.738, p=0.588, and p=0.780) (Table 2).

DISCUSSION

A number of standards have been defined as a result of V-HIT studies performed on healthy adult subjects (6, 7). However, the use of V-HIT in children with vertigo is relatively new, and

Table 2: Comparison of channel functions in the two groups

			Anterior		Lateral		Posterior	
Age	**n**		**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
5-16	13	Study	0.75 (0.64–0.92)	0.85 (0.65–1.12)	0.77 (0.56–0.88)	0.96 (0.75–1.34)	0.86 (0.65–1.13)	0.85 (0.7–1.24)
5-16	9	Control	0.84 (0.68-1)	0.84 (0.68-1.1)	0.89 (0.69-0.98)	0.94 (0.79-1.22)	0.90 (0.76-1.3)	0.86 (0.69-1.2)
		p	*0.027*	0.928	*0.007*	0.738	0.588	0.780

one of the biggest concerns is the standardization of results. Studies have been conducted in recent years that help provide reliable information on the normal values of V-HIT in children (5, 8). Emekci et al. examined 100 adolescents aged 11-18 and did not find any significant age-related changes in VOR-G (8). In the study conducted by McGarvie et al., which also included children, it was shown that the normal values of VOR-G do not significantly change with age (6). However, in the study conducted by Bachmann et al., in which the adult and pediatric populations (<10 years) were compared, no age-related difference was observed within the pediatric population, but a significant difference was found between adult and pediatric subjects in terms of VOR-G values. Especially in the lateral canal VOR-G values, higher thresholds were found in children compared to adults. However, in all subjects, the VOR-G values of the right lateral canal were higher than those of the left side. The authors suggested this might be because the camera recorded the right eye during the test. In the same study, it was recommended to use lower thresholds for right anterior, left posterior plan (RALP) and left anterior, right posterior plan (LARP) VOR-G values in children compared to adults, in that the VOR-G values of these channels in children were found to be quite variable. This study was conducted on normal children under ten years of age and yielded valuable results; however, the small number of subjects included constitutes a limitation (5). In our study, V-HIT evaluation was performed in normal children without any complaints, as well as in children with vertigo. The small subject size, the broad age range, and unequal age distribution made the interpretation of the test results somewhat difficult.

In our study, when a total of 6 semicircular canals were evaluated, it was observed that the left anterior and left lateral canal gains were statistically lower in the pediatric dizziness group. Other channel gain averages were not significantly different between the patient and control groups. A possible reason for this could be that the cause of dizziness in this limited patient group might be due to a disease which does not affect some canal gains.

In many previous studies in the literature, while investigating the relationship between patient age and VOR-G, the subjects were divided into defined age ranges, and the differences between these groups were compared (5, 6, 8). In our study, however, it was impossible to place subjects into age categories due to the small number of patients and the non-homogeneous distribution of their ages.

Another concern with V-HIT is its test-retest reliability. In our study, the test was administered to each patient once, and the results were analyzed afterward. Singh et al. reported that the test-retest reliability of VOR-G and refixation saccades evaluated with V-HIT in both healthy individuals and individuals with vestibulopathy is high. These researchers demonstrated that both measurements were highly reliable and repeatable between the sessions, with the exception of vertical canal refixation saccades in some individuals and measurements in the affected ear in patients with vestibulopathy. In the study conducted by Singh et al., it was stated that inconsistent VOR-G results obtained between repeated measurements in individuals with vestibulopathy might be due to variable channel functions rather than inconsistency in repeated measurements (9). Mahfuz et al. reported no significant changes in VOR-Gs between repeated test applications (10). Therefore, the absence of repeated testing does not appear to be a significant limitation. However, it should be noted that variable values may be obtained between retests, and this may be due to changes in channel functions.

The advantages of the test are that it is both non-invasive and easy for the patient to cooperate with. It can also provide objective information about the semicircular canals. In this respect, it has significant advantages over the caloric test and the rotary chair (11). Khater et al. found that 84% of the children who were examined for dizziness and who had a normal caloric test result showed abnormal V-HIT findings, 13% of whom had lateral canal abnormality. Detection of abnormalities in one or both lateral canals despite normal caloric test results in 13% of children indicates that V-HIT is more sensitive than caloric testing in demonstrating lateral canal function. In addition, V-HIT stands out as an important and superior alternative to caloric test in children who cannot undergo this test due to external or middle ear pathologies and in children who cannot cooperate with the test (12). The youngest of the children in our study was five years old, and the oldest was 16 years old. None of the children had difficulties during the test. There are, however, some disadvantages of this test, such as device dependency, operator requirement, long testing times in some children, and the absence of specially-designed glasses for pediatric patients. The application can be complicated, especially in children with a small head and face, thin and slippery hair, and large pupils (5). Glasses can easily be fixed on the children's heads with simple bandages. However, the use of glasses designed for children will undoubtedly increase the applicability of the test.

CONCLUSIONS

Since it is challenging to evaluate dizziness in pediatric patients, V-HIT may be helpful in cases of clinical necessity. The non-invasiveness of the test is a significant advantage. Although it may be difficult for young children to comply with the test, it is generally well-tolerated. Hardware improvements, such as special eyeglasses designed for children, and increased experience can make the test more feasible.

Ethics Committee Approval: This study was approved by Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee (ATADEK) (Date: 25.03.2022, No: 2022-06/11).

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REFERENCES

1. Niemensivu R, Pyykkö I, Wiener-Vacher SR, Kentala E. Vertigo and balance problems in children—an epidemiologic study in Finland. Int J Pediatr Otorhinolaryngol 2006;70(2):259-65.
2. Jahn K, Langhagen T, Heinen F. Vertigo and dizziness in children. Curr Opin Neurol 2015;28(1):78-82.
3. Michael Halmagyi G, Weber KP, Aw ST, Todd MJ, Curthoys IS. Impulsive testing of semicircular canal function. Neuropathies Audit Vestib eighth cranial nerves 2009;93-109.
4. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys I. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. Neurology 2009;73(14):1134-41.
5. Bachmann K, Sipos K, Lavender V, Hunter LL. Video head impulse testing in a pediatric population: normative findings. J Am Acad Audiol 2018;29(05):417-26.
6. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function–age-dependent normative values of VOR gain in healthy subjects. Front Neurol 2015;6:154.
7. Zou SZ, Li JR, Liu Y, Ding YL, Wang YQ. Preliminary study on age stability of VOR gain values of video head impulse test in healthy subjects. Lin chuang er bi yan hou tou jing wai ke za zhi= J Clin Otorhinolaryngol head, neck Surg 2019;33(5):393-7.
8. Emekci T, Uğur KŞ, Cengiz DU, Men Kılınç F. Normative values for semicircular canal function with the video head impulse test (vHIT) in healthy adolescents. Acta Otolaryngo 2021;141(2):141-6.
9. Singh NK, Govindaswamy R, Jagadish N. Test–retest reliability of video head impulse test in healthy individuals and individuals with dizziness. J Am Acad Audiol 2019;30(09):744-52.
10. Mahfuz MM, Millar JL, Schubert MC. Repeated video head impulse testing in patients is a stable measure of the passive vestibulo-ocular reflex. J Otol 2021;16(3):128-37.
11. Hamilton SS, Zhou G, Brodsky JR. Video head impulse testing (VHIT) in the pediatric population. Int J Pediatr Otorhinolaryngol 2015;79(8):1283-7.
12. Khater AM, Afifi PO. Video head-impulse test (vHIT) in dizzy children with normal caloric responses. Int J Pediatr Otorhinolaryngol 2016;87:172-7.

CASE REPORT
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An Unusual Variation of the Accessory Nerve

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ABSTRACT

In this manuscript, we report an anatomic variation of the spinal accessory nerve for the first time in the literature. The spinal accessory nerve was exited from the skull base in duplicate, and these two branches merged in the anterior triangle of the neck and continued as a common branch in a 68-year-old male patient who underwent total laryngectomy and bilateral modified neck dissection.

Keywords: Anatomy, anatomic variations, cranial nerves, spinal accessory nerve

INTRODUCTION

The spinal accessory nerve (CN 11), with its intracranial and extracranial branches, forms the CN 11 plexus together with other cranial, cervical, and sympathetic nerves. Functionally, it provides the union of the autonomic, motor, and sensory nerves of the mouth, palate, pharynx, and larynx for effective functioning of swallowing, phonation, and respiration (1). This plexus has high individual flexibility. Variable connections between intracranial and extracranial nerve roots and nerves make the neural composition of the plexus very different amongst individuals (2).

The most common cause of CN 11 damage is surgical procedures in the head and neck region. It may occur especially after lymphadenectomies are performed in the posterior cervical triangle, neck dissection, or tumor excision (3). Therefore, knowing the morphology and topography of cervical nerve structures and variations will positively result in head and neck surgeries. This case report describes a branching variant of CN 11 that has not been reported in the literature before.

CASE REPORT

A 68-year-old male patient underwent total laryngectomy and bilateral modified neck dissection due to advanced-stage laryngeal squamous cell carcinoma (T3N2bM0). The 11th CN was found in its standard anatomical location on the left side of the neck. However, it was observed that the nerve exited from the skull base in duplicate and that these two branches merged in the anterior triangle of the neck and continued as a common branch (Figure 1). Stimulating both nerve branches with a Medtronic NIM 3.0 Nerve Monitor nerve stimulator with 0.5 mA caused a contraction in both SCM and trapezius muscles. We preserved both of the nerve branches. There was no variation in the CN 11 and other anatomical structures in the right neck of the patient. We did not observe any complications in the early and late postoperative periods. The patient gave informed consent for the publication of this case report.

DISCUSSION

The accessory nerve has motor fibers consisting of spinal and cranial roots. The spinal root consists of C1 and C5 cervical segments and enters the skull base with the foramen magnum and joins with the cranial roots. The nerve descends inside the skull to the jugular foramen and exits the jugular foramen together with the vagus nerve and the glossopharyngeal nerve (4-7). It is the only nerve among the cranial nerves that receives some of its branches from the spinal cord. CN 11 trunk passes through the jugular foramen into the neck. Then it lies between

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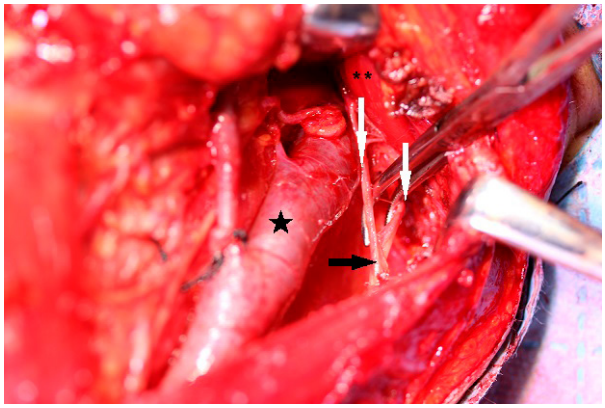

Figure 1: Intraoperative photograph taken during left selective neck dissection, showing the accessory nerve double exiting from the skull base and merging into a single branch. The sternocleidomastoideus muscle was retracted laterally. (The white arrow indicates the separate branches of the duplicated accessory nerve, the black arrow indicates the joining accessory branch, the star indicates internal jugular vein, and double little star indicates posterior belly of digastric muscle)

the internal jugular vein (IJV) and the internal carotid artery. It crosses the IJV at the posterior part of the digastric muscle. The common trunk enters the retrostyloid space (8). CN 11 descends forward and past the IJV laterally, although there are some variations. Then CN 11 generally traverses the transverse process of the atlas anteriorly. Occasionally, it lies medial or lateral to the transverse process of the atlas. It then descends medially to the styloid process and passes the digastric muscles and stylohyoid (6). Then it descends inferiorly to give motor branches to the SCM muscle. The SCM branch extends over the occipital artery and enters the inside of the upper part of the SCM muscle. Once inside the muscle, it connects with fibers from C2 only or C3 only, or both C2 and C3 (9). After that, it enters the posterior triangle inferior to the intersection of the upper and middle third of the sternocleidomastoid muscle, shows a posterior-inferior course, and disappears at the level of the upper part of the trapezius muscle (2, 9).

Anatomical variations of the CN 11 have been reported in the literature. The anterior and posterior rootlets of the first five cervical nerves contribute to the spinal portion of it. Four different patterns have been defined with the intradural connection of the CN 11 and first spinal rootlets. For the type 1 variant, the posterior root of C1 is absent, and CN 11 connects with the anterior root of C1. In the type 2 variant, there is no connection between the CN 11 and the roots of C1. In the type 3 variant, CN 11 connects at the junction of the rootlets of C1 or the anastomotic branch of C1 to the posterior rootlet. Finally, in the type 4 variant, it connects the CN 11 with the C1 root, which does not have a spinal cord connection (10, 11).

In a cadaveric study, it was observed that in 87% of the cases, the CN 11 starts from the anteromedial of the IJV within the jugular foramen. In neck dissections, it was observed that 67% of the nerve was lateral to the IJV after exiting the foramen jugulare (4). In another study, it was observed that the CN 11 crossed the IJV anteriorly (7).

The differences in the course of the CN 11 in the posterior cervical triangle and the differences in the number of branches ending in the trapezius are among the most common variations seen in the literature (5-7). Apart from this, Overland showed that the CN 11 passes inside the IJV (6). In another study, it was shown that by connecting the CN 11 and the facial nerve, both nerves provide the innervation of the SCM muscle. In the same study, it was shown that the CN 11 made intracranial duplication for the first time (7).

In our case, when the SCM was retracted laterally in the second region during neck dissection, it was observed that the CN 11, which was detected in its standard anatomical location, split into two branches before exiting from the skull base. We confirmed the nerve by using the nerve simulator with 0.5 mA as it is in the literature (12). With the stimulation of both nerve branches, muscle activation was observed in both the SCM and the trapezius muscle. The fact that the nerve converges distally before entering the SCM makes our case different from the first duplication described by Tubbs et al. (7). The variation described with this feature is the first in the literature.

CN 11 is one of the essential structures of the head and neck. It is vital for the surgeon to know the anatomy of the CN 11, as iatrogenic injuries to the nerve will significantly impair the patient's quality of life. So, care should be taken when working around the nerve, bearing in mind that variations can occur.

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- N.İ., A.K.; Data Acquisition- N.İ., A.K.; Data Analysis/Interpretation- N.İ., A.K., E.M.G.; Drafting Manuscript- N.İ., B.G.Ş.; Critical Revision of Manuscript- N.İ., E.M.G., A.K.; Final Approval and Accountability- N.İ., A.K., E.M.G., B.G.Ş;

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REFERENCES

1. Khaki AA, Shokouhi G, Shoja MM, et al. Ansa cervicalis as a variant of spinal accessory nerve plexus: a case report. Clin Anat 2006;19(6):540-3.
2. Brown H. Anatomy of the spinal accessory nerve plexus: relevance to head and neck cancer and atherosclerosis. Exp Biol Med (Maywood) 2002;227(8):570-8.
3. McGarvey AC, Chiarelli PE, Osmotherly PG, Hoffman GR. Physiotherapy for accessory nerve shoulder dysfunction following neck dissection surgery: a literature review. Head Neck 2011;33(2):274-80.
4. Saman M, Etebari P, Pakdaman MN, Urken ML. Anatomic relationship between the spinal accessory nerve and the jugular vein: a cadaveric study. Surg Radiol Anat 2011;33(2):175-9.

5. Symes A, Ellis H. Variations in the surface anatomy of the spinal accessory nerve in the posterior triangle. Surg Radiol Anat 2005;27(5):404-8.
6. Overland J, Hodge JC, Breik O, Krishnan S. Surgical anatomy of the spinal accessory nerve: review of the literature and case report of a rare anatomical variant. J Laryngol Otol 2016;130(10):969-72.
7. Tubbs RS, Ajayi OO, Fries FN, Spinner RJ, Oskouian RJ. Variations of the accessory nerve: anatomical study including previously undocumented findings-expanding our misunderstanding of this nerve. Br J Neurosurg 2017;31(1):113-5.
8. Salgarelli AC, Landini B, Bellini P, Multinu A, Consolo U, Collini M. A simple method of identifying the spinal accessory nerve in modified radical neck dissection: anatomic study and clinical implications for resident training. Oral Maxillofac Surg 2009;13(2):69-72.
9. Watkinson JC, Gleeson M. 2016. Neck: the accessory nerve. In: Standring S, editor. Gray's Anatomy: The Anatomical Basis of Clinical Practice. 41st ed. London: Elsevier Limited P 467-8.
10. Ouaknine G, Nathan H. Anastomotic connections between the eleventh nerve and the posterior root of the first cervical nerve in humans. J Neurosurg 1973;38(2):189-97.
11. Hagenah R, Kosak M, Freckmann N. Anatomic topographical relationship of the intraspinal accessory root to the upper cervical roots and to the vessels of the cranial cervical region. Acta Anat (Basel) 1983;115(2):158-67.
12. Midwinter K, Willatt D. Accessory nerve monitoring and stimulation during neck surgery. J Laryngol Otol 2002;116(4):272-4.

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